

ERABI

EVIDENCE-BASED REVIEW
of moderate to severe
ACQUIRED BRAIN INJURY

15. Acute Interventions for Acquired Brain Injury

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Key Points

Intracranial pressure monitoring may improve mortality, but not neurological function in patients post ABI when compared to no monitoring.

Intracranial pressure monitoring might be similar to an imaging/clinical based monitoring approach in terms of morbidity and mortality outcomes; however, the imaging/clinical based monitoring group is likely to receive more interventions.

Intraparenchymal fiber optic monitors may be superior to external ventricular drains in monitoring intracranial pressure, preventing complications, and reducing the need for further treatment, however, there may be no differences in long term between devices.

Head elevation of 30° likely lowers intracranial pressure post ABI, however, its benefit on cerebral perfusion pressure is less certain.

Head elevation of 60° may lower intracranial pressure post-ABI.

Head elevation of 15° may effectively lower elevated intracranial pressure post ABI; meanwhile, the evidence for elevations of 45° and 60° are not as strong.

It is unclear if head elevation of 30° can effectively lower elevated intracranial pressure post ABI.

It is unclear if there is a correlation between increasing elevation angle and reduction in intracranial pressure; the strongest evidence suggests there is not.

It is unclear whether head elevation causes an improvement in cerebral perfusion pressure post ABI.

Head elevations ranging from 0°-60° may decrease mean arterial pressure post ABI.

It is unclear whether therapeutic hypothermia (32-35°C) is an effective intervention for lowering elevated intracranial pressure or improving long-term outcomes/mortality in patients post ABI.

Therapeutic hypothermia increases the risk of complications such as pneumonia.

It is unclear whether therapeutic hypothermia is superior to standard care alone at improving intracranial pressure, or morbidity and mortality outcomes in ABI patients. The strongest evidence suggests that compared to standard care there is a similar effect on intracranial pressure and a detrimental effect on morbidity and mortality.

When used, very mild hypothermia (35-37°C) may be more effective than mild hypothermia (32-34°C) at reducing intracranial pressure; however, the effect on morbidity and mortality is unclear. Consideration for cooler temperatures may be warranted with more severe injuries.

Therapeutic hypothermia, either intracranial pressure or oxygenation managed may have the same effect on intracranial pressure, morbidity and mortality in individuals with an ABI.

Selective, long-term hypothermia can be more effective than systemic, short-term hypothermia in improve intracranial pressure and long-term outcomes in ABI patients.

Hypothermia combined with standard therapy might be more effective than hypothermia alone at improving intracranial pressure, cerebral perfusion pressure and oxygenation in ABI patients.

Hypothermia may improve outcomes and reduce mortality post ABI.

Very mild hypothermia (35-36°C) may be more effective than mild hypothermia (32-34°C) at improving outcomes with fewer complications post ABI.

Hyperventilation may effectively lower elevated intracranial pressure post TBI; however, decreased cerebral blood flow and subsequent ischemia are potential complications.

The addition of tromethamine to a hyperventilation protocol is likely superior at improving long-term outcomes compared to hyperventilation alone.

Hyperoxia (PaO₂=200-250 mmHg) may improve cerebral oxygenation following hyperventilation post ABI.

Continuous rotational therapy might not improve intracranial pressure in individuals with severe TBI.

Prone positioning may increase intracranial pressure but improve cerebral oxygenation post ABI. The effects of prone positioning on cerebral perfusion and mean arterial pressure are unclear.

Conventional physiotherapy alone, or in combination with verticalization may improves long term outcomes, disability, cognitive functioning and recovery from coma.

Verticalization in combination with conventional physiotherapy may be superior to conventional physiotherapy alone at improving recovery from coma.

Verticalization using the Erigo robot may be superior to the MOTomed machine, and conventional therapy at reducing sympathetic stress.

Manipulation of body positions may increase intracranial pressure more than the supine position.

Although limited evidence exists, non-invasive active intrathoracic pressure might improve ICP and CPP, with no serious adverse effects, in patients post TBI.

Propofol may improve intracranial pressure and cerebral perfusion pressure post ABI, without producing adverse outcomes.

Propofol and vasopressor treatment in combination, but not as monotherapy, might increase the risk of developing propofol infusion syndrome post ABI.

Propofol, especially at higher doses, likely improves favourable outcomes, intracranial pressure and cerebral perfusion pressure more effectively than morphine.

Propofol may be no different than dexmedetomidine or morphine with midazolam in its effect on morbidity outcomes, or intracranial, cerebral perfusion, and mean arterial pressure.

The combination of morphine and midazolam may confound the comparison between propofol and morphine, however, it is prudent to conclude propofol is at least as safe and effective as morphine.

Midazolam is likely not different than propofol at improving mortality, disability, or neurological outcomes.

High doses of midazolam might be associated with hypotension, specially following intubation.

Midazolam may have no effect on intracranial pressure but may reduce mean arterial pressure and cerebral perfusion pressure in patients, post-ABI.

Remifentanyl might not improve intracranial pressure, cerebral perfusion pressure, cerebral blood flow velocity, or mean arterial pressure post ABI

Sufentanil might decrease mean arterial pressure, cerebral perfusion pressure, heart rate and transiently increase intracranial pressure— especially in patients with low blood pressure.

There are conflicting results regarding the effect different opioids may have on intracranial pressure and cerebral perfusion pressure effects post ABI; where fentanyl, morphine, sufentanil, and alfentanil might increase intracranial pressure and decrease cerebral perfusion pressure, remifentanyl may not affect intracranial pressure compared to controls.

Sufentanil used in combination with midazolam may decrease intracranial pressure and mean arterial pressure post ABI.

There are conflicting reports regarding whether pentobarbital is superior to conventional management at improving intracranial pressure. The strongest evidence suggests there is no difference.

Thiopental may decrease intracranial pressure, cerebral perfusion pressure, and mean arterial pressure post ABI.

Thiopental may be more effective than pentobarbital at controlled refractory intracranial pressure, and less likely to develop adrenal insufficiency. However, thiopental may still be associated with leuko- and granulocytopenias. When used, combination with hypothermia may result in greater long-term outcomes.

Barbiturate therapy should be avoided until all other measures for controlling elevated intracranial pressure are exhausted; special attention should be paid to monitoring immunological function, adrenal function, and blood pressure status if used.

Pentobarbital might decrease energy expenditure and nitrogen metabolism in individuals with an ABI refractory to standard therapy.

It is unclear whether Dexanabinol in cremophor-ethanol solution is effective in controlling intracranial pressure and improving cerebral perfusion pressure, and clinical outcomes post TBI. The strongest evidence suggests no beneficial effects.

KN38-7271, a dual cannabinol agonist, is likely effective at improving intracranial pressure, cerebral perfusion pressure and survival post TBI at high doses.

Progesterone does not improve functional outcomes post TBI, with the potential exception of patients who are not severely ill upon admission (Glasgow coma scale score ≥ 5)

Progesterone is likely associated with the development of phlebitis and thrombophlebitis.

Progesterone has no effect on intracranial pressure, but does reduce mortality, and improves functional and neurological outcomes post ABI.

Anatibant, regardless of dose, likely does not cause serious adverse events, affect morbidity, mortality or disability in patients post ABI.

It is unclear if a higher dose of anatibant is superior to a lower dose at improving intracranial pressure, however it may improve functional outcomes up to 6 months post injury.

Bradycor can prevent acute elevations in intracranial pressure and reduce therapeutic intensity levels post ABI; however, its effect on morbidity and mortality outcomes is not clear.

Dimethyl sulfoxide may cause temporary improvements in intracranial pressure and cerebral perfusion pressure post ABI; however, these improvements may not be sustained long-term.

DMSO might be able to transiently lower intracranial pressure; however, it is associated with the development of electrolyte imbalances. Both responses appear to be dose-dependent.

Corticosteroids such as methylprednisolone, dexamethasone, and other glucocorticoids may worsen outcomes, and should not be used. However, methylprednisolone may be effective at improving mortality when specific complications, such as acute respiratory distress syndrome secondary to sepsis, arise.

Triamcinolone may improve outcomes in individuals post ABI with a Glasgow Coma Scale score less than 8 and a focal lesion.

Conivaptan is likely superior to standard therapy at lowering intracranial pressure post ABI.

Vasopressin and catecholamine treatment may be similar for improving intracranial pressure, morbidity and mortality outcomes post ABI.

Elevated intracranial pressure may be effectively reduced by paracetamol, however concurrent decreases in cerebral perfusion, mean arterial pressure, and core body temperature can be expected.

Hypertonic saline may lower elevated intracranial pressure and potentially increases cerebral perfusion pressure and blood flow post ABI. The improvement in intracranial pressure may last up to 12 hours

, though short-term improvements are more common.

Hypertonic saline may increase serum sodium, time spent in the ICU, but not mortality post ABI.

Contused brain tissue may increase in volume after administration of hypertonic saline post ABI.

It is unclear whether hypertonic saline is more effective than mannitol at lowering intracranial pressure or reducing hospital length of stay.

Hypertonic saline can improve cerebral perfusion pressure, cerebral blood flow, and brain tissue oxygenation more effectively than mannitol. However, hypertonic solution is not different than mannitol in terms of morbidity and mortality associated with treatment.

Hypertonic saline is superior to barbiturates, propofol, and fentanyl at lowering intracranial pressure post TBI.

Hypertonic saline may be similar to Ringer's lactate at improving intracranial pressure and clinical outcomes post TBI.

Hypertonic saline may have similar effects on intracranial pressure when compared to sodium bicarbonate; however, sodium bicarbonate sustains the improvement for longer periods of time.

Mannitol may effectively improve intracranial pressure and cerebral perfusion pressure post ABI; however, this benefit may only be seen in hypertensive (intracranial pressure > 20 mmHg) patients.

Mannitol effectively decreases intracranial pressure post ABI but can increase urine output and plasma sodium and chloride; furthermore, high doses may yield improved intracranial pressure control, lower mortality rates and better clinical outcomes compared to lower doses.

Prophylactic mannitol administration may not be associated with different morbidity or mortality outcomes compared to its standard use post TBI.

Mannitol may be equally effective as hypertonic saline at reducing intracranial pressure and cerebral perfusion pressure, and less effective than Ringer's (sodium) lactate at reducing intracranial pressure.

Enteral urea may lower elevated intracranial pressure in patients with ABI and syndrome of inappropriate antidiuretic hormone secretion.

Thawed plasma may be superior to packed red blood cells at improving neurological function and disability in patients with multiple injuries post TBI.

Platelet transfusion in patients receiving anti-platelet therapy likely improves platelet dysfunction, but not mortality post ABI. Patients may also be at higher risk of requirement for intervention, and a longer hospital stay.

Ventricular cerebrospinal fluid drainage, regardless of amount drained, likely improves intracranial and cerebral perfusion pressure post ABI.

Continuous cerebrospinal fluid drainage may be more effective than intermittent drainage at acutely lowering elevated intracranial pressure post ABI, with no differences existing in long-term outcomes.

Cerebrospinal fluid drainage may effectively lower elevated intracranial pressure post ABI, using either a ventricular or lumbar device. It is unclear how long this improvement is sustained for. In addition, ventricular devices may potentially increase cerebral perfusion pressure and cerebral blood flow.

External lumbar devices may effectively lower intracranial pressure in patients' refractory to first line treatments.

Conflicting results exist as to whether a decompressive craniectomy can lower elevated intracranial pressure post ABI; however, the vast majority of the data support its efficacy as an effective intervention.

The effect of a decompressive craniectomy on cerebral perfusion pressure is unclear.

It is unclear whether a decompressive craniectomy is associated with improved long-term outcomes and mortality; however young age, early decompressive craniectomy, large decompressive craniectomy, and higher Glasgow Coma Score scores may all be predictors for favourable outcomes.

Decompressive craniectomy is more effective than standard treatment at reducing intracranial pressure; however, it is unclear which treatment best improves morbidity and mortality post ABI. Initial Glasgow Outcome Scale score, but not intracranial pressure monitoring post decompressive craniectomy, might be a predictor for improved outcomes in patients post ABI.

Decompressive craniectomy may be similar to controlled decompression in reducing elevated intracranial pressure and improving Glasgow Outcome Scale scores.

It is unclear whether bone flap size affects intracranial pressure or morbidity outcomes in patients receiving a decompressive craniectomy post TBI. The strongest evidence supports the use of a larger (12x15cm) bone flap for better intracranial pressure control and morbidity outcomes.

Decompressive craniectomies and craniotomies may be similar at reducing intracranial pressure post ABI, but a decompressive craniectomy could be superior at improving good outcomes. It is unclear which procedure improves mortality the most.

Decompressive craniectomies may worsen mortality, recovery and complications in patients post ABI; however young age, early decompressive craniectomy, large decompressive craniectomy, and higher Glasgow Coma Scale scores may all be predictors for favourable outcomes.

It is unclear whether a decompressive craniectomy is superior to a craniotomy at improving mortality and long-term outcomes post ABI. However, large studies have trended towards showing improved morbidity and mortality following a craniotomy.

An intracranial hemorrhage evacuation with a decompressive craniectomy may be inferior to an intracranial hemorrhage evacuation, or the same as an intracranial hemorrhage evacuation with a craniotomy at improving mortality and long-term outcomes in patients post ABI.

Trepanation after a thick subdural intracranial hemorrhage might increase patient mortality.

It is unclear whether a decompressive craniectomy is superior to standard care at improving Glasgow Outcome Scale scores and mortality in patients post ABI.

The type of decompressive craniectomy (with dural slits or expansile duraplasty) post acute subdural hematoma may not affect mortality and neurological outcomes.

Synthetic skin substitutions might be associated with increased rates of infections and mortality post TBI; however, its use may be warranted in patients where skin closure is not possible.

Multimodal stimulation is more effective than standard care at improving consciousness and cognitive function post ABI, however its improvement in physical arousal behaviours are not as clear.

Sensory stimulation may be most effective when it is early, frequent, and sustained as well as specific, directed, and regulated.

Sensory stimulation may be most effective when stimuli are familiar or delivered by a familiar individual.

Auditory sensory stimulation may improve functional outcomes; however, the evidence is unclear.

Multi-sensory stimulation may cause physiological or biochemical sympathetic arousal; however, it is unlikely it improves more concrete parameters such as heart rate, motor ability, or recovery post ABI.

Music therapy may improve consciousness in individuals in a coma post ABI.

The effects of median nerve electrical stimulation on consciousness and arousal from coma in individuals post ABI is unclear, however, the strongest evidence suggests there are no benefits.

Median nerve electrical stimulation may be superior to standard care at improving consciousness and function long-term.

Median nerve stimulation may increase cerebral perfusion pressure and dopamine levels in individuals in a coma post ABI.

Physical therapy in the acute phase post ABI may improve motor and cognitive function.

Amantadine improves consciousness, cognitive function, and disability; however, it might not affect emergence from coma post ABI. It is important to note that these benefits are only seen during amantadine administration, and so treatment must be continued to sustain the improvements made.

Amantadine may be more effective than standard care at improving consciousness and decreasing mortality in patients in a coma post ABI.

Citicoline and antiepileptics may not be effective interventions for restoring consciousness post ABI, however, further research is required.

A hypertonic saline and dextran infusion combination is likely the same as normal saline at improving mortality and morbidity outcomes in patients post TBI. Brain injury serum markers may predict the development of unfavourable outcomes.

Hypertonic saline may increase hospital length of stay and rates of infections, especially in patients with severe TBIs.

Mannitol may increase urine output, lower serum sodium, transiently decrease systolic blood pressure, but has the same mortality compared to hypertonic solution.

Albumin may increase mortality, especially in patients with severe TBI, compared to hypertonic solution; however, there may be no difference in neurological outcomes between treatments.

Recombinant erythropoietin administration likely improves mortality and neurological outcomes, and acutely lowers brain cell destruction markers in patients post ABI.

Tranexamic acid in combination with standard care is likely superior to standard care alone at reducing intracranial hemorrhage growth in patients post TBI.

Selenium in addition to standard care is likely not different than standard care at improving morbidity and neurological outcomes in patients post TBI and may even be associated with nausea and facial flushing.

Prophylactic statin use may not improve mortality or neurological outcomes in patients post TBI.

Early propranolol intervention may decrease mortality, but increase time spent on a ventilator in patients post TBI.

Dexmedetomidine might improve sedation, neurological outcomes and decrease the need for opioid administration, however caution should be taken due to its ability to lower blood pressure.

Diclofenac Sodium might decrease core body temperature, however its benefit in preventing fever is outweighed by its ability to compromise systemic and cerebral perfusion.

Tracheostomies might improve mortality in individuals post ABI; however, individuals undergoing the procedure are generally older, more injured, and require more treatment.

Adherence to TBI treatment guidelines below 60% may be associated with increased patient mortality

Intracranial pressure monitor placement may improve short-term mortality, but not long-term mortality or morbidity outcomes

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Abbreviations

AANS	American Association of Neurological Surgeons
ABI	Acquired Brain Injury
CPP	Cerebral Perfusion Pressure
CSF	Cerebrospinal Fluid
DC	Decompressive Craniectomy
DMSO	Dimethyl Sulfoxide
DOC	Disorders of Consciousness
EBIC	European Brain Injury Consortium
EVD	External Ventricular Drain
GCS	Glasgow Coma Scale
GOS	Glasgow Outcome Scale
HTS	Hypertonic Saline
ICH	Intracranial Hemorrhage
ICP	Intracranial Pressure
IPM	Intraparenchymal Fiberoptic Monitor
MAP	Mean Arterial Pressure
mmHg	mm of mercury
PaCO ₂	Partial Pressure of Carbon Dioxide in Arterial Blood
PaO ₂	Partial Pressure of Oxygen in Arterial Blood
PCT	Prospective Controlled Trial
PEDro	Physiotherapy Evidence Database rating scale
RCP	Royal College of Physicians
RCT	Randomized Controlled Trial
RLAS	Rancho Los Amigos Scale
SAH	Subarachnoid Hemorrhage
TBI	Traumatic Brain Injury
WNSSP	Western Neuro Sensory Stimulation Profile

Acute Interventions for Acquired Brain Injury

15.0 Introduction

This module reviews the available evidence pertaining to interventions for acute care following Acquired Brain Injury (ABI). The majority of interventions focus on the management of intracranial pressure, with additional interventions for prompting emergence from coma, and miscellaneous outcomes. For the purposes of ERABI, acute interventions were considered any treatment or intervention that was initiated within 14 days of ABI or ABI diagnosis.

15.1 Management of Intracranial Pressure

During the initial stages of an ABI, irreversible damage to the central nervous system occurs, which is commonly referred to as the primary injury. Subsequently, a chain of events leads to ongoing (secondary) brain injury, which is caused by edema, hypoxia, and ischemia (Werner & Engelhard, 2007). These pathological processes are a result of increased Intracranial Pressure (ICP), the release of toxic amounts of excitatory neurotransmitters, and impaired ionic homeostasis (Werner & Engelhard, 2007). Considering the primary injury occurs immediately upon insult and is irreversible, acute brain injury treatment focuses on preventing or minimizing the extent of secondary injury. As such, interventions have focused on targeting intracranial hypertension, oxygenation, and ion homeostasis in order to reduce cellular injury.

High ICP is one of the most frequent causes of death and disability following severe ABI. High ICP is defined as ICP \geq 20mmHg, within any intracranial space including the subdural, intraventricular, extradural, or intraparenchymal compartments (Sahuquillo & Arian, 2006). Following ABI, the brain is extremely vulnerable to secondary ischemia due to systemic hypotension and/or diminished cerebral perfusion resulting from elevations in ICP (Doyle et al., 2001). For these reasons, the acute care of patients with ABI includes the maintenance of adequate blood pressure and management of rises in ICP.

Elevated ICP after an ABI is generally due to edema or inflammation within the cranial cavity (Rabinstein, 2006). There are various types of edema classified by their different pathophysiology's, the most common of which are: vasogenic, cytotoxic, and interstitial edema (Rabinstein, 2006). Vasogenic edema results from the breakdown of the blood brain barrier, which causes increased permeability and the movement of proteins and fluid into the extravascular space. Cytotoxic edema develops from the inability of cellular ionic pumps to maintain a normal concentration gradient across the cell membrane, causing increases in intracellular water content and cell swelling. Finally, interstitial edema is the forced flow of fluid from intraventricular compartments to the parenchyma, which is most commonly due to an obstruction in drainage.

The Monro-Kellie hypothesis states that the intracranial compartment has fixed volumes of the following components: cerebral tissue, cerebral blood, and Cerebrospinal Fluid (CSF). As one compartment increases in volume or a mass lesion is added to the compartment, compensation must occur to maintain a normal ICP. This compensation initially involves displacement of CSF and venous blood into the spinal canal. However, once a critical volume is reached in the intracranial compartment, cerebral compliance decreases and elastance increases resulting in larger changes in ICP with smaller changes in volume. Therefore, small reductions in CSF can have a large impact on ICP control at this stage (Vella et al., 2017). Multiple therapies are used to maintain normal ICPs in patients with a Traumatic Brain Injury (TBI). In order for treatments to be effective, however, interventions need to target the specific form of edema

that is responsible for the increase in ICP. The degree and timing of ICP elevation are also important determinants of clinical outcomes, adding a sense of urgency to initiate ICP interventions as soon as possible (Vella et al., 2017).

There are two broad categories of therapies used to alleviate increased ICP in patients with TBI; surgical and non-surgical (medical) interventions (Lazaridis et al., 2018; Vella et al., 2017). Non-surgical interventions focus on reducing cerebral edema, reducing metabolic demand, and increasing cerebral blood flow. These interventions include the use of both pharmacological agents (diuretics, corticosteroids, barbiturates, etc.) and non-pharmacological interventions (hypothermia, hyperventilation, head posture, body rotation). Conversely, surgical therapies employ physical interventions to reduce ICP by either decreasing the volume of fluid (blood, CSF) or increasing the size of the cranial compartment (Davanzo et al., 2017). Some of the most commonly performed procedures include: ventriculostomy with therapeutic drainage, evacuation of mass lesions, and decompressive craniectomy.

The understanding of the negative effects associated with cellular level post-traumatic stress have generated interest in exploring compounds that serve as neuroprotective agents. These compounds have been used in conjunction with standard therapy to optimally reduce cellular damage caused by increases in ICP. Traditional therapies have included sedatives such as barbiturates and opiates in an attempt to down-regulate cellular metabolism. Newer initiatives have begun to target free radical production and oxidative stresses, which affect membrane viability.

Guideline Recommendations

In an attempt to standardize acute management of ABI, several consensus guidelines have been developed. The two most prominent sets of guidelines are those developed by the American Association of Neurological Surgeons (AANS) in 2016 (Carney & Ghajar, 2007), and by the European Brain Injury Consortium (EBIC) in 1997 (Maas et al., 1997). These guidelines have gained credibility worldwide and are widely recognized as influencing clinical practice. As such, we have chosen to add recommendations made by either organization into our evaluation of each intervention. However, the conclusions presented in the levels of evidence statements and conclusion boxes in this module are based on our methodology.

15.1.1 Intracranial Pressure Monitoring

The Brain Trauma Foundation has stated that all comatose patients with TBI should be monitored with an ICP monitor. Despite their recommendations, studies have reported a lack of compliance with the proposed ICP monitoring guidelines in part due to a perceived lack of evidence (Hesdorffer et al., 2002). Providing evidence for the efficacy of this guideline proves difficult, as prospective studies are all confronted with a similar ethical dilemma that arises when attempting to randomize patients into a group not receiving an accepted standard therapy.

The ICP monitoring landscape shifted when Chesnut et al. (2012) published a landmark study by conducting a randomized controlled trial using an intensive care center which did not routinely use ICP monitoring in their care of TBI. Despite the controversial reception to the article, primarily surrounding the ethics of the study design, this paper has opened the door for subsequent studies to compare ICP monitoring to other types of care in terms long-term and mortality outcomes in patients with TBI.

There are different types of ICP monitors available which can be broadly classified into invasive (Parenchymal Monitors, External Ventricular Drains [EVDs], fibreoptic monitors, etc), and non-invasive

(Transcranial Doppler Ultrasonography, Tympanic Membrane Displacement, Optic Nerve Sheath Diameter, MRI, CT, etc) (Raboel et al., 2012). Invasive monitors are the more accurate tool, however, they come at the expense of higher risk of complications such as infections (Davanzo et al., 2017). Parenchymal monitors as their name suggest insert directly into the parenchyma to calculate ICP. Due to the pressure gradient created during a TBI, parenchymal monitors may not be the most accurate for measuring CSF pressure (Davanzo et al., 2017). On the other hand, EVDs are placed in the lateral ventricle with the primary function of draining CSF. In addition to allowing CSF drainage however, EVDs can be used as an ICP monitor and as a result they are the preferred ICP monitor (Le Roux, 2016; Raboel et al., 2012). The development of fiberoptic monitors, which attach to the end of the EVD catheter and provides a constant ICP reading regardless of the EVD setting or function, have gained traction as a more accurate measurement of ICP (Le Roux, 2016).

This section will examine the existing literature to elucidate the benefit of ICP monitoring in patients post ABI.

Table 15.1 Intracranial Pressure Monitors for the Acute Management of Patients Post ABI

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Chesnut et al. (2012) Bolivia& Ecuador RCT PEDro=8 N=324	<p>Population: TBI=200. <i>Pressure-monitoring group (n=157):</i> Median Age=29 yr; Gender: Male=143, Female=14. Median time to admission to study hospital= 3.5 h. Median motor GCS score=5. <i>Imaging-Clinical Examination (ICE) group (n=167):</i> Mean Age=29 yr; Gender: Male=140, Female=27, Median time to admission to study hospital=2.9 h, Median motor GCS score=4.</p> <p>Intervention: Patients were randomly assigned to either the ICP-monitoring, or the Imaging and Clinical Examination (ICE) group. Patients in the ICP-monitoring group had an intraparenchymal monitor placed as soon as possible. Patients in the ICE group were treated in accordance to hospital protocol. Outcomes were assessed at discharge, 3 and 6 mo.</p> <p>Outcome measures: Survival, Duration and Level of Impaired Consciousness, Functional Status and Orientation (3mo- GOSE, DSR, GOAT), Functional and Neuropsychological Status (6 mo), Hospital Length of Stay (LOS), Systemic Complications.</p>	<ol style="list-style-type: none"> 1. There were no significant differences between the groups in survival, 14 d or 6 mo mortality, hospital LOS, incidence of neurological worsening. 2. Patients in the pressure-monitoring group had a significant higher rate of decubitus ulcers compared to the ICE group (p=0.03) 3. The median interval during which patients received brain-specific treatment, total number of treatments, use of high dose barbiturates, and proportion of patients treated with HTS or hyperventilation was significantly higher in the ICE group (p=0.05)
Agrawal et al. (2017) USA & India Cohort N=1345	<p>Population: Severe TBI; <i>ICPM not used (n=848):</i> Median Age=32 yr; Gender: Male=756, Female=92; Median Time Post Injury=3.46 hr; Median Admission GCS=6. <i>ICPM used (n=497):</i> Median Age=31 yr; Gender: Male=438, Female=59; Median Time Post Injury=3.08 hr; Median Admission GCS=7.</p> <p>Intervention: Patients who received invasive intracranial pressure monitoring (ICPM) during ICU admission were compared with controls.</p> <p>Outcome Measures: Hospital Mortality, Glasgow Outcome Scale (GOS).</p>	<ol style="list-style-type: none"> 1. The probability of hospital mortality was significantly lower in patients who received ICPM by about 9% (p=0.001). ICPM utilization was also associated with a significantly lower mortality at 6mo by about 6% (p=0.03). 2. There were no significant treatment effects on probability of poor function (defined by GOS) at 6mo (p=0.46).

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
<p>Chesnut et al. (2012) Bolivia& Ecuador RCT PEDro=8 N=324</p>	<p>Population: TBI=200. <i>Pressure-monitoring group (n=157):</i> Median Age=29 yr; Gender: Male=143, Female=14. Median time to admission to study hospital= 3.5 h. Median motor GCS score=5. <i>Imaging-Clinical Examination (ICE) group (n=167):</i> Mean Age=29 yr; Gender: Male=140, Female=27, Median time to admission to study hospital=2.9 h, Median motor GCS score=4. Intervention: Patients were randomly assigned to either the ICP-monitoring, or the Imaging and Clinical Examination (ICE) group. Patients in the ICP-monitoring group had an intraparenchymal monitor placed as soon as possible. Patients in the ICE group were treated in accordance to hospital protocol. Outcomes were assessed at discharge, 3 and 6 mo. Outcome measures: Survival, Duration and Level of Impaired Consciousness, Functional Status and Orientation (3mo- GOSE, DSR, GOAT), Functional and Neuropsychological Status (6 mo), Hospital Length of Stay (LOS), Systemic Complications.</p>	<ol style="list-style-type: none"> 1. There were no significant differences between the groups in survival, 14 d or 6 mo mortality, hospital LOS, incidence of neurological worsening. 2. Patients in the pressure-monitoring group had a significant higher rate of decubitus ulcers compared to the ICE group (p=0.03) 3. The median interval during which patients received brain-specific treatment, total number of treatments, use of high dose barbiturates, and proportion of patients treated with HTS or hyperventilation was significantly higher in the ICE group (p=0.05)
<p>Kasotakis et al. (2012) USA Case Control N=377</p>	<p>Population: TBI; Mean Age=46.5 yr; Gender: Male=295, Female=83; Mean GCS=6.7. Intervention: Participants who received External Ventricular Drainage (EVD) or Intraparenchymal Fiberoptic Monitor (IPM) for CSF drainage were compared. Outcome Measures: Intracranial Pressure (ICP), Glasgow Outcome Scale (GOS), Mortality, Length of Stay (LOS), Additional Treatments, Complications.</p>	<ol style="list-style-type: none"> 1. Mean ICP monitoring duration was significantly longer in EVD than IPM (7.3 days versus 3.8 days, p<0.001). 2. There was no significant difference between EVD and IPM in mean GOS at 1 mo (2.5 versus 2.7, p=0.45) or mortality (32.2% versus 20.9%, p=0.82). 3. Mean LOS in ICU was significantly longer in EVD than IPM (9.5 days versus 7.6, p=0.004), but there was no difference in hospital LOS (16.4 days versus 15.6 days, p=0.57). 4. Surgical decompression was significantly higher in EVD than IPM (51.9% versus 33.6%, p=0.001). 5. Device-related complications were significantly higher in the EVD group than in the IPM group (31.1% versus 11.2%, p<0.05).

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

Two studies were reviewed comparing patients receiving ICP monitoring post ABI to either no monitoring (Agrawal et al., 2017) or imaging and clinical based (ICE) monitoring (Chesnut et al., 2012). When compared to no imaging, ICP monitoring was associated with lower mortality in the hospital and 6 months after discharge (Agrawal et al., 2017). Despite the improvement in mortality, there was no significant difference between the groups in terms of GOS scores at 6 months post-discharge. When ICP monitoring

is compared to ICE monitoring, as it was in the BEST:TRIP study, the researches found no differences in mortality (14 d, 6 mo), hospital length of stay, or incidence of neurological worsening (Chesnut et al., 2012). Both interventions were nearly identical in the rates of complications, with the exception of a higher rate of decubitus (pressure) ulcers in the pressure monitoring group. It is important to note that the rate at which patients received ICP-lowering interventions (high-dose barbiturates, HTS, hyperventilation, and total number of treatments) was significantly higher in the ICE group. The increased intervention frequency may be due to increased clinician suspicion of raised ICP, which develops in the absence of access to a discrete ICP value. Presumably, this increase in interventions could predispose an individual to higher rates of complications; however, there were no reported outcomes to support this. The effectiveness of an external ventricular drain (EVD) in managing elevated ICP when compared to an intraparenchymal fiberoptic monitor (IPM) is unclear. The results from a large retrospective study found the EVD to be inferior to the IPM (Kasotakis et al., 2012). While there were no significant differences between treatments in terms of mortality and long-term outcomes, the EVD had significantly higher rates of surgical decompression and device-related complications. In addition, the authors also found that the EVD required longer ICP monitoring and ICU stay than the IPM.

Conclusions

There is level 1b evidence that intracranial pressure monitoring is not different to imaging/clinical based monitoring at improving mortality, hospital length of stay, or neurological worsening in patients post TBI.

There is level 1b evidence that there is a higher rate of decubitus ulcers in the intracranial pressure monitoring group when compared to imaging/clinical based monitoring group in patients post TBI.

There is level 1b evidence that patients in the imaging/clinical based monitoring group receive high-dose barbiturates, hypertonic saline infusion and hyperventilation interventions at a higher frequency when compared to the intracranial pressure monitoring group post TBI.

There is level 2 evidence that intracranial pressure monitoring may improve mortality in-hospital, and 6 months post-discharge in patients post ABI compared to no monitoring.

There is level 2 evidence that intracranial pressure monitoring may not improve Glasgow Outcome Scale scores in patients post ABI compared to no monitoring.

There is level 3 evidence that an intraparenchymal fiberoptic monitor may yield lower intensive care unit length of stay, device complications, need for surgical decompressions, and need for intracranial pressure monitoring compared to an external ventricular drainage post ABI.

Intracranial pressure monitoring may improve mortality, but not neurological function in patients post ABI when compared to no monitoring.

Intracranial pressure monitoring might be similar to an imaging/clinical based monitoring approach in terms of morbidity and mortality outcomes; however, the imaging/clinical based monitoring group is likely to receive more interventions.

Intraparenchymal fiber optic monitors may be superior to external ventricular drains in monitoring intracranial pressure, preventing complications, and reducing the need for further treatment, however, there may be no differences in long term between devices.

15.1.2 Non-Pharmacological Interventions

15.1.2.1 Head Posture

The standard practice in most intensive care units when managing an ABI is to elevate the head above the level of the heart in an effort to reduce ICP. Head elevation is thought to reduce ICP by facilitating intracranial venous outflow while maintaining, and perhaps even improving, CPP and cardiac output (Ng et al., 2004); (Schulz-Stubner & Thiex, 2006). In addition, placing patients in an elevated head posture facilitates early provision of enteral nutrition while reducing the risk of gastric reflux and pulmonary aspiration when compared to the supine position (Ng et al., 2004).

In a systematic review, Fan (2004) found 11 studies with a pooled sample of 178 participants. The authors noted that all studies found significant reductions in ICP associated with head elevation, while only six studies found significant improvements in CPP. A meta-analysis by Jiang et al. (2015) examined a total of 10 studies with a pooled sample of 237 participants. The authors found that a head elevation of 30° yielded a large effect in ICP reduction when compared to 0°. To summarize multiple studies, authors found a moderate effect at 10° and large effects at 15° and 45° when compared to 0°. Large effects were also observed at 30° and 45° when compared to 15°. As well, the authors found no difference in ICP reduction between 30° and 45°.

Although head elevation during the management of ABI is well accepted, there is evidence suggesting that keeping patients in a flat position may be beneficial. Ng et al. (2004) note that maintaining individuals with a TBI in a flat position reduces the risk of systemic hypotension inherent in a semi-recumbent posture. Furthermore, some authors argue that a horizontal body position increases CPP, which improves cerebral blood flow (Winkelman, 2000).

The EBIC stated that no consensus existed regarding the benefits of head elevation to 30 degrees when compared to the recumbent position (Maas et al., 1997). There are no AANS recommendations for head posture. Studies examining the evidence on head elevation in ABI are presented in Table 15.2.

Table 15.2 Head Posture for the Acute Management of Intracranial Pressure Post ABI

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Ledwith et al. (2010) USA RCT Crossover PEDro=5 N=33	Population: ABI; Mean Age=48.3 yr; Gender: Male=22, Female=11; GCS Range≤8. Intervention: Participants were placed in 12 different head and body positions, each for 2 hr, in random order. Body positions included the supine, supine with knee bent, left lateral position and right lateral position. In each position, the head of bed (HOB) was	1. P _{bt} O ₂ decreased in 4 of the positions: supine with HOB 30° (p=0.006), supine with HOB 45° (p=0.004), left lateral with HOB 30° (p=0.046) and right lateral with HOB 30° (p=0.028). 2. ICP was significantly reduced when individuals were placed in the supine

Author Year Country Research Design PEdro Sample Size	Methods	Outcomes
	elevated to 15, 30° or 45°. Outcomes were assessed before and 15 min after each position change. Outcome Measures: Brain Tissue Oxygen Pressure (P_{btO_2}), Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP).	with HOB 45° ($p=0.002$), left lateral with HOB 15° ($p=0.026$), right lateral with HOB 15° ($p=0.002$) and the knee elevation with HOB 30° ($p=0.039$). 3. Only left lateral with HOB 30° had a significant effect on CPP ($p<0.05$).
Winkelman (2000) USA RCT Crossover PEDro=4 N=8	Population: TBI; Mean Age=28.0 yr; Gender: Male=6, Female=2; GCS Range ≤ 8 . Intervention: Participants were placed with the backrest elevated at 30° and at 0° for 65-75 min in a random order. Outcomes were assessed 5, 15, 30 and 60 min after each position. Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP).	1. Significant improvements in both ICP and CPP occurred immediately after changes in backrest position from 0° to 30° ($p=0.001$) and during equilibrium at the 30° position ($p=0.003$).
March et al. (1990) USA RCT Crossover PEDro=3 N=4	Population: TBI; Mean Age=23.0 yr; Gender: Male=2, Female=2; Mean GCS=6.5. Intervention: Participants received backrest manipulation in 3 different positions: 30° head elevation, 30° head elevation with knee gatch raised, and flat to reverse Trendelenburg position. Subjects were initially placed in the flat position for 15 min, followed by 15 min in one of the three randomly assigned alternate backrest positions. Outcomes were assessed at each position. Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Cerebral Blood Flow (CBF).	1. No significant changes were noted on any of the measures among the 4 backrest positions ($p>0.05$).
Mahfoud et al. (2010) Germany Pre-Post N=40	Population: ABI; Mean Age=54 yr; Gender: Male=18, Female=15. Intervention: Participants had their heads elevated to 30° and 60° from a flat position. Outcomes were assessed at each position. Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Mean Arterial Pressure (MAP).	1. Mean ICP was significantly reduced ($p<0.001$) from 0° to 30° (-6.9 mmHg) and from 0° to 60° (-8.5 mmHg). 2. Mean CPP was significantly reduced ($p<0.05$) from 0° to 30° (-5.3 mmHg) and from 0° to 60° (-10.2 mmHg). 3. Mean MAP was significantly reduced ($p<0.05$) from 0° to 30° (-12.1 mmHg) and from 0° to 60° (-18.6 mmHg). 4. There was a significant correlation between ICP and CPP ($r=-0.5$, $p=0.003$), and between CPP and MAP ($r=0.81$, $p<0.001$).
Schulz-Stiibner & Thiex (2006) Germany Case Series N=10	Population: ABI; GCS Range ≤ 8 . Intervention: Participants were put in the flat position with a positive end expiratory pressure (PEEP) of 5, 10 and 15 cm H ₂ O. Participants had their head elevated to 30° with a positive end expiratory pressure (PEEP) of 5 cm H ₂ O. PEEP was then increased to 10 and 15 cm H ₂ O. Outcomes were assessed beforehand after each position change.	1. When participants had their heads lowered to a flat position, ICP was significantly increased and CPP was significantly reduced ($p<0.05$). 2. In the flat position, an increase in PEEP from 5 to 10 cm H ₂ O increased ICP without dropping CPP significantly ($p>0.05$).

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
	Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP).	<ol style="list-style-type: none"> 3. In the flat position an increase in PEEP from 5 to 15 cm H₂O increased ICP with a significant drop in CPP (p<0.05). 4. When the head was elevated to 30° and PEEP changed from 5 to 10 cm H₂O, ICP and CPP did not change significantly (p>0.05). 5. When the head was elevated to 30° and PEEP was increased to 15 cmH₂O, ICP significantly increased (p<0.05) and CPP did not change significantly (p>0.05).
Ng et al. (2004) Singapore Pre-Post N=38	Population: TBI; Mean Age=34.05 yr; Median GCS=7.0. Intervention: Participants were elevated to a 30° head-up position then subsequently lowered to a 0° position. Outcomes were assessed before and 15 min after each position change. Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Mean Arterial Pressure (MAP), Global Cerebral Oxygenation (GCO), Regional Cerebral Oxygenation (RCO).	<ol style="list-style-type: none"> 1. ICP was significantly lower at 30° than at 0° of head elevation (p<0.0005). 2. CPP was slightly but not significantly higher at 30° than at 0° (p=0.412). 3. Those who had lower ICP at baseline were found to have the greatest decrease in ICP when the head was elevated 30°. 4. MAP, GCO and RCO were not affected significantly by head elevation.
Moraine et al. (2000) Belgium Pre-Post N=37	Population: TBI=13, SAH=9, ICH=7, Tumor=3, Other=5; Mean Age=52 yr; Gender: Male=22, Female=15; Mean GCS=6. Intervention: Participants were placed into 4 positions of head elevation: 0°, 15°, 30° and 45°. Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP).	<ol style="list-style-type: none"> 1. Mean ICP significant decreased from 25 mmHg at 0° to 20 mmHg at 15°, 14 mmHg at 30°, and 16 mmHg at 45° (all p<0.01). 2. Mean CPP significantly decreased from 62mmHg at 0° to 57 mmHg at 45° (p<0.01), but not at 15° or 30°.
Meixensberger et al. (1997) Germany Case Series N=22	Population: ABI; Mean Age=36.8 yr; Gender: Male=11, Female=11; GCS: 3-5=9, 6-8=8, 9-12=5. Intervention: Participants were placed in a 30° and then 0° body position each for 10-15 min. Outcomes were assessed before and after each position. Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Brain Tissue Oxygen Pressure (P _{bt} O ₂), Mean Arterial Pressure (MAP).	<ol style="list-style-type: none"> 1. Compared with 30°, ICP was significantly higher (p<0.001) and CPP was significantly lower (p<0.01) at the 0°. 2. P_{bt}O₂ and MAP pressure were unaffected by head position.
Schneider et al. (1993) Germany Pre-Post N=25	Population: TBI=17, SAH=5, ICH=3; Mean Age=48y r; Mean GCS=6. Intervention: Participants were placed into 4 positions of head elevation: 0°, 15°, 30° and 45°. Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Mean Arterial Pressure (MAP), Jugular Venous Oxygen Saturation (S _{jv} O ₂).	<ol style="list-style-type: none"> 1. Mean ICP significantly decreased from 19.8 mmHg at 0° to 14.3 mmHg at 15°, 11.0 mmHg at 30°, and 10.2 mmHg at 45° (all p<0.001). 2. Mean MAP significantly decreased from 79.9 mmHg at 0° to 75.7 mmHg at 15° (p<0.01), 72.3 mmHg at 30° (p<0.001), and 68.9 mmHg at 45° (p<0.001). 3. There was no significant change in CPP or S_{jv}O₂ associated with any elevation.

Author Year Country Research Design PE德罗 Sample Size	Methods	Outcomes
Feldman et al. (1992) USA Case Series N=22	<p>Population: TBI=22; Mean Age=35 yr; Gender: Male=19, Female=3; Mean Time Post Injury=72 hr; GCS: 3-5=3, 6-8=14, 9-12=5.</p> <p>Intervention: Participants had their heads initially elevated to 30° (n=13) or 0° (n=9). Head elevation was changed to the alternate position after 45 min. Outcomes were assessed at each position.</p> <p>Outcome Measures: Intracranial Pressure (ICP), Mean Carotid Pressure (MCP), Cerebral Perfusion Pressure (CPP), Cerebral Blood Flow (CBF), Cerebrovascular Resistance (CR), Cerebral Metabolic Rate of Oxygen (CMRO₂), Arteriovenous Oxygen Difference (AOD).</p>	<ol style="list-style-type: none"> ICP and MCP were significantly lower at 30° than at 0° (p=0.0062 and p=0.001). All of the other physiological parameters were not significantly affected by the change in head elevation.
Park & Ha (1992) South Korea Pre-Post N=34	<p>Population: TBI; Gender: Male=9, Female=25; GCS Range=5-8.</p> <p>Intervention: Participants had their heads elevated to 30° from a flat position.</p> <p>Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP).</p>	<ol style="list-style-type: none"> There was a significant decrease in mean ICP from 23 mmHg at 0° to 18.6 mmHg at 30° (t=4.22, p<0.001). There was no significant change in CPP after elevation.
Rosner & Coley (1986) USA Pre-Post N=18	<p>Population: ABI; Mean Age=36 yr; Gender: Male=9, Female=9; Mean GCS=7.7.</p> <p>Intervention: Participants were progressively subjected to 6 different positions of head elevation: 0°, 10°, 20°, 30°, 40°, and 50°.</p> <p>Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Central Venous Pressure (CVP), Systemic Arterial Pressure (SAP).</p>	<ol style="list-style-type: none"> For every 10° increase in head elevation, mean ICP decreased by 1 mmHg (p<0.1) and CPP decreased by 2-3 mmHg (p<0.05). There were significant reductions in SAP (p<0.001) and CVP (p<0.01) with head elevation.
Parsons & Wilson (1984) USA Pre-Post N=18	<p>Population: TBI; Age Range=5-67 yr; Gender: Male=13, Female=5; Mean GCS=6.5.</p> <p>Intervention: Participants had their heads elevated to 35° from a flat position.</p> <p>Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Mean Arterial Pressure (MAP).</p>	<ol style="list-style-type: none"> ICP and MAP significantly decreased at 35° (p<0.05) but increased when returned to 0°. There was no significant change in CPP after elevation.
Durward et al. (1983) Canada Case Series N=11	<p>Population: TBI=11; GCS Range<8.</p> <p>Intervention: Participants were placed into 4 positions of head elevation: 0°, 15°, 30° and 60°. Each position was maintained for 5-10 min. Outcomes were assessed at each position.</p> <p>Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP).</p>	<ol style="list-style-type: none"> ICP decreased significantly from 0° to 15° (p<0.001). This decrease in ICP was maintained at 30° (p<0.001) but was not significantly different from the ICP at 15°. ICP at 60° was not significantly different from 0° of elevation. CPP was not significantly affected by 15° or 30° of head elevation. Elevation of 60° caused a significant reduction of CPP compared with 0° (p<0.02).
Ropper et al. (1982) USA	<p>Population: TBI=13, ICH=5, Stroke=1; Age Range=15-77 yr.</p> <p>Intervention: Participants had their heads elevated to</p>	<ol style="list-style-type: none"> ICP was significantly lower at 60° in 10 participants (p<0.05).

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Case Series N=19	60° from a flat position. Outcome Measure: Intracranial Pressure (ICP).	2. ICP was lower at 0° in 2 participants (p>0.05). 3. ICP did not change in 7 participants.
Kenning et al. (1981) USA Case Series N=24	Population: TBI=15, Other=9; Mean Age=36 yr; Mean GCS=8.2. Intervention: Participants had their heads elevated to 45° and 90° from a flat position. Outcome Measure: Intracranial Pressure (ICP).	1. At baseline, 13 participants had elevated levels and 11 had normal levels. 2. ICP was reduced at 45° and/or 90° in all participants. 3. ICP was lower at 90° than at 45° in most participants. 4. In those with initial elevated ICP, reductions were maintained for 24-48 hr.

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

Head elevation was found to significantly reduce ICP when compared to a flat position in numerous studies. Reductions in ICP were observed at 15° elevation (Durward et al., 1983; Ledwith et al., 2010; Moraine et al., 2000; Schneider et al., 1993), 30° elevation (Durward et al., 1983; Feldman et al., 1992; Ledwith et al., 2010; Meixensberger et al., 1997; Moraine et al., 2000; Ng et al., 2004; Park & Ha, 1992; Parsons & Wilson, 1984; Rosner & Coley, 1986; Schneider et al., 1993; Schulz-Stubner & Thiex, 2006; Winkelman, 2000) 45° elevation (Kenning et al., 1981; Mahfoud et al., 2010; Moraine et al., 2000; Schneider et al., 1993), and 60° elevation (Mahfoud et al., 2010; Ropper et al., 1982). Several studies reported that reductions in ICP following head elevation were correlated with significant improvements in CPP (Ledwith et al., 2010; Mahfoud et al., 2010; Meixensberger et al., 1997; Moraine et al., 2000; Schulz-Stubner & Thiex, 2006; Winkelman, 2000) (Meixensberger et al., 1997; Winkelman, 2000), although other studies did not find changes in CPP (Durward et al., 1983; Feldman et al., 1992; Ng et al., 2004; Park & Ha, 1992; Parsons & Wilson, 1984; Rosner & Coley, 1986; Schneider et al., 1993). Only one study reported that head elevation did not improve ICP or CPP (March et al., 1990). However, due to the small sample size, these results should be taken with caution.

In most studies, a greater degree of elevation was associated with a greater reduction in ICP. For example, Rosner and Coley (1986) found that ICP decreased by 1 mmHg with every 10° of elevation. In an earlier study, however, Durward et al. (1983) found no significant difference in ICP reduction between different degrees of elevation. Ledwith et al. (2010) suggested that no single position is optimal for improving neurodynamic parameters in those who sustain an ABI. Participants were placed into different positions with three levels of head elevation (15°, 30°, and 45°) in a randomized order. The authors reported significant reductions in ICP with head elevations of 30° and 45° in the supine position and 15° in the right and left lateral positions; all the reductions were similar in magnitude.

The main concerns associated with head elevation are the development of systemic hypotension, followed by a subsequent decrease in CPP. After reviewing the studies gathered, there does not seem to be a consensus as to the effect of head elevation on CPP. However, four studies noted a decrease in mean arterial pressure associated with various head elevations; 15°, 30°, 45° ((Schneider et al., 1993), 30°, 60°

(Mahfoud et al., 2010), 30° elevation (Feldman et al., 1992), and 10°, 20°, 30°, 40°, 50° (Rosner & Coley, 1986). These findings coupled by the ambiguous results on the effects of CPP suggest that care should be taken to monitor for the development of hypotension during head elevation when treating patients with ABI.

Conclusions

There is level 2 evidence that head elevations of 15° compared to 0° can effectively reduce elevated intracranial pressure post ABI when compared to a flat position.

There is conflicting (level 2) evidence that head elevations 30° compared to 0° can effectively reduce elevated intracranial pressure post ABI when compared to a flat position.

There is conflicting (level 2) evidence regarding whether or not head elevation can improve cerebral perfusion pressure post ABI.

There is conflicting (level 2 and level 4) evidence whether increasing the head elevation angle is correlated with greater intracranial pressure improvement post ABI. Level 2 evidence suggests that there is no angle-dependent benefit.

There is level 4 evidence that head elevation of 45° and 60° may effectively reduce elevated intracranial pressure post ABI when compared to a flat position.

There is level 4 evidence that head elevation of 10°-60° may decrease mean arterial pressure post ABI.

There is level 2 evidence that head elevation of 30° from a flat position may effectively reduces elevated intracranial pressure compared to head elevation of 0° in individuals post ABI.

There is level 4 evidence that head elevation of 60° from a flat position may effectively reduce elevated ICP post ABI.

There is conflicting (level 2 and level 4) evidence regarding whether or not head elevation of 30° effectively improves cerebral perfusion pressure post ABI. With level 2 evidence supporting the use of head elevation to improve cerebral perfusion pressure.

Head elevation of 30° likely lowers intracranial pressure post ABI, however, its benefit on cerebral perfusion pressure is less certain.

Head elevation of 60° may lower intracranial pressure post-ABI.

Head elevation of 15° may effectively lower elevated intracranial pressure post ABI; meanwhile, the evidence for elevations of 45° and 60° are not as strong.

It is unclear if head elevation of 30° can effectively lower elevated intracranial pressure post ABI.

It is unclear if there is a correlation between increasing elevation angle and reduction in intracranial pressure; the strongest evidence suggests there is not.

It is unclear whether head elevation causes an improvement in cerebral perfusion pressure post ABI.

Head elevations ranging from 0°-60° may decrease mean arterial pressure post ABI.

15.1.2.2 Hypothermia

As early as half a century ago, hypothermia was explored as a neuroprotective treatment to reduce secondary brain injury in ABI (Fay, 1943). It is believed that hypothermia can control elevated ICP by a variety of mechanisms including reducing cerebral metabolism, decreasing the inflammatory response, and decreasing the release of excitotoxic levels of glutamate and free radicals post ABI (Alderson et al., 2004; Chen et al., 2001; Clifton, 2004; Globus et al., 1995; Marion, 1997; Yan et al., 2010).

It is important to note that prolonged hypothermia is believed to be associated with various adverse effects including arrhythmias, coagulopathies, sepsis and pneumonia, which could ultimately lead to a poorer clinical outcome (Alderson et al., 2004; Schubert, 1995). It has also been suggested that there may be a threshold during rewarming, above which, pressure reactivity may reach damaging levels (Lavinio et al., 2007) and that there is a critical window beyond which hypothermia may be ineffective (Clifton et al., 2009).

The AANS noted that prophylactic hypothermia showed no significant association with improved outcomes relative to normothermic controls (Carney et al., 2017). However, they reported an increased risk of mortality when target temperatures were achieved within 2.5 hours of injury and maintained for more than 48 hours. There are no EBIC recommendations for hypothermia. Studies evaluating the effects of hypothermia in ABI populations are presented in Table 15.3.

Table 15.3 Hypothermia for the Acute Management of Intracranial Pressure Post ABI

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Andrews et al. (2015) UK Eurotherm3235 RCT PEDro=9 N _{initial} =387 N _{final} =376	<p>Population: TBI; <i>Treatment Group (TG, n=195):</i> Mean Age=37.4 yr; Time Post Injury: <12 hr=19, ≥12 hr=176; GCS: 1-2=56, 3-6=139. <i>Control Group (CG, n=192):</i> Mean Age=36.7 yr; Time Post Injury: <12hr=15, ≥12 hr=177; GCS: 1-2=51, 3-6=141.</p> <p>Intervention: Participants were randomly assigned to receive therapeutic hypothermia (TG) or standard care (CG). Hypothermia involved reducing body temperature to 32-35°C for ≥48 hr using intravenous cold fluid infusion. Outcomes were assessed at 6mo, and physiological measures were monitored 0-7 days.</p> <p>Outcome Measures: Glasgow Outcome Scale</p>	<ol style="list-style-type: none"> Good outcomes (GOSE>4) occurred in 25.7% of TG and 36.5% of CG (p=0.03) at 6mo. Adjusted odds for a poor outcome (GOSE≤4) at 6 mo were significant (OR=1.69, p=0.03). Adjusted common odds for GOSE score at 6 mo were significant (OR=1.53, p=0.04). Mortality at 6 mo was higher in the hypothermia group compared to control [1.45 (1.01-2.10), p=0.05]. There was no significant difference between groups in LOS in ICU (MD=0.05,

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
	Extended (GOSE), Modified Oxford Handicap Scale (MOHS), Length of Stay (LOS), Mortality, Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Mean Arterial Pressure (MAP).	<p>p=0.54) or MOHS grade at 28 d (OR=1.65, p=0.10).</p> <p>6. There was no significant difference between groups in ICP (MD=-0.48, p=0.55), MAP (MD=1.20, p=0.16), or CPP (MD=1.61, p=0.11) over 1-7 d.</p>
<p>Maekawa et al. (2015) Japan BHYP RCT PEDro=7 N=150</p> <p>Suehiro et al. (2015) Japan BHYP Post Hoc Analysis N=135</p>	<p>Population: TBI; <i>Treatment Group (TG, n=99):</i> Mean Age=39 yr; Gender: Male=69, Female=30; Median Time Post Injury=0.7 hr; Mean GCS=5.8. <i>Control Group (CG, n=51):</i> Mean Age=39 yr; Gender: Male=34, Female=17; Median Time Post Injury=0.8 hr; Mean GCS=5.9.</p> <p>Intervention: Participants were randomly assigned to receive therapeutic hypothermia (32-34° C, TG) or fever control (35-37° C, CG) for ≥72 hr. Temperature was lowered using intravenous cold fluid infusion, cooling blankets, and/or cold gastric lavage. Outcomes were assessed at 6mo, and physiological measures were monitored 0-7 days.</p> <p>Outcome Measures: Glasgow Outcome Scale (GOS), Mortality, Core Body Temperature (T_c), Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Mean Arterial Pressure (MAP), Central Venous Pressure (CVP).</p> <p>Population: TBI; <i>Treatment Group (TG, n=88):</i> Mean Age=41 yr; Gender: Male=59, Female=29; Mean GCS=5.7. <i>Control Group (CG, n=47):</i> Mean Age=38yr; Gender: Male=31, Female=16; Mean GCS=5.9.</p> <p>Intervention: Subset of participants from the Maekawa et al. (2015) were analyzed according to CT classification: diffuse I (n=2), diffuse II (n=40), diffuse III (n=22), diffuse IV (n=4), evacuated mass lesion (n=62), non-evacuated mass lesion (n=3), and unknown (n=2).</p> <p>Outcome Measures: Glasgow Outcome Scale (GOS), Mortality, Intracranial Pressure (ICP), Mean Arterial Pressure (MAP).</p>	<p>1. The rates of poor outcomes (GOS<4) were 53% in the TG and 48% in the CG.</p> <p>2. There was no significant difference between groups in likelihood of poor outcome (RR=1.24, p=0.597) or mortality (RR=1.82, p=0.180).</p> <p>3. T_c was significantly lower in the TG at 0 days (p=0.002), 1 day (p<0.001), and 3 days (p<0.001) than in the CG.</p> <p>4. There were no significant differences between groups in ICP, CPP, MAP, or CVP at any time point.</p> <p>1. In diffuse injury III, the rate of mortality was significantly higher in the TG than in the CG (54% versus 11%, p=0.041).</p> <p>2. In each injury group, all other differences in rates of good outcome and mortality between conditions were not significant.</p> <p>3. In diffuse injury II, ICP was significantly lower in the TG at 1 day (p=0.016) and MAP was significantly lower in the TG at 3 days (p=0.04).</p>
<p>Zhao et al. (2011) China RCT PEDro=6 N=81</p>	<p>Population: TBI; <i>Treatment Group (TG, n=40):</i> Mean Age=36.9 yr; Gender: Male=29, Female=11; GCS: 3-5=15, 6-8=25. <i>Control Group (CG, n=41):</i> Mean Age=37.5yr; Gender: Male=30, Female=11; GCS: 3-5=16, 6-8=25.</p> <p>Intervention: Participants were randomly assigned to receive hypothermia (33°C, TG) or normothermia (37°C, CG) for >72 hr. Temperature was lowered using a semiconductor blanket. Outcomes were assessed at 3mo and physiological measures were</p>	<p>1. Good outcome (GOS≥4) was significantly higher in the TG than in the CG (75% versus 51%, p=0.038).</p> <p>2. Death was higher in the CG than in the TG (10% versus 3%) but the difference was not significant (p>0.05).</p> <p>3. After adjusting for age, GCS, and ICP, hypothermia was an independent predictor of good outcome (RR=4.9, p<0.05).</p>

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	monitored during treatment. Outcome Measures: Glasgow Outcome Scale (GOS), Intracranial Pressure (ICP).	4. Mean ICP was significantly lower in the TG than in the CG at 24 hr ($p<0.01$) and 72 hr ($p<0.01$) after treatment.
Harris et al. (2009) USA RCT PEDro=7 N=25	Population: TBI; Mean Age=35.4 yr; Gender: Male=22, Female=3; Median Time Post Injury=6.0 hr; GCS: 5-8=7, 3-4=18. Intervention: Participants were randomized to receive localized hypothermia treatment (33°C, treatment) via a cooling cap or normothermia (control) for 24 hr. Outcomes were assessed during treatment. Outcome Measures: Intracranial Pressure (ICP), Temperature, Glasgow Outcome Scale (GOS), Functional Independence Measure (FIM).	1. After the first 3 hr of treatment, the mean intracranial temperature was significantly lower in the treatment group than in the control group ($p<0.05$), but not at 4 and 6 hr ($p=0.08$); the target temperature was rarely achieved. 2. There were no significant differences between groups on GOS or FIM.
Qiu et al. (2007) China RCT PEDro=7 N=80	Population: TBI; <i>Treatment Group (TG, n=40):</i> Mean Age=41.3 yr; Gender: Male=27, Female=13; Mean Time Post Injury=6 hr; GCS: $<6=23$, $\geq 6=17$. <i>Control Group (CG, n=40):</i> Mean Age=40.2 yr; Gender: Male=25, Female=15; Mean Time Post Injury=6 hr; GCS: $<6=24$, $\geq 6=16$. Intervention: Patients were randomized to receive hypothermia (33-35°C, TG) or normothermia (CG) for 4 days. Outcomes were assessed before and after treatment. Outcome Measures: Intracranial Pressure (ICP), Serum Superoxide Dismutase (SOD), Neurological Outcomes, Complications.	1. Mean ICP of the TG at 24, 48 and 72 hr was significantly lower than the CG. ($p<0.001$, $p<0.001$, $p<0.05$ respectively). 2. Mean SOD levels were significantly higher at 3 days and 7 days in the TG ($p=0.000$). 3. Percentage of favourable neurological outcomes at 1 yr was significantly higher in the TG than the CG (70% versus 47.5%; $p=0.041$). 4. Pulmonary infection and thrombocytopenia were significantly higher in the TG than the CG ($p=0.025$, $p=0.044$ respectively). All other complications were not significantly different between groups.
Smrcka et al. (2005) Czech Republic RCT PEDro=6 N=72	Population: TBI; Mean Age=41 yr; Gender: Male=51, Female=21; Mean GCS=4. Intervention: Participants were randomized to receive hypothermia (34°C, n=35) or normothermia (n=37). Hypothermia was delivered for 72 hr via cooling blankets. Outcomes were assessed before, after treatment, and at 6 mo follow-up. Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Glasgow Outcome Scale (GOS).	1. Mean ICP was significantly lower in the hypothermia group than the normothermia group after treatment (11.77 mmHg versus 17.65 mmHg, $p<0.0001$). 2. Mean CPP was significantly higher in the hypothermia group than the normothermia group after treatment (78.23 mmHg versus 72.16 mmHg, $p<0.0001$). 3. GOS at 6 mo was significantly higher in the hypothermia group than in the normothermia group (4.09 versus 3.19, $p=0.0131$).
Zhi et al. (2003) China RCT PEDro=6	Population: TBI; Mean Age=42 yr; Gender: Male=291, Female=105; Time Post Injury<24 hr; Mean GCS=6. Intervention: Participants were randomized to receive hypothermia (32-35°C; n=198) or	1. Mean ICP was significantly reduced after hypothermia when compared to normothermia within 24 hr (21.4mmHg versus 25.5 mmHg, $p<0.05$), at 3 days (14.8mmHg versus 22 mmHg, $p<0.05$),

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N=396	<p>normothermia (36-37°C; n=198). Hypothermia was delivered for 1-7 days via cooling blankets. Outcomes were assessed at baseline, 1 day, 3 days, 7 days, and 6 mo.</p> <p>Outcome Measures: Intracranial Pressure (ICP), Glasgow Outcome Scale (GOS).</p>	<p>and 7 days (14 mmHg versus 20.6 mmHg, p<0.05).</p> <p>2. On the GOS at 6 mo, the hypothermia group had a significantly higher rate of good outcome (GOS=5; 39% versus 20%, p<0.05) and a significantly lower rate of death (26% versus 36%, p<0.05) when compared to the normothermia group.</p>
<p>Clifton et al. (2001) USA NABISH I RCT PEDro=6 N=392</p> <p>Clifton et al. (2012) USA NABISH I & II Post Hoc Analysis N=489</p>	<p>Population: TBI; <i>Treatment Group (TG, n=199):</i> Mean Age=31 yr; Time Post Injury<6 hr; Mean GCS=5.6. <i>Control Group (CG, n=193):</i> Mean Age=32 yr; Time Post Injury<6 hr; Mean GCS=5.8.</p> <p>Intervention: Participants were randomly assigned to receive therapeutic hypothermia (33°C, TG) or normothermia (37°C, CG) for ≥48 hr. Temperature was lowered using ice, gastric lavage, and/or cool ventilation. Outcomes were assessed at 6 mo, and physiological measures were monitored 0-4 days.</p> <p>Outcome Measures: Glasgow Outcome Scale (GOS), Mortality, Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Mean Arterial Pressure (MAP), Therapy Intensity Level (TIL).</p> <p>Population: Trial 1: <i>Treatment Group (TG, n=199):</i> Mean Age=31 yr; Time Post Injury <6 hr; Mean GCS=5.6. <i>Control Group (CG, n=193):</i> Mean Age=32 yr; Time Post Injury<6 hr; Mean GCS=5.8. Trial 2: TBI; <i>Treatment Group (TG, n=52):</i> Mean Age=26 yr; Time Post Injury<2.5 hr; GCS: 3-4=19, 5-8=33. <i>Control Group (CG, n=45):</i> Mean Age=31 yr; Time Post Injury<2.5 hr; GCS: 3-4=23, 5-8=22.</p> <p>Intervention: Participants from Clifton et al. (2001a, 2011) were analyzed and pooled for meta-analysis.</p> <p>Outcome Measures: Glasgow Outcome Scale (GOS), Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Mean Arterial Blood Pressure (MABP)</p>	<p>1. There was no significant difference between groups in terms of poor outcome (RR=1.0, p=0.99) or mortality (RR=1.0, p=0.79).</p> <p>2. There was no significant difference between groups in ICP at any time point.</p> <p>3. CPP was significantly higher in the TG group at 1 day (p=0.003) and significantly lower in the TG at 3 days (p=0.003) and 4 days (p=0.01).</p> <p>4. MAP was significantly lower in the CG group at 1 day (p=0.003) and significantly higher in the CG at 3 day (p<0.001) and 4 day (p<0.001).</p> <p>5. TIL was significantly higher in the TG at 3 day (p=0.005).</p> <p>6. TG has significantly higher rate of hospital days with complications than CG (78% versus 70%, p=0.005).</p> <p>1. Trial 2: In participants with hematomas removed, the rate/likelihood of poor outcome was significantly higher in the CG than the TG (69% versus 33%; RR=0.44; p=0.02). All participants in the latter group reached 35°C in <1.5 hr and 33°C in <5.5 hr.</p> <p>2. Trial 1: In participants with hematomas removed, the rate of poor outcome was 45% of the TG reaching 35°C in <1.5 hr (n=31), 61% in of the TG reaching 35°C in >1.5 hr (n=23), and 60% in the CG (n=35); these differences were not significant (RR=0.74, p=0.16).</p> <p>3. Trials 1+2: In participants with hematomas removed, the rate of poor outcome was significantly lower in those treated with early hypothermia (35°C in <1.5 hr) than those treated with late hypothermia (35°C in >1.5 hr) or normothermia (41% versus 62%, p<0.009).</p> <p>4. In Trial 1 the percentage of patients with critically high ICP (>30 mmHg) was</p>

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		<p>significantly lower in the hypothermia group versus the controls ($p=0.04$). In trial 2 however, no significant differences were found between the groups.</p> <p>5. No significant differences were found between the hypothermia and normothermia groups regarding the incidence of critical CPP (<60 mmHg) or MABP (<70 mmHg) in either trial.</p>
<p>Lee et al. (2010) China RCT PEDro=6 N=45</p>	<p>Population: TBI; <i>Treatment Group 1 (TG1, n=15):</i> Mean Age=44.0 yr; Gender: Male=9, Female=6; Mean GCS=6.4. <i>Treatment Group 2 (TG2, n=14):</i> Mean Age=38.8 yr; Gender: Male=8, Female=6; Mean GCS=6.5. <i>Control Group (CG, n=16):</i> Mean Age=43.5 yr; Gender: Male=10, Female=6; Mean GCS=6.4.</p> <p>Intervention: Participants were randomized to receive guided normothermia (CG), ICP/ CPP-managed hypothermia (TG1), or hypothermia and brain tissue oxygen management (TG2). Outcomes were assessed before and after treatment.</p> <p>Outcome Measures: Intracranial Pressure (ICP), Glasgow Outcome Scale (GOS) Scores, Mortality.</p>	<ol style="list-style-type: none"> ICP values progressively increased in the first 3d but showed smaller changes and were significantly lower in TG1 and TG2 than CG at the same time points ($p<0.05$). Favourable outcomes (GOS=4 & 5) were noted in 50% of the CG, 60% of TG1 and 71.4% of TG2. Mortality was highest in the CG (12.5%) while it was 6.7% in TG1 and 8.5% in TG2; there was no statistical significance between groups ($p>0.05$).
<p>Jiang et al. (2006) China RCT PEDro=6 N=215</p>	<p>Population: TBI; Mean Age=33 yr; Gender: Male=167, Female=48; Mean Time Post Injury=3 hr; GCS Range\leq8.</p> <p>Intervention: Participants received hypothermia (33-35°C) for short term (2 d, n=107) or long term (5 d, n=108) via cooling blankets. Outcomes were assessed during treatment and at 6 mo follow-up.</p> <p>Outcome Measures: Intracranial Pressure (ICP), Glasgow Outcome Scale (GOS), Complications.</p>	<ol style="list-style-type: none"> ICP significantly decreased in both groups after treatment ($p<0.05$). ICP after 2 days was significantly higher in the short-term group than in the long-term group ($p<0.05$). Rate of favourable outcome at 6 mo (GOS=4-5) was significantly higher in the long-term group than in the short-term group (43.5% versus 29.0%, $p<0.05$). There was no significant difference between groups in rates of complications.
<p>Liu et al. (2006) China RCT PEDro=5 N=66</p>	<p>Population: TBI; Mean Age=40.6 yr; Gender: Male=42, Female=24; GCS: 3-5=37, 6-8=29.</p> <p>Intervention: Participants were randomized to receive selective brain cooling (SBC, n=22), mild systemic hypothermia (MSH, n=21), or conventional treatment (control, n=23). SBC consisted of cooling the head and neck to 33-35°C using a cooling cap and neckband with circulating 4°C water. MSH was achieved using a cooling blanket and refrigerated ice bags to achieve a rectal temperature of 33-35°C. Both hypothermia treatments lasted for up to 6hr/d for 3 days. Outcomes were assessed before and after treatment.</p> <p>Outcome Measures: Intracranial Pressure (ICP),</p>	<ol style="list-style-type: none"> Both hypothermia groups showed a significant decrease in ICP levels relative to the control group at 24, 48 and 72 hr post injury ($p<0.05$). SOD levels were significantly higher in the hypothermia groups at 3 days and 7 days post injury ($p<0.01$). The percentage of patients with good GOS scores 2 yr post injury were 72.7%, 57.1% and 34.8% in the SBC, MSH and control groups respectively.

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	Serum Superoxide Dismutase (SOD), Glasgow Outcome Scale (GOS).	
Shiozaki et al. (2001) Japan RCT PEDro=6 N=91	<p>Population: TBI; <i>Treatment Group (TG, n=45):</i> Mean Age=35 yr; Gender: Male=35, Female=10; Mean GCS=5.5. <i>Control Group (CG, n=46):</i> Mean Age=42yr; Gender: Male=31, Female=15; Mean GCS=5.1.</p> <p>Intervention: Participants were randomized to receive hypothermia (34°C, TG) or normothermia (37°C, CG). Hypothermia was delivered for 48hr via cooling blankets and nasogastric lavage with iced saline. Outcomes were assessed at baseline, after treatment, and at 3 mo follow-up.</p> <p>Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Glasgow Outcome Scale (GOS), Therapeutic Intensity Level (TIL), Complications.</p>	<ol style="list-style-type: none"> 1. There was no significant difference between groups in control of ICP and CPP after treatments. 2. On the GOS, there was no significant difference between TG and CG in rates of favourable outcome (GOS=4-5; 47% versus 57%), unfavourable outcome (GOS=2-3; 36% versus 28%), or death (GOS=1; 18% versus 13%). 3. For TIL, the TG had a significantly higher rate of neuromuscular blocking agents than the CG (63% versus 35%, p<0.011); the rates of other treatments were similar. 4. The TG had significantly higher rates of several complications than the CG, including pneumonia (49% versus 15%, p=0.001) and meningitis (28% versus 10%, p=0.039).
Jiang et al. (2000) China RCT PEDro=6 N=87	<p>Population: TBI; <i>Treatment Group (TG, n=43):</i> Mean Age=42.2yr; Gender: Male=35, Female=8; Mean GCS=5.0. <i>Control Group (CG, n=44):</i> Mean Age=40.6; Gender: Male=37, Female=7; Mean GCS=5.1.</p> <p>Intervention: Participants were exposed to prolonged mild hypothermia (33-35°C, TG) or normothermia (37-38°C, CG) for 3-14d. Outcomes were assessed before and after treatment.</p> <p>Outcome Measures: Mortality, Glasgow Outcome Scale (GOS), Intracranial Pressure (ICP).</p>	<ol style="list-style-type: none"> 1. Mortality rate was significantly lower in the TG than the CG (25.58% versus 45.45%, p<0.05). 2. Rate of favourable outcome on GOS was significantly higher in the TG than the CG (46.51% versus 27.27%, p<0.05). 3. Hypothermia caused a significant reduction in ICP (p<0.01) and inhibited hyperglycemia (p<0.05).
Marion et al. (1997) USA RCT PEDro=5 N=82	<p>Population: TBI; <i>Treatment Group (TG, n=40):</i> Mean Age=31yr; Gender: Male=36, Female=4; Mean Time Post Injury=10hr; GCS: 3-4=18, 5-7=22. <i>Control Group (CG, n=42):</i> Mean Age=35yr; Gender: Male=33, Female=9; Mean Time Post Injury=10hr; GCS: 3-4=16, 5-7=26.</p> <p>Intervention: Participants were randomized to receive hypothermia for 24 hr (33°C) or normothermia for 5 days (37-39°C). Hypothermia was achieved using cooling blankets and cold saline gastric lavage. Outcomes were assessed before and after treatment.</p> <p>Outcome Measures: Glasgow Outcome Scale (GOS), Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Heart Rate (HR), Cerebral Blood Flow (CBF).</p>	<ol style="list-style-type: none"> 1. The TG had significantly more patients with favorable outcome on the GOS compared to the CG at both 3 mo (38% versus 17%, p=0.03), and 12 mo (62% versus 38%, p=0.05). 2. Participants with GCS=3-4 did not benefit from hypothermia, whereas those with scores of 5-7 did. 3. Among participants with GCS=5-7, significantly more patients in the TG had a favorable GOS outcome at 6mo than those in the CG (73% versus 35%, p=0.008). 4. During the cooling period, the TG had significantly lower ICP (p=0.01), CBF (p=0.05), HR (p<0.001) and higher CPP (p=0.05) compared with CG.

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<p>Marion et al. (1993) USA RCT PEDro=6 N=40</p>	<p>Population: TBI; <i>Treatment Group (TG, n=20)</i>: Mean Age=31.9 yr; Gender: Male=17, Female=3; Time Post Injury<6 hr; Mean GCS=5.3. <i>Control Group (CG, n=20)</i>: Mean Age=32.1 yr; Gender: Male=17, Female=3; Time Post Injury<6 hr; Mean GCS=4.7. Intervention: Participants were randomized to receive hypothermia for 24 hr (32-33°C, TG) or normothermia for 5 days (37-38°C, CG). Hypothermia was achieved using cold saline gastric lavage and cooling blankets. Outcomes were assessed before and after treatment. Outcome Measures: Intracranial Pressure (ICP), Cerebral Blood Flow (CBF), Cerebral Metabolic Rate for Oxygen (CMRO₂), Glasgow Outcome Scale (GOS).</p>	<ol style="list-style-type: none"> 1. ICP (p=0.004) and CBF (p=0.021) were significantly lower in the TG than CG during cooling. 2. CMRO₂ in the TG was significantly lower during cooling and higher at 5 days compared with the CG (p<0.001). 3. There was a trend toward a better outcome on GOS at 3 mo post injury in the TG than the CG (60% versus 40%, p=0.24).
<p>Shiozaki et al. (1993) Japan RCT PEDro=5 N=33</p>	<p>Population: TBI; <i>Treatment Group (TG, n=16)</i>: Mean Age=35.3 yr; Gender: Male=6, Female=10; GCS Range≤8. <i>Control Group (CG, n=17)</i>: Mean Age=35.4 yr; Gender: Male=10, Female=7; GCS Range≤8. Intervention: Participants were randomized to receive hypothermia for 2 days (33.5-34.5°C, TG) or normothermia (CG). Outcomes were assessed before and after treatment. Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Glasgow Outcome Scale (GOS).</p>	<ol style="list-style-type: none"> 1. In the TG, hypothermia significantly reduced ICP (p<0.01) and increased CPP (p<0.01). 2. Fifty percent of the patients in the TG survived compared with only 18% in the CG (p<0.05), while 31% in the TG and 71% in the CG died from uncontrollable ICP (p<0.05). 3. Thirty-eight percent of the TG had good GOS outcome at 6mo compared with only 6% of the CG.
<p>Sun et al. (2016) China Pre-Post N=62</p>	<p>Population: TBI; Mean Age=36.8 yr; Gender: Male=37, Female=25; Mean GCS=5.20. Intervention: Patients were treated using mild hypothermia alone or mild hypothermia combined with conventional intracranial pressure (ICP) procedures. Outcome Measures: Intracranial Pressure (ICP), Brain Tissue Oxygenation (PbtO₂), Jugular Venous Oxygen Saturation (SjvO₂), Cranial Perfusion Pressure (CPP), End-Tidal Carbon Dioxide Pressure (ETCO₂).</p>	<ol style="list-style-type: none"> 1. Within 24 hr of hypothermia treatment ICP declined and PbtO₂, SjvO₂, and CPP increased significantly (all p<0.05). 2. Mild hypothermia combined with a 25 g dose of mannitol caused a significant reduction in ICP after 30 min (p<0.05), but rebounded at 90 min. However, the group treated with 50 g mannitol remained stable at 90 min (p<0.05). 3. For the patients that were still invalid after mannitol treatment, endotracheal intubation was performed, and they were treated with mechanically assisted aeration. The drop in ICP was significantly greater for the 25-29 mmHg ETCO₂ group compared with the 30-34 mmHg ETCO₂ group (p<0.05). 4. For the 26 patients that still remained invalid, a decompressive craniectomy in combination with mild hypothermia was performed. In these patients, ICP decreased significantly (p<0.05).

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Flynn et al. (2015) UK Pre-Post N=17	<p>Population: TBI; <i>Treatment Group (TG, n=9)</i>: Mean Age=41yr; Gender: Male=7, Female=2; Time Post Injury<72 hr; Median GCS=7. <i>Control Group (CG, n=8)</i>: Mean Age=34yr; Gender: Male=8, Female=0; Time Post Injury<72 hr; Median GCS=7.</p> <p>Intervention: Participants were randomly assigned to receive therapeutic hypothermia (TG) or standard care (CG). Hypothermia involved reducing body temperature to 32-35°C for at least 48 hr using intravenous cold fluid infusion. Outcomes were assessed at baseline and for the first 6hr of treatment.</p> <p>Outcome Measure: Intracranial Pressure (ICP).</p>	<ol style="list-style-type: none"> 1. In the TG, mean ICP significantly decreased from baseline to 1hr (4.3 mmHg, p<0.04) and was maintained up to 6hr; there was a significant main effect of time (F=6.13, p<0.01). 2. In the CG, there was no significant change in ICP over the 6 hr and no significant main effect of time (p>0.05). 3. The difference between groups for change in ICP over the 6 hr was statistically significant; there was a significant group x time interaction (F=4, p<0.02).
Sahuquillo et al. (2009) Spain Pre-Post N=24	<p>Population: TBI; Median Age=25 yr; Gender: Male=17, Female=7; Median Time Post Injury=72 hr; Median GCS=7.</p> <p>Intervention: Participants received hypothermia (32.5°C) for up to 14 days via cooling blankets and catheter.</p> <p>Outcome Measures: Intracranial Pressure (ICP), Glasgow Outcome Scale (GOS), Complications.</p>	<ol style="list-style-type: none"> 1. Median ICP was significantly reduced from 23.8 mmHg at baseline to 16 mmHg after treatment (U=45.0, p<0.001). 2. At 6 mo, 37.5% of participants died (GOS=1), 25% had GOS=3, 8.3% had GOS=4, and 29.2 % had GOS=5. 3. The incidence of pneumonia was 50%.
Tokutomi et al. (2009) Japan PCT N=61	<p>Population: ABI. <i>Treatment Group 1 (TG1, n=30)</i>: Mean Age=45 yr; Gender: Male=21, Female=9; Mean Time Post Injury=2.6 hr; Mean GCS=4.3. <i>Treatment Group 2 (TG2, n=31)</i>: Mean Age=40 yr; Gender: Male=26, Female=5; Mean Time Post Injury=3.1 hr; Mean GCS=4.2.</p> <p>Intervention: Participants received hypothermia at 35°C (TG1) or at 33°C (TG2).</p> <p>Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Mortality, Complications.</p>	<ol style="list-style-type: none"> 1. Both groups exhibited decreases in ICP below 20 mmHg with no differences in the incidence of intracranial hypertension or low CPP. 2. Patients in TG1 showed a trend toward decreased mortality and fewer complications.
Qiu et al. (2006) China Cohort N=90	<p>Population: TBI; <i>Treatment Group (TG, n=45)</i>: Mean Age=40.1 yr; Gender: Male=29, Female=16; GCS Range≤8. <i>Control Group (CG, n=45)</i>: Mean Age=41.8 yr; Gender: Male=30, Female=15; GCS Range≤8.</p> <p>Intervention: Participants received selective brain cooling (TG) or normothermia (CG). Cooling was achieved using a cooling cap and neck band for 3d.</p> <p>Outcome Measures: Intracranial Pressure (ICP), Glasgow Outcome Score (GOS).</p>	<ol style="list-style-type: none"> 1. At 24, 48 and 72 hr ICP was significantly lower in the TG than the CG (19.14 versus 23.41, 19.72 versus 20.97 and 17.29 versus 20.13 mmHg respectively (p<0.01). 2. There was also significant difference in GOS at 6 mo between TG and CG (68.7% versus 46.7%, p<0.05).
Hayashi et al. (2005) Japan PCT N=41	<p>Population: TBI; <i>Treatment Group (TG, n=20)</i>: Mean Age=28.9 yr; Mean GCS=5. <i>Control Group (CG, n=21)</i>: Mean Age=33.6 yr; Mean GCS=4.7.</p> <p>Intervention: Participants received either hypothermia (32-36°C, TG) or normothermia (CG). Hypothermia was delivered for 72-84 hr via cooling blankets and nasogastric lavage with iced saline.</p>	<ol style="list-style-type: none"> 1. The TG had a higher rate of favourable outcome (GOS=4-5) than the CG (55% versus 25%). 2. The TG had lower rates of unfavourable outcome (GOS=2-3; 10% versus 20%) and death (35% versus 60%) than the CG.

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
	Outcomes were assessed before and after treatment, and at 6 mo follow-up. Outcome Measure: Glasgow Outcome Scale (GOS).	3. Within the TG, those who received very mild hypothermia (35-36°C, n=10) had a higher rate of favourable outcome (80% versus 30%) than those who received mild hypothermia (32-34°C, n=10). 4. Those who received very mild hypothermia had a lower rate of complications than those who received mild hypothermia (30% versus 0%).
Tokutomi et al. (2003) Japan Case Series N=31	Population: TBI; Mean Age=39.5 yr; Gender: Male=26, Female=5; GCS Range≤5. Intervention: Participants received hypothermia induced by surface cooling with water-circulating blankets. Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP).	1. Incidence of elevated ICP decreased significantly with hypothermia (p<0.0001). 2. ICP decreased significantly at brain temperatures <37°C and decreased more sharply at 35-36°C, but no differences were observed at temperatures <35°C (p<0.05). 3. CPP peaked at 35-36°C and decreased with further decreases in temperature.
Gal et al. (2002) Czech Republic PCT N=30	Population: TBI; <i>Treatment Group (TG, n=15):</i> Mean Age=35 yr; Gender: Male=9, Female=6; Mean GCS=4.5. <i>Control Group (CG, n=15):</i> Mean Age=39 yr; Gender: Male=10, Female=5; Mean GCS=4.3. Intervention: Participants received hypothermia (34°C, TG) or normothermia (36.5-37.5°C) for 72 hr. Hypothermia was achieved using forced air cooling combined with circulating water mattress cooling. Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Glasgow Outcome Score (GOS).	1. There was a significant reduction in ICP in the TG compared with the CG (p=0.0007). 2. There was a significant increase in CPP (p=0.0007) with unchanged (p=0.90) systolic arterial pressure values in the TG compared with CG. 3. No significant differences between groups in GOS outcome 6 mo (p=0.084) although 87% of patients in the TG reached good neurological recovery (GOS 4-5) compared with only 47% in the CG.
Polderman et al. (2002) Netherlands PCT N=136	Population: TBI; <i>Treatment Group (TG, n=64):</i> Mean Age=39.2 yr; GCS Range≤8. <i>Control Group (CG; n=72):</i> Mean Age=34.2 yr; GCS Range≤8. Intervention: Participants were treated with moderate hypothermia (32-34°C) using water-circulating blankets (TG) or conventional treatment (CG). Outcome Measures: Intracranial Pressure (ICP), Glasgow Outcome Score (GOS), Mortality.	1. ICP decreased markedly in all patients during cooling. 2. Actual mortality rates were significantly lower in the TG compared with the CG (62% versus. 72%, p<0.05). 3. The number of patients with good neurological outcome on the GOS was higher in the TG than CG (15.7% versus. 9.7%, p<0.02).
Chen et al. (2001) China PCT N=30	Population: ABI. Intervention: Participants received hypothermia (33-35°C, treatment) for 10 hr/day over 3-10 days or conventional treatment (control). Outcome Measure: Mortality.	1. Mortality was significantly lower in the treatment than control group.
Tateishi et al. (1998) Japan	Population: ABI; Mean Age=36.9yr; Gender: Male=5, Female=4; Time Post Injury<24hr; Mean GCS=7.	1. There was a significant reduction in ICP 3 hr after cooling (p<0.05); 4 patients

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Case Series N=9	Intervention: Participants received mild hypothermia (33-35°C) for a maximum of 6 days induced by repeated intragastric cooling using a nasoduodenal tube of iced half-saline infused during 15-30 min supplemented with surface cooling. Outcome Measures: Intracranial Pressure (ICP), Glasgow Outcome Scale (GOS).	experienced systemic infection complications. 2. Seven patients showed good outcome on GOS 6-12 mo after discharge.
Metz et al. (1996) Germany Pre-Post N=10	Population: TBI; Mean Age=31 yr; Gender: Male=7, Female=3; Mean Time Post Injury=16 hr; Mean GCS=3.5. Intervention: Participants received hypothermia (32.5°C) via cooling blankets for 24 hr. Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP).	1. Mean ICP significantly decreased from 24 mmHg at baseline to 14 mmHg after treatment ($p<0.05$). 2. There was no significant change in CPP after treatment.

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

In the reviewed studies, therapeutic hypothermia involved cooling patients to 32-36°C for at least 12 hours. A number of studies found significant reductions in ICP following hypothermia when compared to baseline values (Flynn et al., 2015; Metz et al., 1996; Sahuquillo et al., 2009; Tateishi et al., 1998; Tokutomi et al., 2003) or a normothermia control group (Gal et al., 2002; Jiang et al., 2000; Lee et al., 2010; Liu et al., 2006; Marion et al., 1993; Qiu et al., 2006; Qiu et al., 2007; Shiozaki et al., 1993; Smrcka et al., 2005; Zhao et al., 2011; Zhi et al., 2003). A portion of these studies also reported significant increases in CPP accompanying the reduction in ICP (Gal et al., 2002; Marion et al., 1993; Marion et al., 1997; Shiozaki et al., 1993; Smrcka et al., 2005; Tokutomi et al., 2003).

Overall, it was reported that therapeutic hypothermia improved neurological outcomes (Hayashi et al., 2005) and reduced mortality (Chen et al., 2001) when compared to normothermia or control groups. However, the results of several studies suggested that very mild hypothermia [35-36°C (Tokutomi et al., 2009), 35-37°C (Maekawa et al., 2015)], may be just as effective as mild hypothermia (32-34°C) at improving ICP. However, while Tokutomi *et al.* reported fewer complications and mortality, Maekawa *et al.* found no differences in rates of good outcome and mortality between conditions. A post-hoc analysis of Maekawa *et al.* further stratified patients by diffuseness of injury and noted a decrease in ICP in patients with ABI and diffuse II injury, and an increased rate of mortality in diffuse III injury patients following mild hypothermia treatment (Suehiro et al., 2015). The findings of this post-hoc analysis suggest that although mild hypothermia may be effective in reducing ICP and improving morbidity and mortality, cooler temperatures may be necessary for specific type of ABIs. Upon further analysis, Hayashi et al. went on to suggest that very mild hypothermia (35-36°C) may be more effective than mild hypothermia (32-34°C) at improving neurological outcomes with fewer complications. Although both studies reported positive outcomes, different cooling protocols were employed by the groups (72-84 hr, Hayashi et al.; 10 hr/d, 3-10 d, Chen et al.). As a result, further studies are required to elucidate the optimal hypothermia protocol.

The length of time in hypothermia varied greatly between studies (1-14 days). One trial reported that hypothermia delivered over five days, using cooling blankets, showed a greater ICP reduction and more favourable long-term outcomes than a two-day treatment (Jiang et al., 2006). Furthermore, most studies utilized systemic hypothermia- primarily achieved with cooling blankets and/or gastric lavage. Only a few studies delivered selective hypothermia, a technique which Liu et al. (2006) reported may yield greater improvements in ICP and other outcomes when compared to systemic treatment. Two studies delivered hypothermia selectively, only to the head (Qiu et al. 2006; Harris et al. 2009) . Despite the difference in protocol, similar reductions in ICP were reported. On the contrary, one high-quality RCT did not find any significant improvements in ICP or CPP following therapeutic hypothermia (Andrews et al., 2015; Clifton et al., 2001; Maekawa et al., 2015). Of note, this study did report that the number of patients with ICP>30mmHg was significantly lower in the hypothermia group compared to the control group.

While hypothermia treatment is used to acutely reduce ICP in patients with ABI, the intervention also has an effect on long term patient outcomes. At three to six months post-ABI, some studies reported that patients treated with hypothermia had more favourable outcomes on the GOS/GOSE and lower rates of mortality than those treated with normothermia (Hayashi et al., 2005; Jiang et al., 2000; Jiang et al., 2006; Lee et al., 2010; Liu et al., 2006; Marion et al., 1993; Marion et al., 1997; Polderman et al., 2002; Qiu et al., 2006; Qiu et al., 2007; Shiozaki et al., 1993; Smrcka et al., 2005; Yamamoto et al., 2002; Zhi et al., 2003). However, these findings were not replicated in similar studies (Gal et al., 2002; Harris et al., 2009; Shiozaki et al., 2001; Zhao et al., 2011) or in multicentre trials such as the North American Brain Injury Study (Clifton et al., 2001; Clifton et al., 2011). Furthermore, some studies reported that therapeutic hypothermia was associated with an increased risk of serious complications (Clifton et al., 2001; Clifton et al., 2011; Qiu et al., 2006; Qiu et al., 2007; Sahuquillo et al., 2009). Pulmonary infections such as pneumonia were noted during cooling, and cardiovascular issues such as arrhythmia and hypotension were noted during rewarming.

Three studies compared either therapeutic hypothermia to conventional treatment, or hypothermia and standard care to controls (Andrews et al., 2015; Flynn et al., 2015; Polderman et al., 2002). Two of the studies found a significant decrease in ICP in the hypothermia group compared to the conventional treatment group (Andrews et al., 2015; Flynn et al., 2015; Polderman et al., 2002). However the largest study, a high quality RCT, reported no difference between the groups in ICP, MAP, CPP (Andrews et al., 2015; Flynn et al., 2015; Polderman et al., 2002). Conflicting results also exist amongst these studies regarding mortality and morbidity outcomes, with one group suggesting an improvement following hypothermia (Andrews et al., 2015; Flynn et al., 2015; Polderman et al., 2002), and the other finding an increase in negative outcomes (GOSE) and mortality (Andrews et al., 2015; Flynn et al., 2015; Polderman et al., 2002).

In the combinational study, ICP, CPP, and oxygenation improved significantly more in the hypothermia + 25 g mannitol group compared to hypothermia alone (Sun et al., 2016). A rebound of all measured parameters occurred after 90 min, however, it was found that this could be avoided by increasing the dose of mannitol to 50 g.

One study stands alone in the protocol it employed. Lee et al. (2010) compared controls to both ICP/ CPP-managed, and brain tissue oxygen managed hypothermia. Irrespective of the treatment, both treatment groups had significantly lower ICP and displayed a trend towards lower mortality compared to controls. However, no significant differences were found between treatment groups in any parameter reported.

Conclusions

There is conflicting (level 1a) evidence regarding whether or not therapeutic hypothermia (32-35°C) effectively reduces elevated intracranial pressure post ABI compared to normothermia.

There is conflicting level 1a evidence whether or not therapeutic hypothermia (32-35°C) is associated with more favourable Glasgow Outcome Scale (extended) scores or mortality rates post ABI compared to normothermia treatment.

There is level 1a evidence that therapeutic hypothermia (32-35°C) increases the risk of complications such as pneumonia during treatment in patients post ABI.

There is level 1b evidence that very mild hypothermia (35-37°C) is just as effective as mild hypothermia (32-34°C) at lowering intracranial pressure in ABI patients.

There is conflicting (level 1b and level 2) evidence that very mild hypothermia (35-37°C) improves long term outcomes and mortality rates to a greater extent than mild hypothermia (32-34°C) in ABI patients. There is level 1b evidence that outcomes are the same.

There is level 1b evidence that very mild hypothermia (35-37°C) is effective at lowering intracranial pressure in diffuse II ABI patients, but increases mortality in diffuse III ABI patients.

There is level 1b evidence that hypothermia interventions may be more effective at decreasing intracranial pressure and improving long-term outcomes when administered for long-term (120 hours) compared to short term (48 hours)

There is conflicting (level 1b and level 2) evidence that therapeutic hypothermia may improve intracranial pressure and mortality and long-term outcomes when compared to standard therapy in ABI patients. The higher quality level 1b evidence suggests there is no improvement in intracranial pressure, and there is a negative impact in long-term outcomes and mortality.

There is level 1b evidence that intracranial pressure/cerebral perfusion pressure and brain tissue oxygen managed hypothermia are similar at reducing intracranial pressure in individuals with an ABI when compared to controls.

There is level 2 evidence that selective hypothermia may be superior to systemic hypothermia in improving intracranial pressure post ABI.

There is level 2 evidence that systemic hypothermia improves favourable outcomes (Glasgow Outcome Scale score >4) and reduces mortality compared to conventional treatment post ABI.

There is level 2 evidence that very mild hypothermia (35-36°C) may more effective than mild hypothermia (32-34°C) at improving neurological outcomes with fewer complications in patients post ABI.

There is level 4 evidence that hypothermia treatment combined with mannitol may be more effective at sustaining improved intracranial pressure, cerebral perfusion pressure, and oxygenations compared to hypothermia alone post ABI.

It is unclear whether therapeutic hypothermia (32-35°C) is an effective intervention for lowering elevated intracranial pressure or improving long-term outcomes/mortality in patients post ABI.

Therapeutic hypothermia increases the risk of complications such as pneumonia.

It is unclear whether therapeutic hypothermia is superior to standard care alone at improving intracranial pressure, or morbidity and mortality outcomes in ABI patients. The strongest evidence suggests that compared to standard care there is a similar effect on intracranial pressure and a detrimental effect on morbidity and mortality.

When used, very mild hypothermia (35-37°C) may be more effective than mild hypothermia (32-34°C) at reducing intracranial pressure; however, the effect on morbidity and mortality is unclear. Consideration for cooler temperatures may be warranted with more severe injuries.

Therapeutic hypothermia, either intracranial pressure or oxygenation managed may have the same effect on intracranial pressure, morbidity and mortality in individuals with an ABI.

Selective, long-term hypothermia can be more effective than systemic, short-term hypothermia in improve intracranial pressure and long-term outcomes in ABI patients.

Hypothermia combined with standard therapy might be more effective than hypothermia alone at improving intracranial pressure, cerebral perfusion pressure and oxygenation in ABI patients.

Hypothermia may improve outcomes and reduce mortality post ABI.

Very mild hypothermia (35-36°C) may be more effective than mild hypothermia (32-34°C) at improving outcomes with fewer complications post ABI.

15.1.2.3 Hyperventilation

Controlled hyperventilation to achieve a Partial Pressure of Carbon Dioxide in Arterial Blood (PaCO₂) of 30-35 mmHg during the first day's post ABI has been reported to improve ICP outcomes. Hyperventilation causes cerebral vasoconstriction, which leads to decreased cerebral blood flow and volume, thus leading to a decrease in ICP (Muizelaar et al., 1991). While reducing blood flow to an injured tissue seems paradoxical, the brain is able to maintain a normal cellular metabolism by increasing the amount of oxygen that is extracted from the blood (Diringer et al., 2000).

One concern that arises with intensive or prolonged hyperventilation is the exacerbation of metabolic acidosis, a condition commonly caused by ABIs. Depletion of oxygen shifts the injured brain from aerobic

to anaerobic metabolism, resulting in the build up of lactic acid — a compound that acidifies CSF and has been correlated with poor outcomes (De Salles et al., 1987; DeSalles et al., 1986). However, since hyperventilation decreases cerebral CO₂, the respiratory alkalosis generated by expelling CO₂ helps neutralize the detrimental impact of the developing metabolic acidosis. It is important to note that this process of acid neutralization depends on the availability of bicarbonate in the CSF, and thus prolonged hyperventilation may not be an appropriate therapeutic measure as it may deplete bicarbonate levels, favoring ischemia and leading to poorer outcomes. Several studies have also discussed concerns related to pre-hospital intubation leading to inappropriate hyperventilation (Lal et al., 2003; Warner et al., 2007).

The AANS has made Level II recommendations against the use of intensive prophylactic hyperventilation (PaCO₂≤25mmHg) (Carney et al., 2017). The EBIC recommended mild to moderate hyperventilation (PaCO₂=30-35mmHg) to manage high ICP and CPP in association with sedation and analgesia (Maas et al., 1997). If ICP remains uncontrolled, even with osmolar therapy and cerebrospinal fluid (CSF) drainage, then intensive hyperventilation (PaCO₂<30mmHg) was recommended (Maas et al., 1997). Studies examining the effects of hyperventilation on ICP and blood flow are presented in Table 15.4.

Table 15.4 Hyperventilation for the Acute Management of Intracranial Pressure Post ABI

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Muiselaar et al. (1991) USA RCT PEDro=7 N=113	Population: TBI; <i>Treatment Group 1 (TG1, n=36):</i> Mean Age=28 yr; Gender: Male=27, Female=9; Mean GCS=5.6. <i>Treatment Group 2 (TG2, n=36):</i> Mean Age=34 yr; Gender: Male=22, Female=14; Mean GCS=5.6. <i>Control Group (CG; n=41):</i> Mean Age=32 yr; Gender: Male=29, Female=12; Mean GCS=5.7. Intervention: Participants were randomized to receive normal ventilation (PaCO ₂ >35 mmHg, CG), hyperventilation (PaCO ₂ =25 mmHg, TG1) or hyperventilation plus intravenous tromethamine (0.3 M, TG2) for 5 days. Outcomes were assessed before and after treatment. Outcome Measure: Glasgow Outcome Score (GOS).	<ol style="list-style-type: none"> At 3 mo and 6 mo, the number of patients with favorable outcome (GOS=4-5) was significantly lower in TG1 group than in CG and TG2. The interaction between group and GOS was found to be significant (p<0.02), indicating that the detrimental effect of hyperventilation was limited to patients with better prognosis on admission (GCS=4-5). At 12 mo, this difference in outcome between groups was no longer significant (p=0.13). There were no significant differences in GOS outcome at any of the 3 time points between TG2 and CG.
Mohammed et al. (2013) Trinidad Case Series N=197	Population: ABI; Median Age=39 yr; Gender: Male=164, Female=33; Median GCS=5. Intervention: Participants who received therapeutic hyperventilation were retrospectively analyzed. Outcome Measures: Clinical Outcome, Mortality.	<ol style="list-style-type: none"> Overall mortality was 38.6%. Mortality was higher after intensive treatment (PaCO₂ <30 mmHg, 46.8%) than moderate treatment (PaCO₂ ≥30 mmHg, 33.6%), but this difference was not significant (p=0.06). GCS at discharge was a significant predictor of outcome (OR=0.17, p<0.001), but GCS at admission was not (OR=0.87, p=0.95).
Coles et al. (2002) UK	Population: TBI; Mean Age=32 yr, Gender: Male=26, Female=7; Time Post Injury<7 days; GCS Range<13. Intervention: Participants who received therapeutic	<ol style="list-style-type: none"> Hyperventilation significantly decreased ICP (p<0.001), increased CPP (p<0.0001), and worsened CBF (p<0.0001).

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Case Series N=33	hyperventilation (PaCO ₂ <30 mmHg) were retrospectively analyzed. Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Cerebral Blood Flow (CBF).	
Oertel et al. (2002) USA Pre-Post N=33	Population: TBI; Mean Age=33 yr; Gender: Male=28, Female=5; Median GCS=7. Intervention: Participants received hyperventilation (PaCO ₂ <30 mmHg) over 13 days. Outcome Measures: Intracranial Pressure (ICP), Mean Arterial Pressure (MAP).	1. Hyperventilation significantly decreased ICP (p<0.001) but not MAP (p=0.11) after treatment.
Diringer et al. (2000) US Case Series N=9	Population: TBI; Mean Age=27 yr; Gender: Male=8, Female=1; Mean Time Post Injury=11.2 hr; Mean GCS=5.6. Intervention: Participants who received therapeutic hyperventilation (PaCO ₂ <30 mmHg) were retrospectively analyzed. Outcome Measures: Cerebral Blood Flow (CBF), Cerebral Blood Volume (CBV), Cerebral Venous Oxygen Content (CvO ₂), Cerebral Metabolic Rate of Oxygen (CMRO ₂).	1. Hyperventilation significantly decreased CBF (p<0.001), CBV (p<0.001), and CvO ₂ (p<0.02), but not CMRO ₂ .
Thiagarajan et al. (1998) India Case Series N=18	Population: TBI; Mean Age=28 yr; Gender: Male=12, Female=6; Median GCS=7. Intervention: Participants who received therapeutic hyperventilation (PaCO ₂ =25 mmHg) and hyperoxia (PaO ₂ =200-250 mmHg) were retrospectively analyzed. Outcome Measures: Jugular Venous Bulb Oxygen Saturation (SjvO ₂), Arteriovenous Oxygen Content Difference (AVDO ₂).	1. Hyperventilation significantly decreased SjvO ₂ and AVDO ₂ (p<0.0001), but values returned to baseline when hyperoxia was induced (or PaCO ₂ =30 mmHg).

Discussion

The findings of two studies demonstrated that prolonged, moderate hyperventilation can effectively lower elevated ICP in individuals following ABI (Coles et al., 2002; Oertel et al., 2002). In comparing intensive (PaCO₂<30mmHg) hyperventilation to moderate (PaCO₂≥30mmHg) hyperventilation, a higher mortality was found in the former group, but the results were not statistically significant (Mohammed F, 2013). In another study, it was found that early, brief, moderate hyperventilation did not impair global cerebral metabolism in patients with severe TBI, and thus it is unlikely to cause further neurological injury (Diringer et al., 2000). Similar conclusions were reached by Brandi et al. (2018), noting that the reduction of cerebral oxygenation was within physiological limits and cerebral metabolism was ultimately not impaired. However, the decrease in cerebral blood flow and oxygenation should not be taken lightly given the devastating potentials of brain ischemia, and the ability of relatively short (40min) periods of hyperventilation to precipitate cerebral desaturation.

Potential detrimental effects following hyperventilation are particularly concerning in ABI, and the issue has been addressed in two earlier studies. In a small retrospective study, Thiagarajan et al. (1998) noted that hyperoxia ($\text{PaO}_2=200\text{-}250$ mmHg) was able to counteract the reduced cerebral oxygenation following hyperventilation. In a large clinical trial, Muizelaar et al. (1991) evaluated the effects of prolonged hyperventilation in combination with intravenous tromethamine. Long-term outcomes were significantly better in individuals who received the combination therapy than those who received hyperventilation alone and similar to those who received normal ventilation. The authors suggested that the presence of a buffer system, such as tromethamine, can help neutralize cerebral bicarbonate depletion due to hyperventilation.

Conclusions

There is level 1b evidence that hyperventilation plus intravenous tromethamine is superior than hyperventilation alone at improving long-term outcomes in patients post ABI.

There is level 4 evidence that hyperventilation may lower elevated intracranial pressure post TBI.

There is level 4 evidence that brief (40 min) periods of hyperventilation can decrease cerebral blood flow and cerebral oxygen saturation in patients post TBI.

There is level 4 evidence that hyperoxia ($\text{PaO}_2=200\text{-}250$ mmHg) can improve cerebral oxygenation following hyperventilation post ABI.

Hyperventilation may effectively lower elevated intracranial pressure post TBI; however, decreased cerebral blood flow and subsequent ischemia are potential complications.

The addition of tromethamine to a hyperventilation protocol is likely superior at improving long-term outcomes compared to hyperventilation alone.

Hyperoxia ($\text{PaO}_2=200\text{-}250$ mmHg) may improve cerebral oxygenation following hyperventilation post ABI.

15.1.2.4 Rotational Therapy and Prone Positioning

The concept of continuous lateral rotational therapy has been used for the prevention of secondary complications resulting from immobilization. These complications include pressure ulcers, pneumonia from atelectasis, deep vein thrombosis, pulmonary emboli, muscle atrophy, and contractures (Dittmer & Teasell, 1993). Additionally, there are some indications that continuous rotational therapy may be useful in managing elevations in ICP.

Use of the prone position has been shown to be an effective treatment for patients with acute respiratory insufficiency in the ICU (Pelosi et al., 2002). However, many studies have excluded patients with ABI due to fears of increasing ICP during the rotation process and in the prone position (Johannigman et al., 2000).

The EBIC and the AANS guidelines have made no recommendations regarding continuous rotational therapy or prone positioning in acute ABI for the prevention of secondary injury.

Table 15.5 Rotational Therapy and Prone Positioning for the Acute Management of Intracranial Pressure Post ABI

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Frazzitta et al. (2016) Italy & Austria RCT PEDro=5 N _{initial} =40 N _{Final} =31	<p>Population: Severe ABI; <i>Early verticalization</i> (<i>n</i>=15): Mean Age=53 yr; Gender: Male=9, Female=6. <i>Controls</i> (<i>n</i>=16): Mean Age=69 yr; Gender: Male=11, Female=5.</p> <p>Intervention: Patients with severe ABI underwent fifteen 30 min sessions of verticalization using a tilt table with a robotic stepping device in addition to conventional physiotherapy. Controls received conventional physiotherapy alone.</p> <p>Outcome Measures: Glasgow Coma Scale (GCS), Disability Rating Scale (DRS), Coma Recovery Scale-Revised (CRSr), Level of Cognitive Functioning (LCF).</p>	<ol style="list-style-type: none"> 1. All outcome measures improved significantly over the treatment period ($p<0.001$). 2. The early verticalization group showed significantly more improvement in the CRSr test compared with controls ($p=0.006$). 3. No other outcome measures were significantly different between groups.
Rocca et al. (2016) Switzerland RCT PEDro=3 N=30	<p>Population: ABI; Mean Age=54.2 yr; Gender: Male=17, Female=13.</p> <p>Intervention: Patients were randomized into 1 of 3 groups. The MOTomed Letto group utilized an automatic system for leg mobilization in a supine position. The Erigo group utilized a tilting table with an integrated leg movement system, which allows progressive verticalization of the patient. The 3rd group received standard care. Between day(s) 1-7 patient were mobilized in bed, while post day 7 patients were mobilized out of bed, or as soon as able. From the time of admission patients were mobilized every day in bed. Patients were mobilized out of bed after a minimum of 7 days.</p> <p>Outcome Measures: Production of Catecholamines, cardio-respiratory parameters.</p>	<ol style="list-style-type: none"> 1. There were no significant intra or inter group changes in blood pressure throughout the trial. 2. Significant within and between group differences were found for increased epinephrine rate both after MOTomed (both $p=0.023$) and standard mobilization (both $p=0.046$). Epinephrine increased more in the MOTomed group compared to the standard mobilization group. 3. Plasmametanephrine concentration significantly increased after MOTomed treatment ($p=0.023$). 4. Overall, plasmanormetanephrine concentration significantly increased after standad physiotherapy ($p=0.046$).
Roth et al. (2014) Germany Case Series N=29	<p>Population: SAH=15, TBI=8, ICH=5, Stroke=1; Mean Age=57 yr; Gender: Male=9, Female=20.</p> <p>Intervention: Participants were examined in the supine and prone positions.</p> <p>Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Mean Arterial Pressure (MAP).</p>	<ol style="list-style-type: none"> 1. Mean ICP significantly increased from 9.5 to 15.4 mmHg in prone position ($p<0.0001$). 2. Mean CPP decreased from 82-80 mmHg in prone position, but the difference was not significant ($p=0.0591$). 3. Mean MAP significantly decreased from 72.6-64.7 mmHg in prone position ($p<0.001$). 4. ICP>20 mmHg rates were significantly higher in prone position (18% versus 4%, $p<0.0001$).

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
		5. CPP<70 mmHg rates were significantly higher in prone position (24% versus 18%, p=0.0022).
Nekludov et al. (2006) Sweden Case Series N=8	Population: TBI; Mean Age=53.63 yr; Gender: Male=6, Female=2; GCS Range≤8 Intervention: Participants were examined in the supine and prone positions. Outcome Measures: Arterial Oxygenation (AO ₂), Intracranial Pressure (ICP), Mean Arterial Pressure (MAP), Cerebral Perfusion Pressure (CPP).	1. There was a significant improvement in AO ₂ in the prone position (p=0.02). 2. There were significant increases in ICP (p=0.03), MAP (p=0.05), and CPP (p=0.03) in the prone position.
Thelandersson et al. (2006) Sweden Case Series N=11	Population: TBI=6, ICH=2, SAH=3; Mean Age=51 yr; Gender: Male=7, Female=4. Intervention: Participants were examined in the supine and prone positions. Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Mean Arterial Pressure (MAP), Partial Pressure of Oxygen (PaO ₂), Oxygen Saturation (SaO ₂).	1. No significant changes were demonstrated in ICP, CPP or MAP in the prone position. 2. PaO ₂ and SaO ₂ were significantly increased in the prone position and after 10min in the supine post-prone position (p<0.05).
Tillet et al. (1993) USA Case Series N=58	Population: TBI; Mean Age=33.2 yr; Gender: Male=44, Female=14; Time Post Injury=24 hr; Mean GCS=6. Intervention: Patients underwent continuous rotational therapy with side-to-side rotation maintained at 40°. Outcome Measure: Intracranial Pressure (ICP).	1. No significant differences in ICP were demonstrated during rotation compared to non-rotation during any of the time periods (2-5d post admission). 2. Findings showed a statistically significant difference in ICP when patients were rotated to the side of the lesion (p=0.025).
Lee (1989) China Case Series N=30	Population: ABI; GCS Range<8. Intervention: Participants were placed into four different positions: supine; supine with head down 30°; 75% supine; and 75% prone. Outcomes were assessed at each position. Outcome Measure: Intracranial Pressure (ICP).	1. Compared with the supine position, ICP increased significantly for supine with head down 30° (p<0.01), 75% supine (p<0.01) and 75% prone (p<0.01).

Discussion

A multi-center RCT, reported that all outcome measures (GCS, DRS, LCF, CRSr) improved significantly over the duration of the study in both treatment groups (Frazzitta et al., 2016). However, CRSr scores were significantly greater in the treatment group (fifteen 30 min sessions of verticalization + conventional physiotherapy) compared to the control group (physiotherapy alone). In another RCT, different mobilization techniques and their effect on patient stress— as determined by plasma catecholamine levels and hypotensive incidents were investigated (Rocca et al., 2016). While all groups similarly affected

blood pressure, only the MOTOMed and standard mobilization interventions significantly increased patient plasma catecholamine levels from baseline. Results of this study suggest that mobilization with the Erigo robot (tilting table with an integrated leg movement system) is superior to both the MOTOMed robot and standard mobilization, as it does not cause hypotension and results in less sympathetic stress.

A single study was identified which examined the effects of continuous rotational therapy on ICP (Tillett et al., 1993). The study failed to find any direct benefit of the therapy for managing elevated ICP but did suggest that patients with unilateral brain injuries should not be rotated towards the side of the lesion in order to avoid further increases in ICP.

Three case series investigated the effects of prone positioning on various physiological measures. Two studies reported significant increases in ICP during prone positioning (Lee, 1989; Nekludov et al., 2006; Roth et al., 2014). Two studies demonstrated increased cerebral oxygenation in patients when they were prone (Nekludov et al., 2006; Thelandersson et al., 2006), which was maintained upon return to the supine position (Thelandersson et al., 2006). One study found increases in CPP and MAP when patients were prone (Nekludov et al., 2006), while other studies reported that these values decreased (Roth et al., 2014) or did not change (Thelandersson et al., 2006). Due to the small sample sizes and retrospective nature of these studies, further prospective research is required to determine the efficacy of prone positioning.

A single case study was identified investigating the effects of different body positions on ICP (Lee, 1989). Compared to the supine position, all other positions, supine with head down 30°; 75% supine; and 75% prone significantly increased ICP. The results of this early study suggest that manipulating body position during the acute stages post ABI should not be considered, as changes may increase ICP and have detrimental sequelae.

Conclusions

There is level 2 evidence that conventional physiotherapy alone, or in combination with verticalization may improve Glasgow Coma Scale, Coma Recovery Scale-Revised, Level of Cognitive Functioning, and Disability Rating Scale scores compared to controls in patients post ABI.

There is level 2 evidence that verticalization plus conventional physiotherapy may be superior to conventional physiotherapy alone at improving Coma Recovery Scale-Revised scores in patients post ABI.

There is level 2 evidence that verticalization using the Erigo robot may cause less sympathetic stress in patients with ABI compared to the verticalization using the MOTOMed machine, or conventional therapy.

There is level 4 evidence that continuous rotational therapy does not improve intracranial pressure following severe TBI.

There is level 4 evidence that the prone position may increase intracranial pressure but improve cerebral oxygenation post ABI.

There is conflicting (level 4) evidence that prone positioning improves cerebral perfusion and mean arterial pressure in patients post ABI.

There is level 4 evidence that the positions supine with head down 30°; 75% supine; and 75% prone may increase intracranial pressure more than the supine position in patients post ABI.

Continuous rotational therapy might not improve intracranial pressure in individuals with severe TBI.

Prone positioning may increase intracranial pressure but improve cerebral oxygenation post ABI. The effects of prone positioning on cerebral perfusion and mean arterial pressure are unclear.

Conventional physiotherapy alone, or in combination with verticalization may improve long term outcomes, disability, cognitive functioning and recovery from coma.

Verticalization in combination with conventional physiotherapy may be superior to conventional physiotherapy alone at improving recovery from coma.

Verticalization using the Erigo robot may be superior to the MOTomed machine, and conventional therapy at reducing sympathetic stress.

Manipulation of body positions may increase intracranial pressure more than the supine position.

15.1.2.5 Direct Thoracic Pressure Regulators

The technique of generating negative thoracic pressure through non-invasive methods is a common intervention used in shock and resuscitation settings. Increased negative thoracic pressure increases venous return to the heart, increases preload, and maintains appropriate cardiac output to perfuse vital end organs (Kwon et al., 2015). Theoretically, the creation of negative intrathoracic pressure between positive pressure expirations can also benefit patients with TBI by increasing cerebral venous return to the heart, thus reducing ICP, all the while maintaining appropriate cerebral perfusion to circumvent the development of ischemia. One of the biggest potential advantages of this intervention is that it can be performed noninvasively and presumably with fewer complications compared to the available pharmacological and surgical interventions.

The use of intrathoracic pressure regulators had only been investigated in animal TBI models, with studies reporting decreases in ICP and improvements in CPP and CBF in porcine models (Metzger et al., 2008; Metzger et al., 2015). The promising results from the animal models have encouraged efforts in translational research to investigate its efficacy in humans.

The EBIC and the AANS guidelines have made no recommendations regarding direct thoracic pressure regulators in acute patients with ABI for the prevention of secondary injury, or improvement of cerebral perfusion.

Table 15.6 Direct Thoracic Pressure Regulators for the Acute Management of Intracranial Pressure Post ABI

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Metzger et al. 2018 USA Pre-Post test N=5	<p>Population: TBI=2, SAH=1, ICH=1, Undisclosed=1; Mean Age=43 yr; Gender: Male=3, Female=2; Mean Time Post Injury to intervention=5.6 d.</p> <p>Intervention: Non-invasive active Intrathoracic Pressure regulation (aIPR) was used for 120 min to provide negative intrathoracic pressure regulation. Measurements were taken every 5 min starting 30 min before machine activation and concluding 30 min after the completion of the intervention.</p> <p>Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Mean Arterial Pressure (MAP).</p>	<ol style="list-style-type: none"> 1. Three patients required Mannitol treatment prior to intervention. 2. On average, ICP was significantly lower in all 5 patients during, and 30min after treatment compared to before (21% change, p=0.005). 3. On average, CPP was significantly increased in all 5 patients during, and 30min after treatment compared to before (16% change, p=0.04) 4. There was no change in MAP.

Discussion

A single study investigating the effects of direct intrathoracic pressure management on ICP was reviewed. Metzger et al. (2018) outlined a protocol involving the use of non-invasive active intrathoracic pressure regulation for 120 min, and discovered that ICP and CPP improved significantly during and up to 30 min after the intervention. In addition, no serious adverse effects were reported at any point during the intervention. Future studies designed with longer surveillance periods are warranted to delineate how long after treatment ICP and CPP remain optimized, and to properly assess for the effects of the intervention on patient morbidity (GOS, GOSE) and mortality.

Conclusions

There is level 4 evidence that non-invasive active intrathoracic pressure regulation for 120 min improves intracranial and cerebral perfusion pressure but has no effect on mean arterial pressure in patients post TBI.

There is level 4 evidence that non-invasive active intrathoracic pressure regulation for 120 min is not associated with any serious adverse effects in patients post TBI.

Although limited evidence exists, non-invasive active intrathoracic pressure might improve ICP and CPP, with no serious adverse effects, in patients post TBI.

15.1.3 Pharmacological Interventions

15.1.3.1 Propofol

Propofol is a fast-acting sedative that is absorbed and metabolized quickly, leading to pronounced effects of short duration (Adembri et al., 2007). Propofol decreases peripheral vascular tension resulting in potential neuroprotective effects, which may be beneficial in acute ABI care. Experimental results have shown positive effects on cerebral physiology including reductions in cerebral blood flow, cerebral oxygen metabolism, electroencephalogram activity, and ICP (Adembri et al., 2007). However, administration of high doses can result in propofol infusion syndrome, which is characterized by severe metabolic acidosis, rhabdomyolysis, cardiac dysrhythmias, and potential cardiovascular collapse (Corbett et al., 2006).

The AANS reported evidence for the recommendation of propofol in controlling of ICP, but not for improvement in mortality or long-term outcomes (Carney et al., 2017). They also indicated that high-dose propofol can produce significant morbidity. The earlier EBIC recommended sedation as part of the treatment course for ABI but made no specific mention of propofol (Maas et al., 1997).

Table 15.7 Propofol for the Acute Management of Intracranial Pressure Post ABI

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Colton et al. (2014b) USA Case Series N=117	Population: TBI; Mean Age=40.0 yr; Gender: Male=93, Female=24; Median GCS=6. Intervention: Participants were included in retrospective analysis after having received one of the following ICP therapies: hypertonic saline (HTS), mannitol, propofol, fentanyl, and barbiturates. Outcome Measure: Intracranial Pressure (ICP).	<ol style="list-style-type: none"> 1. Treatment with HTS resulted in the largest ICP decrease of the treatments examined. 2. Propofol and fentanyl escalations resulted in smaller but significant ICP reductions. 3. Mannitol resulted in statistically insignificant reductions in the first hr but rebounded by the second hr.
Smith et al. (2009) USA Case Series N=146	Population: TBI; GCS Ranges≤8. Intervention: Patients who received propofol and/or vasopressors were included in retrospective analysis. Outcome Measures: Propofol Infusion Syndrome (PRIS), Mortality.	<ol style="list-style-type: none"> 1. Only 3 patients on both propofol and vasopressors developed PRIS. 2. There were no patients on only propofol or vasopressors who developed PRIS. 3. PRIS was not linked to mortality (p>0.05).
Farling et al. (1989) Ireland Case Series N=10	Population: TBI; Mean Age=36.8 yr; Gender: Male=9, Female=1; Mean GCS=4.9. Intervention: Patients received an intravenous infusion of 1% propofol (2-4 mg/kg/hr). Measurements were obtained for 24 hr. Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Mean Arterial Pressure (MAP), Heart Rate (HR), Adverse Outcomes.	<ol style="list-style-type: none"> 1. ICP was significantly reduced at 2 hr (- 2.1 mmHg, p<0.05). 2. CPP was significantly increased at 24 hr (+9.8 mmHg, p<0.05). 3. No significant differences were seen in MAP or HR. 4. Propofol was not associated with any adverse outcomes.
Multimodal Propofol Interventions		
James et al. (2012) USA RCT Crossover PEDro=5	Population: TBI=4, SAH=3, ICH=1; Mean GCS=6.1. Intervention: Patients were randomized to receive sedation with either propofol (25.5 µg/kg/min) or dexmedetomidine (0.54 µg/kg/hr) for 4hr. Crossover occurred after 2 hr.	<ol style="list-style-type: none"> 1. No significant differences in ICP or CPP were found between the propofol and dexmedetomidine groups.

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
N=8	Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP).	
Kelly et al. (1999) USA RCT PEDro=8 N=42	Population: TBI; <i>Propofol (PROP, n=23)</i> : Mean Age=39 yr; Gender: Male=18, Female=5; Mean Time Post Injury=34 hr; Median GCS=7. <i>Morphine (MOR, n=19)</i> : Mean Age=38 yr; Gender: Male=17, Female=2; Mean Time Post Injury=38 hr; Median GCS=6. Intervention: Patients were randomized to receive sedation with either PROP (20 mg/mL) or MOR (Avg. 10 mg/h). Both groups received additional bolus of MOR (1-3 mg/hr) for at least 48 hr for analgesic purposes. Assessments were made at baseline, days 1, 2, 3, and 4, and at 6 mo. Outcome Measures: Intracranial pressure (ICP), Glasgow Outcome Scale (GOS), Disability Rating Scale (DRS).	<ol style="list-style-type: none"> 1. On day 3, ICP was significantly lower in PROP compared to MOR (p<0.05). 2. ICP therapy in PROP was also less intensive than MOR. 3. At 6 mo, scores were not significantly different between groups for mortality or favourable outcome rates (GOS\geq4). 4. In subgroup analysis, PROP was divided into high-dose (100 mg/kg, n=10) and low-dose (<100 mg/kg, n=13) groups. The high-dose group showed higher mean CPP on day 2 (81 mmHg versus 68 mmHg) and lower mean ICP on day 3 (14 mmHg versus 15 mmHg) compared to low-dose (p>0.05). 5. High-dose group demonstrated more favourable outcomes in the GOS (70% versus 38.5%) and the DRS (80% versus 46.2%) compared to the low-dose group (p>0.05).
Stewart et al. (1994) UK PCT N=15	Population: ABI; <i>Propofol (PROP, n=9)</i> : Mean Age=30.5 yr; Gender: Male=8, Female=1; Severity of Injury: Moderate=2, Severe=7; <i>Morphine and Midazolam (M+M, n=6)</i> : Mean Age=30.5 yr; Gender: Male=6, Female=0; Severity of Injury: Moderate=1, Severe=5. Intervention: Patients received sedation with either PROP (150-400 mg/hr) or morphine (0-4 mg/hr) with midazolam (0-5 mg/hr). Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Mean Arterial Pressure (MAP), Global Brain Metabolism (AVDO ₂), Glasgow Outcome Scale (GOS).	<ol style="list-style-type: none"> 1. PROP led to a decrease in AVDO₂ at 4 hr (6.0\pm2.6 mL/dL to 3.0\pm0.6 mL/dL, p<0.02). 2. No difference was reported between groups in ICP, CPP, and MAP. 3. No difference was reported between groups in functional outcomes on GOS at 6mo.

Discussion

Propofol was investigated for its beneficial role as an intervention post-ABI. Farling et al. (1989) in a case series of 10 subjects, reported that propofol administration reduced ICP, increased CPP, and was not associated with any adverse outcomes. Overall, this study suggests that propofol is an effective agent at providing safe and effective sedation. Given the retrospective nature and small sample size, results and conclusions drawn from this study should be taken with caution. The effects of propofol in patients with ABI will be further discussed later in the “comparative section” as its efficacy is directly contrasted to other sedatives.

In a retrospective review, Smith et al. (2009) identified three patients with propofol infusion syndrome. The authors noted that each of these patients were receiving both propofol and vasopressors, and that no patient on either propofol or vasopressors alone developed propofol infusion syndrome. Due to lack of a control group and the retrospective nature of the study, care should be taken when interpreting the conclusions reached. However, the evidence suggests that patients receiving both propofol and vasopressors are at the highest risk of developing propofol infusion syndrome, and thus careful monitoring is needed in this patient population.

Three studies comparing the effects of propofol to other sedatives were reviewed. In a crossover RCT, treated patients with ABI with either propofol or dexmedetomidine initially, followed by a crossover halfway through the treatment period (James et al., 2012). The authors reported no significant differences between the groups after treatment in terms of ICP and CPP. As a result of these findings, they recommend that the “*choice of sedative regimen be based on the profile of the sedative and the individual goals for a patient*”.

The remaining 2 studies compared propofol to morphine, or a combination of morphine and midazolam. While Stewart et al. (1994) found that propofol provided sedation similar to a combination of midazolam and morphine with no differences in changes to ICP, CPP, and MAP, Kelly et al. (1999) noted propofol was significantly more effective than morphine at reducing ICP - especially at higher doses. With respect to morbidity outcomes, one study reported no difference (Stewart et al., 1994) and the other an increase (Kelly et al., 1999) in favourable outcomes compared to the other treatment. Despite the disagreement in relationship directionality between studies, it can be concluded that propofol is at least as safe to use as morphine alone, or morphine with midazolam.

Conclusions

There is level 4 evidence that propofol may improve intracranial pressure and cerebral perfusion pressure, with no associated adverse outcomes post ABI.

There is level 4 evidence that propofol and vasopressor treatment may increase the risk of developing propofol infusion syndrome post ABI.

There is level 1b evidence that propofol is more effective than morphine at improving favourable outcomes and reducing intracranial pressure post TBI- specially at higher doses.

There is level 2 evidence that propofol is similar to midazolam and morphine with regards to sedation, morbidity, changes in intracranial pressure, cerebral perfusion, and mean arterial pressure post ABI.

There is level 2 evidence that propofol may not differ from dexmedetomidine in its effect on intracranial pressure and cerebral perfusion pressure post ABI.

Propofol may improve intracranial pressure and cerebral perfusion pressure post ABI, without producing adverse outcomes.

Propofol and vasopressor treatment in combination, but not as monotherapy, might increase the risk of developing propofol infusion syndrome post ABI.

Propofol, especially at higher doses, likely improves favourable outcomes, intracranial pressure and cerebral perfusion pressure more effectively than morphine.

Propofol may be no different than dexmedetomidine or morphine with midazolam in its effect on morbidity outcomes, or intracranial, cerebral perfusion, and mean arterial pressure.

The combination of morphine and midazolam may confound the comparison between propofol and morphine, however, it is prudent to conclude propofol is at least as safe and effective as morphine.

15.1.3.2 Midazolam

Midazolam is a fast-acting benzodiazepine with a short half-life and inactive metabolites (McCollam et al., 1999). Midazolam is an anxiolytic and displays anti-epileptic, sedative, and amnesic properties. It is a protein-bound, highly lipid-soluble drug that crosses the blood brain barrier and has a rapid onset of action - one to five minutes in most patients (McClelland et al., 1995). However, delayed elimination of midazolam resulting in prolonged sedation has been demonstrated in some critically ill patients.

Studies conducted in the operating room or intensive care unit have demonstrated midazolam to be relatively safe in euvolemic patients or in the presence of continuous hemodynamic monitoring for early detection of hypotension (Davis et al., 2001). Midazolam has been found to reduce CSF pressure in patients without intracranial mass lesions as well as decrease cerebral blood flow and cerebral oxygen consumption (McClelland et al., 1995).

The AANS made no recommendations regarding the efficacy of midazolam but, if used, suggested a 2.0 mg test dose followed by a 2.0-4.0 mg/hr infusion (Carney et al., 2017). The earlier EBIC recommended sedation but made no specific reference to midazolam (Maas et al., 1997).

Table 15.8 Midazolam for the Acute Management of Intracranial Pressure Post ABI

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Ghori et al. (2008) Ireland RCT PEDro=8 N=30	<p>Population: TBI; Midazolam (MDZ, n=15): Age Range: 18-65 yr; Gender: Male=14, Female=1; Mean Time Since Injury=12.86 hr; Median GCS=4.73. Propofol (PROP, n=13): Age Range: 18-65 yr; Gender: Male=13, Female=0; Mean Time Since Injury=9.07 hr; Median GCS=5.07.</p> <p>Intervention: Patients were randomly allocated to receive MDZ (n=15) or PROP (n=13) sedation. Outcomes were assessed at baseline and 3 mo.</p> <p>Outcome Measures: Glasgow Outcome Score (GOS), Mortality, Disability.</p>	<ol style="list-style-type: none"> 1. There was no significant difference between MDZ and PROP groups in number of patients with good outcomes (53% versus 54%). 2. Of the patients who had a poor outcome, there was no significant difference in the mortality rate between MDZ and PROP groups (20% versus 38%; p=0.07). 3. Of the patients who had a poor outcome, there was no significant difference in the severe disability rate between MDZ and PROP groups (20% versus 15%; p=0.8).

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Sanchez-Izquierdo-Riera et al. (1998) Spain RCT PEDro=5 N=100	Population: TBI; Mean Age=35.4 yr; Gender: Male=75, Female=25. Intervention: Patients were randomized to receive continuous intravenous infusion of midazolam (0.1-0.35 mg/kg/hr, n=34), propofol at 1.5- 6mg/kg/hr (n=33), or propofol at 0.1-0.2 mg/kg/hr (n=33). All patients received morphine. Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Triglyceride levels, Wake-up time, Sedation.	<ol style="list-style-type: none"> 1. No significant differences were found in ICP or CPP among treatment groups. 2. High levels of triglyceride were found in patients receiving propofol ($p<0.05$). 3. Wake-up time was significantly shorter in patients receiving propofol compared to those receiving midazolam (110 min/190 min versus 660 min, $p<0.01$). 4. All regimens achieved similar levels of sedation and had similar incidences of adverse effects.
Davis et al. (2001) USA Case Series N=184	Population: TBI; Northern Cohort (n=66): Mean Age=32.9 yr; Gender: Male=53, Female=13. Southern Cohort (n=118): Mean Age=31.2 yr; Gender: Male=89, Female=29. Intervention: Patients received 0.1 mg/kg midazolam without a restricted maximal dose (Group 1) or with a maximal dose of 5 mg (Group 2). Outcome Measures: Systolic Blood Pressure (SBP), Hypotension, Dose.	<ol style="list-style-type: none"> 1. Patients in the Group 1 received significantly higher doses than those in Group 2 (0.106 mg/kg versus 0.059mg/kg, $p<0.0001$). 2. A significant relationship was found between dose and hypotension following intubation ($p=0.032$) as well as decrease in SBP ($p=0.022$).
Papazian et al. (1993) France Case Series N=12	Population: TBI; Mean Age=28.3 yr; Gender: Male=11, Female=1; Mean GCS=5.2. Intervention: Patients received intravenous infusion of 0.15 mg/kg midazolam over a 1min period. Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Mean Arterial Pressure (MAP).	<ol style="list-style-type: none"> 1. Significant reductions in MAP (89 mmHg to 75 mmHg, $p<0.0001$) and CPP (71 mmHg to 55.8 mmHg, $p<0.0001$) were observed, but not in ICP. 2. Patients with low initial ICP (<18 mmHg) experienced greater reductions in MAP and greater increases in ICP compared to those with high initial ICP (≥ 18 mmHg; $p<0.0001$).
Multimodal Midazolam Interventions		
Stewart et al. (1994) UK PCT N=15	Population: ABI; Propofol (PROP, n=9): Mean Age=30.5 yr; Gender: Male=8, Female=1; Severity of Injury: Moderate=2, Severe=7; Morphine and Midazolam (M+M, n=6): Mean Age=30.5 yr; Gender: Male=6, Female=0; Severity of Injury: Moderate=1, Severe=5. Intervention: Patients received sedation with either PROP (150-400 mg/hr) or morphine (0-4 mg/hr) with midazolam (0-5 mg/hr). Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Mean Arterial Pressure (MAP), Global Brain Metabolism (AVDO ₂), Glasgow Outcome Scale (GOS).	<ol style="list-style-type: none"> 1. PROP led to a decrease in AVDO₂ at 4 hr (6.0 ± 2.6 mL/dL to 3.0 ± 0.6 mL/dL, $p<0.02$). 2. No difference was reported between groups in ICP, CPP, and MAP. 3. No difference was reported between groups in functional outcomes on GOS at 6mo.

Discussion

Two studies compared midazolam and propofol interventions in patients with ABI. In patients with severe TBI, those receiving midazolam had similar levels of ICP and CPP after treatment when compared to those receiving propofol, although propofol was associated with a shorter wake-up time (Sanchez-Izquierdo-Riera et al., 1998). Furthermore, all treatments had similar incidences of adverse effects, with the exception of the high levels of triglycerides found in patients receiving propofol. In addition, a separate RCT compared midazolam to propofol and found no differences in GOS scores, mortality, or disability between treatments (Ghori et al., 2008). Based on the studies reviewed, no differences in long term outcomes exist between propofol and midazolam. However, care should be taken as to avoid high doses of the latter to prevent hypotension in patients post ABI.

One case series found that higher doses of midazolam were associated with hypotension following intubation, as well as decreases in systolic blood pressure (Davis et al., 2001). While, an early retrospective study by Papazian et al. (1993) reported that midazolam did not yield significant reductions in ICP, but was associated with a decrease in both CPP and MAP. Furthermore, subgroup analysis revealed that patients with low initial ICP (<18mmHg) experienced greater decreases in MAP compared to those with high initial ICP (\geq 18mmHg) The results of this study call into question the utility of midazolam in ABI treatment, as there was no reduction in ICP and blood flow to the brain was further compromised.

The remaining study compared propofol to morphine, or a combination of morphine and midazolam. Stewart et al. (1994) found that propofol provided sedation similarly to a combination of midazolam and morphine with no differences in changes to ICP, CPP, MAP and mortality. Despite the disagreement in relationship directionality between studies, it can be concluded that propofol is at least as safe to use as morphine alone, or morphine with midazolam.

Conclusions

There is level 1b evidence that midazolam is no different than propofol at improving Glasgow Outcome Scale scores, mortality, or disability in patients post ABI.

There is level 2 evidence that midazolam is not different from propofol in its effect on intracranial pressure or cerebral perfusion pressure post ABI.

There is level 4 evidence that high doses of midazolam are associated with decreases in systolic blood pressure and hypotension following intubation in patients post ABI.

There is level 2 evidence that propofol is similar to midazolam and morphine with regards to sedation, morbidity, changes in intracranial pressure, cerebral perfusion, and mean arterial pressure post ABI.

There is level 4 evidence that midazolam has no effect on intracranial pressure but decreases mean arterial pressure and cerebral perfusion pressure post TBI.

Midazolam is likely not different than propofol at improving mortality, disability, or neurological outcomes.

High doses of midazolam might be associated with hypotension, specially following intubation.

Midazolam may have no effect on intracranial pressure but may reduce mean arterial pressure and cerebral perfusion pressure in patients, post-ABI.

Propofol may be no different than dexmedetomidine or morphine with midazolam in its effect on morbidity outcomes, or intracranial, cerebral perfusion, and mean arterial pressure.

15.1.3.3 Opioids

Opioids are pharmaceuticals with analgesic and nervous system depressant properties that primarily act on the CNS and gastrointestinal tract by binding to opioid receptors. The pharmacodynamic response each opioid elicits is determined by both the type of opioid receptor it binds, and its affinity for that receptor. Morphine has been the most commonly used opioid following ABI, while fentanyl and its derivatives have gained popularity due to their more rapid onset and shorter duration of effect (Metz et al., 2000). However, controversy persists regarding the effect of opioids on ICP and CPP. It has been reported that opioids can increase cerebral blood flow (CBF), which may lead to an increase in ICP (Bunegin et al., 1989; de Nadal et al., 2000; Marx et al., 1989; Werner et al., 1995) in the presence of intracranial pathology.

The AANS and the EBIC made no recommendations regarding opioids in acute ABI.

Table 15.9 Opioids for the Acute Management of Intracranial Pressure Post ABI

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Remifentanyl		
Engelhard et al. (2004) Germany Pre-Post N=20	Population: TBI; Mean Age=46 yr; Gender: Male=13, Female=7; GCS Range<8. Intervention: Remifentanyl was administered first as intravenous bolus (0.5 ug/kg), and subsequently as a 20 min continuous infusion (0.25 ug/kg/min). Outcomes were assessed for 20min before and after remifentanyl administration. Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Mean Arterial Pressure (MAP), Cerebral Blood Flow Velocity (CBFV).	1. No changes were observed in ICP, CPP, MAP, or CBFV following administration of bolus or continuous infusion of remifentanyl.
Sufentanyl		
Werner et al. (1995) Germany/USA Pre-Post N=30	Population: TBI; Gender: Male=21, Female=9; GCS Range<6. Intervention: Patients received an intravenous bolus of 3 µg/kg sufentanyl for 10 sec. Patients were monitored for 30min.	1. MAP decreased by more than 10 mmHg in 12 patients. 2. ICP was constant in patients with stable MAP (n=18) but was significantly

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
	Outcome Measures: Mean Arterial Pressure (MAP), Intracranial Pressure (ICP).	increased in those with decreased MAP (p<0.05).
Albanese et al. (1993) France Case Series N=10	Population: TBI; Age Range=18-50 yr; Gender: Male=10, Female=0; GCS Range≤8. Intervention: Patients received an intravenous bolus of sufentanil (1 µg/kg, 6 min), followed by continuous intravenous infusion (0.005 µg/kg/min). Outcome Measures: Intracranial Pressure (ICP), Mean Arterial Pressure (MAP), Cerebral Perfusion Pressure (CPP), Heart Rate (HR).	<ol style="list-style-type: none"> 1. There was a significant increase in ICP (53%, p<0.05) that peaked after 5 min and gradually returned to baseline after 15min. 2. There was a significant decrease in MAP (24%, p<0.05) and in CPP (38%, p<0.05). Though they gradually increased after 5min, they remained significantly reduced from baseline (22% and 23%, respectively). 3. There was a significant decrease in HR (15%, p<0.05).
Multimodal Opioid Interventions		
Karabinis et al. (2004) Greece RCT PEDro=5 N=161	Population: TBI; <i>Remifentanil Group (n=84):</i> Mean Age=46.8 yr; Gender: Male=44, Female=40; Time Post Injury<24 hr; Mean GCS=8.4. <i>Fentanyl Group (n=37):</i> Mean Age=49.6 yr; Gender: Male=24, Female=13; Time Post Injury<24 hr; Mean GCS=8.8. <i>Morphine Group (n=40):</i> Mean Age=47.3 yr; Gender: Male=25, Female=15; Time Post Injury<24 hr; Mean GCS=8.6. Intervention: Patients were randomized in a 2:1:1 ratio into one of three treatment arms: 1) analgesia-based sedation with 9 µg/kg/hr remifentanil for 5-10 min (and propofol at 0.5 mg/kg/hr if necessary); 2) hypnotic-based treatment with fentanyl; or 3) hypnotic-based treatment with morphine. Opioids were titrated to achieve optimal sedation in all three treatment groups. Outcome Measures: Time to neurological assessment, Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP).	<ol style="list-style-type: none"> 1. Sedation with remifentanil required significantly less time to neurological assessments (0.41 hr), compared to fentanyl (0.71 hr, p=0.001) or morphine (0.82 hr, p<0.001). 2. No differences in ICP or CPP between remifentanil and fentanyl/morphine groups were found.
De Nadal et al. (2000) Spain RCT Crossover PEDro=8 N=30	Population: TBI; Mean Age=30 yr; Gender: Male=23, Female=7; Mean Time Post Injury=17.8hr; GCS Range≤8. Intervention: Patients were randomized to receive intravenous morphine (0.2 mg/kg) or fentanyl (2 µg/kg) over 1 min. Crossover occurred after 24 hr. Treatment was initiated at 0 min and measurements were repeated at 5-10 min intervals until 60 min. Outcome Measures: Autoregulation, Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Mean Arterial Pressure (MAP), Central Venous Pressure (CVP), CO ₂ and O ₂ Partial Pressures (PP), Heart Rate (HR).	<ol style="list-style-type: none"> 1. Autoregulation was abolished in 18 patients and preserved in 12. No significant changes in ICP were observed between those with preserved and abolished autoregulation after treatment. 2. Both morphine and fentanyl induced significant increases in ICP at 5 min (p=0.008 and p=0.044, respectively), which remained significantly higher up to 60 min (p=0.008 and p=0.044, respectively). 3. Both morphine and fentanyl induced significant decreases in MAP at 5min (p=0.002 and p=0.016, respectively),

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
		<p>which remained significantly lower with fentanyl up to 60 min ($p=0.016$).</p> <ol style="list-style-type: none"> 4. Increase in ICP coupled with decrease in MAP resulted in a transient decrease in CPP, reaching a minimum value of 6 mmHg at 5 min after morphine and 65 mmHg after fentanyl. Both values were significantly lower than baseline ($p=0.001$ and $p<0.0001$, respectively). 5. No significant differences were observed after the use of either opioid for CVP, PPs, or HR.
<p>Albanese et al. (1999) France RCT Crossover PEDro=5 N=6</p>	<p>Population: TBI; Age Range=20-45 yr; Gender: Male=6, Female=0; GCS Range\leq8. Intervention: Patients were randomized to receive an initial 6 min injection of either 1 $\mu\text{g}/\text{kg}$ sufentanil, 100 $\mu\text{g}/\text{kg}$ alfentanil, or 10 $\mu\text{g}/\text{kg}$ fentanyl, followed by a 1 hr infusion of the same drug at 0.005 $\mu\text{g}/\text{kg}/\text{min}$, 0.7 $\mu\text{g}/\text{kg}/\text{min}$, and 0.075 $\mu\text{g}/\text{kg}/\text{min}$, respectively. Crossovers occurred at 24 hr intervals. Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Mean Arterial Pressure (MAP), Heart Rate (HR), End-Tidal CO_2, O_2 Saturation.</p>	<ol style="list-style-type: none"> 1. Sufentanil, alfentanil, and fentanyl were associated with significant mean increases in ICP peaking before 6 min (9 mmHg, 8 mmHg, and 5.5 mmHg, respectively; $p<0.05$) that returned to baseline by 15 min. 2. Sufentanil, alfentanil, and fentanyl were associated with significant mean decreases in MAP (21 mmHg, 24 mmHg, and 26 mmHg, respectively; $p<0.05$) and thus in CPP (30 mmHg, 31 mmHg, and 34 mmHg, respectively; $p<0.05$). MAP and CPP gradually increased after 5 min, but they remained significantly reduced compared to baseline. 3. No significant difference were observed after the use of any opioid with regard to HR, or End-Tidal CO_2/O_2 saturation.
<p>Kelly et al. (1999) USA RCT PEDro=8 N=42</p>	<p>Population: TBI; <i>Propofol (PROP, n=23)</i>: Mean Age=39 yr; Gender: Male=18, Female=5; Mean Time Post Injury=34 hr; Median GCS=7. <i>Morphine (MOR, n=19)</i>: Mean Age=38 yr; Gender: Male=17, Female=2; Mean Time Post Injury=38 hr; Median GCS=6. Intervention: Patients were randomized to receive sedation with either PROP (20 mg/mL) or MOR (Avg. 10 mg/h). Both groups received additional bolus of MOR (1-3 mg/hr) for at least 48 hr for analgesic purposes. Assessments were made at baseline, days 1, 2, 3, and 4, and at 6 mo. Outcome Measures: Intracranial pressure (ICP), Glasgow Outcome Scale (GOS), Disability Rating Scale (DRS).</p>	<ol style="list-style-type: none"> 1. On day 3, ICP was significantly lower in PROP compared to MOR ($p<0.05$). 2. ICP therapy in PROP was also less intensive than MOR. 3. At 6 mo, scores were not significantly different between groups for mortality or favourable outcome rates ($\text{GOS}\geq 4$). 4. In subgroup analysis, PROP was divided into high-dose (100 mg/kg, $n=10$) and low-dose (<100 mg/kg, $n=13$) groups. The high-dose group showed higher mean CPP on day 2 (81 mmHg versus 68 mmHg) and lower mean ICP on day 3 (14 mmHg versus 15 mmHg) compared to low-dose ($p>0.05$). 5. High-dose group demonstrated more favourable outcomes in the GOS (70% versus 38.5%) and the DRS (80% versus 46.2%) compared to the low-dose group ($p>0.05$).

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
<p>Lauer et al. (1997) USA RCT PEDro=5 N=15</p>	<p>Population: TBI; <i>Morphine Group</i> (n=5): Mean Age=21 yr; Mean GCS=6. <i>Fentanyl Group</i> (n=5): Mean Age=22 yr; Mean GCS=5. <i>Sufentanil Group</i> (n=5): Mean Age=35 yr; Mean GCS=6. Intervention: Patients were randomized to receive continuous intravenous morphine, fentanyl, or sufentanil over a 5 min interval. Continuous bolus infusion was initiated for 4 hr with the same opioid, if the blood pressure did not change >5%. Assessments were made every 15 min for the first 2 hr, and then in every 30min for the last 2hr. Outcome Measures: Intracranial Pressure (ICP), Mean Arterial Pressure (MAP), Cerebral Perfusion Pressure (CPP), Heart Rate (HR).</p>	<ol style="list-style-type: none"> 1. Mean doses of morphine, fentanyl, and sufentanil were 2.98 µg/kg, 0.07 mg/kg, and 0.37 µg/kg, respectively. 2. There was no significant difference in MAP from baseline in any group, except the sufentanil group had reduced MAP at 10- and 45-min post bolus administration (p<0.05). 3. There was no significant change in ICP from baseline in any group. However, the fentanyl group had reduced ICP at 150- and 180-min post bolus administration compared to the morphine and sufentanil groups (p<0.05). 4. There was no significant change in CPP from baseline in any group. However, the fentanyl group had reduced CPP at 60 min post bolus administration compared to with the morphine group, and at 70 min compared to the morphine and sufentanil groups (p<0.05).
<p>Sperry et al. (1992) USA RCT Crossover PEDro=7 N=9</p>	<p>Population: TBI; Mean Age=34 yr; Gender: Male=6, Female=3; Time Post Injury Range=1-3 days; Mean GCS=6. Intervention: Patients were randomized to receive an intravenous bolus of 3 µg/kg fentanyl or 0.6 µg/kg sufentanil over 1 min. Crossover occurred after 24 hr. Outcomes were recorded for 1hr after administration. Outcome Measures: Intracranial Pressure (ICP), Mean Arterial Blood Pressure (MAP), Cerebral Perfusion Pressure (CPP), Heart Rate (HR).</p>	<ol style="list-style-type: none"> 1. Fentanyl resulted in significant increases in mean ICP (8 mmHg, p=0.004), and significant reductions in mean MAP (11 mmHg, p<0.05) from baseline. 2. Sufentanil resulted in significant increases in mean ICP (6 mmHg, p=0.006), and significant reductions in mean MAP (10 mmHg, p<0.05). 3. Both Fentanyl and Sufentanil treatment resulted in significant decreases in CPP from baseline (-17mmHg and -13 mmHg, respectively, p<0.05). 4. No significant change in HR was noted after the use of either opioid.
<p>Colton et al. (2014b) USA Case Series N=117</p>	<p>Population: TBI; Mean Age=40.0 yr; Gender: Male=93, Female=24; Median GCS=6. Intervention: Participants were included in retrospective analysis after having received one of the following ICP therapies: hypertonic saline (HTS), mannitol, propofol, fentanyl, and barbiturates. Outcome Measure: Intracranial Pressure (ICP).</p>	<ol style="list-style-type: none"> 1. Treatment with HTS resulted in the largest ICP decrease of the treatments examined. 2. Propofol and fentanyl escalations resulted in smaller but significant ICP reductions. 3. Mannitol resulted in statistically insignificant reductions in the first hr but rebounded by the second hr.
<p>Scholz et al. (1994) Germany Pre-Post N=10</p>	<p>Population: TBI; Median Age=34 yr; Gender: Male=7, Female=3; GCS Range<6. Intervention: Patients received an intravenous bolus of 2 µg/kg sufentanil for 30 min, after which they received an intravenous infusion of sufentanil (150 (25-200) µg base h⁻¹) and midazolam (9.0 (3.6-13.5) mg h⁻¹) for 48 hr.</p>	<ol style="list-style-type: none"> 1. Following treatment, a significant decrease in mean ICP (16.1 mmHg to 10.8 mmHg, p<0.05) was noted within 15min. 2. At 15 min, mean MAP was significantly decreased (85.5 mmHg to 80.2 mmHg, p<0.05). 3. CPP remained stable after treatment.

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
	Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Mean Arterial Pressure (MAP).	4. The same results were observed at 2 days.
Stewart et al. (1994) UK PCT N=15	Population: ABI; <i>Propofol (PROP, n=9)</i> : Mean Age=30.5 yr; Gender: Male=8, Female=1; Severity of Injury: Moderate=2, Severe=7; <i>Morphine and Midazolam (M+M, n=6)</i> : Mean Age=30.5 yr; Gender: Male=6, Female=0; Severity of Injury: Moderate=1, Severe=5. Intervention: Patients received sedation with either PROP (150-400 mg/hr) or morphine (0-4 mg/hr) with midazolam (0-5 mg/hr). Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Mean Arterial Pressure (MAP), Global Brain Metabolism (AVDO ₂), Glasgow Outcome Scale (GOS).	1. PROP led to a decrease in AVDO ₂ at 4 hr (6.0±2.6 mL/dL to 3.0±0.6 mL/dL, p<0.02). 2. No difference was reported between groups in ICP, CPP, and MAP. 3. No difference was reported between groups in functional outcomes on GOS at 6mo.

Discussion

As discussed in the introduction, a large number of opioid derivatives exist, each with their own physiological and pharmacological properties. It follows that a variety of studies have individually analyzed said derivatives to help elucidate their effects on patients with ABI.

One study researched the effects of IV remifentanyl on patients with ABI. The remifentanyl was administered first as a bolus, then as a continuous infusion, yet despite the different modes of application the study reported no differences in ICP, CPP, MAP, or cerebral blood flow velocity compared to baseline (Engelhard et al., 2004).

The effects of sufentanil on patients with ABI were researched by Werner et al. (1995) and Albanese et al. (1993). While both studies reported decreases in MAP, only Albanese et al. observed additional decreases in CPP and HR. Interestingly, both groups noted an increase in ICP following sufentanil treatment, albeit only transiently in one study (Albanese et al., 1993) or in patients with decreased MAP (Werner et al., 1995). Although the trials were small and not blinded, these results suggest that sufentanil is not an agent that should be considered when attempting to lower ICP post-ABI.

Analgesic sedation with opioids is commonly used in conjunction with hypnotic agents (i.e., midazolam, propofol) to reduce nociceptive stimulation, which makes it difficult to evaluate the effects of opioids in isolation. However, it has been reported that using an opioid such as sufentanil with midazolam significantly improves ICP for a prolonged period of time (2 days), albeit at the expense of decreasing MAP (Scholz et al., 1994).

Several studies conducted RCTs comparing the efficacy of fentanyl to either morphine (de Nadal et al., 2000), sufentanil (Sperry et al., 1992), sufentanil and alfentanil (Albanese et al., 1999), morphine and sufentanil (Lauer et al., 1997) or remifentanyl and morphine (Karabinis et al., 2004). Of the studies

reviewed, 3 reported increases in ICP after opioid administration (Albanese et al., 1999; de Nadal et al., 2000; Sperry et al., 1992). The ICP increase was transient in Albanese et al. with the pressure returning to baseline 15 min after opioid administration. Of the aforementioned studies, all revealed a decrease in CPP and MAP after any type of opioid treatment. The remaining two studies found ICP did not change after opioid administration ((Engelhard et al., 2004; Karabinis et al., 2004; Lauer et al., 1997). Furthermore, CPP and MAP did not change, save for the sufentanil group in Lauer and colleagues' study where a decrease in mean arterial pressure was found. However, the mode of administration has been suggested as a determining factor for increases in ICP (Albanese et al., 1993; Albanese et al., 1999). In the studies where patients received only bolus injections of opioids, significant increases in ICP were seen (de Nadal et al., 2000; Sperry et al., 1992; Werner et al., 1995).

Stewart et al. (1994) found that propofol provided sedation similar to a combination of midazolam and morphine with no differences in changes to ICP, CPP, and MAP. While, Kelly et al. (1999) noted propofol was significantly more effective than morphine at reducing ICP - especially at higher doses. With respect to morbidity outcomes, one study reported no difference (Stewart et al., 1994) and the other an increase (Kelly et al., 1999) in favourable outcomes compared to the other treatment. Despite the disagreement in relationship directionality between studies, it can be concluded that propofol is at least as safe to use as morphine alone, or morphine with midazolam.

Conclusions

There is level 4 evidence that remifentanil may not improve intracranial pressure, cerebral perfusion pressure, mean arterial pressure, or cerebral blood flow velocity post ABI.

There is level 4 evidence that sufentanil may decrease mean arterial pressure, cerebral perfusion pressure, and heart rate post ABI.

There is level 4 evidence that sufentanil may transiently increase intracranial pressure post ABI.

There is level 4 evidence that sufentanil may increase intracranial pressure in patients with low mean arterial pressure post ABI.

There is conflicting (level 1a and level 2) evidence as to whether fentanyl, morphine, or sufentanil increase intracranial pressure, and decrease cerebral perfusion pressure post ABI. The level 1a evidence suggests that it increases intracranial pressure and decreases cerebral perfusion pressure.

There is level 1b evidence that propofol is more effective than morphine at improving favourable outcomes and reducing intracranial pressure post TBI- specially at higher doses.

There is level 2 evidence that alfentanil may result in a decrease in cerebral perfusion pressure and mean arterial pressure, and a transient increase in intracranial pressure, post ABI compared to controls.

There is level 2 evidence that remifentanil may not affect intracranial pressure post ABI compared to controls.

There is level 2 evidence that propofol is similar to midazolam and morphine with regards to sedation, morbidity, changes in intracranial pressure, cerebral perfusion, and mean arterial pressure post ABI.

There is level 4 evidence that sufentanil with midazolam decreases intracranial pressure and mean arterial pressure for 2 days post ABI.

Remifentanil might not improve intracranial pressure, cerebral perfusion pressure, cerebral blood flow velocity, or mean arterial pressure post ABI

Sufentanil might decrease mean arterial pressure, cerebral perfusion pressure, heart rate and transiently increase intracranial pressure— especially in patients with low blood pressure.

There are conflicting results regarding the effect different opioids may have on intracranial pressure and cerebral perfusion pressure effects post ABI; where fentanyl, morphine, sufentanil, and alfentanil might increase intracranial pressure and decrease cerebral perfusion pressure, remifentanil may not affect intracranial pressure compared to controls.

Sufentanil used in combination with midazolam may decrease intracranial pressure and mean arterial pressure post ABI.

Propofol, especially at higher doses, likely improves favourable outcomes, intracranial pressure and cerebral perfusion pressure more effectively than morphine.

Propofol may be no different than dexmedetomidine or morphine with midazolam in its effect on morbidity outcomes, or intracranial, cerebral perfusion, and mean arterial pressure.

15.1.3.4 Barbiturates

Barbiturates have long been proposed as a useful intervention in the control of ICP. They are thought to reduce ICP by suppressing cerebral metabolism, reducing metabolic demands and decreasing cerebral blood volume (Roberts, 2000). Early reports indicated that barbiturates reduced ICP in patients unresponsive to rigorous treatments with conventional ICP management techniques, including mannitol and hyperventilation (Marshall et al., 1979; Rea & Rockswold, 1983; Rockoff et al., 1979). However, most of these early investigations provided only anecdotal or poor evidence, as they were conducted in very small cohorts of patients lacking control comparisons. Later studies explored the negative side effects associated with barbiturate coma, such as adrenal insufficiency (Llompert-Pou et al., 2007) and bone marrow suppression (Stover & Stocker, 1998).

A review found no evidence that barbiturates decreased blood pressure or reduced mortality in 25% of patients (Roberts & Sydenham, 2012). Therefore, it was recommended that barbiturate coma be avoided until all other measures for controlling elevated ICP are exhausted.

The AANS made Level II B recommendations that high-dose barbiturates can be used to control elevated ICP that is refractory to maximum standard medical and surgical treatment (Carney et al., 2017). They also reported Level II evidence against the use of prophylactic barbiturates for inducing electroencephalogram

burst suppression. The earlier EBIC guidelines recommended barbiturate use to increase sedation only after previous sedation, analgesia, hyperventilation, osmotic therapy, and CSF drainage have failed to control ICP (Maas et al., 1997).

Table 15.10 Barbiturates for the Multimodal Acute Management of Intracranial Pressure Post ABI

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
Thiopental		
Stover et al. (1998) Germany Case Control N=52	<p>Population: TBI; <i>Thiopental</i> (n=23): Mean Age=27 yr; Severity: Severe. <i>Control</i> (n=29): Mean Age=44 yr; Severity: Severe.</p> <p>Intervention: Patients were included in retrospective analysis. Some received intravenous thiopental (5-11 mg/kg bolus, followed by continuous infusion of 4-6 mg/kg/hr and 4-6 bursts/min). Others received sedation with fentanyl and midazolam. ICP was targeted <20 mmHg and mean ar-terial pressure > 90 mmHg.</p> <p>Outcome Measures: Infection rate, Granulocyte Count, Leukocyte Count, Bone Marrow Production.</p>	<ol style="list-style-type: none"> 1. Patients requiring barbiturates were significantly younger than those not requiring it (27 yr versus 44 yr, p<0.01). 2. Barbiturates were shown to induce reversible leukopenia and granulocytopenia as well as an increased infection rate. 3. Several patients showed suppressed bone marrow production on histological examination.
Schalen et al. (1992) Sweden Case Series N=38	<p>Population: TBI; Median Age=20 yr; Gender: Male=30, Female=8.</p> <p>Intervention: Patients received high-dose intravenous thiopental at 5-11 mg/kg, followed by a continuous infusion at 4-8 mg/kg/hr for at least 12 hr.</p> <p>Outcome Measures: Intracranial Pressure (ICP), Mean Arterial Pressure (MAP), Cerebral Perfusion Pressure (CPP).</p>	<ol style="list-style-type: none"> 1. There was a decrease in MAP in 31 patients, a small increase in 3, and no change in 4. 2. There was a decrease in ICP in 26 patients, a small increase in 2, and no change in 3. 3. There was a decrease in CPP in 18 patients, an increase in 10, and no change in 3. 4. Though the fall in ICP immediately following infusion of thiopentone reduced the number of patients with decreased CPP (≤ 60 mmHg), continued treatment led to a fall in MABP, ultimately contributing to the decrease in CPP.
Nordby & Nesbakken (1984) Norway PCT N=38	<p>Population: TBI; <i>Thiopental</i> (n=16): Mean Age=20 yr; Mean GCS Score=4.3. <i>Control</i> (n=15): Mean Age=26 yr; Mean GCS=5.2.</p> <p>Intervention: Patients received continuous intravenous thiopental: a loading infusion of 10-20 mg/kg and a maintenance infusion of 3-5 mg/kg/hr to maintain ICP<30 mmHg. Mild hypothermia (32-35^o C) was maintained as soon as barbiturate loading was achieved. Controls consisted of patients not requiring barbiturate infusion.</p> <p>Outcome Measure: Glasgow Outcome Scale (GOS).</p>	<ol style="list-style-type: none"> 1. Better GOS outcomes at 9-12 mo were noted for the thiopental group compared with the control group (p=0.03). 2. Thiopental resulted in 6 patients with good/moderate outcomes, 3 with severe outcomes, and 7 with dead/vegetative outcomes. 3. In contrast, conventional therapy resulted in 2 patients with good/moderate outcomes, and 13 with dead/vegetative outcomes.
Pentobarbital		
Eisenberg et al. (1988)	<p>Population: TBI; <i>Pentobarbital</i> (n=37): Mean Age=25.3 yr; Gender: Male=29, Female=8; Mean</p>	<ol style="list-style-type: none"> 1. Patients receiving barbiturates were nearly twice as likely to achieve adequate

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
USA RCT PEDro=4 N=73	<p>Time Post Injury=83.3 hr; GCS Range=4-7. <i>Conventional Therapy (n=36)</i>: Mean Age=24.3 yr; Gender: Male=33, Female=3; Mean Time Post Injury=89.0 hr; GCS Range=4-7.</p> <p>Intervention: Patients were randomized to receive pentobarbital in addition to ongoing conventional therapy or conventional therapy alone. Pentobarbital was administered first as an initial bolus of 10 mg/kg over 30 min, then as an infusion (5 mg/kg/1hr for 3 hr), and finally as a maintenance dose (1 mg/kg).</p> <p>Outcome Measures: Intracranial Pressure (ICP), Glasgow Outcome Scale (GOS), Survival.</p>	<p>ICP control as those receiving only conventional therapy (OR=1.94, p=0.12).</p> <ol style="list-style-type: none"> The advantage of barbiturate therapy in those without prior cardiovascular complications was over 4-fold (OR=4.40). After declaration of treatment failure (ICP>20 mmHg), 26 of the patients randomized to conventional therapy were crossed over to receive barbiturates. The likelihood of survival at 1 mo was 92% for those who responded to barbiturates. In contrast, 83% of the patients who did not respond to barbiturates died. At 6 mo follow-up, 36% of the responders and 90% of the non-responders were vegetative or had died.
<p>Ward et al. (1985) USA RCT PEDro=6 N=53</p>	<p>Population: TBI; <i>Pentobarbital (n=27)</i>: Mean Age=31.1 yr; Gender: Male=25, Female=2; Mean GCS=5.1. <i>Conventional Therapy (n=26)</i>: Mean Age=35.1 yr; Gender: Male=21, Female=5; Mean GCS=4.9.</p> <p>Intervention: Patients were randomized to receive pentobarbital or conventional therapy. Barbiturates were administered first as a bolus (5-10 mg/kg), subsequently as a 1 hr bolus and continuous infusion for at least 72 hr, and finally as a maintenance dose of 1-3 mg/kg.</p> <p>Outcome Measures: Intracranial Pressure (ICP), Glasgow Outcome Scale (GOS), Mortality.</p>	<ol style="list-style-type: none"> During the first 4 days, there was no significant difference in hr levels of ICP or mortality. Clinical outcomes on the GOS and mortality did not differ between groups at 1 yr.
<p>Schwartz et al. (1984) Canada RCT PEDro=5 N=59</p>	<p>Population: TBI; Gender: Male=47, Female=12. <i>Evacuated Hematoma (n=29)</i>: <i>Pentobarbital (n=15)</i>: Mean Age=32.8 yr; Mean GCS=5.1; <i>Mannitol (n=14)</i>: Mean Age=35.7 yr; Mean GCS=4.9. <i>No Hematoma (n=30)</i>: <i>Pentobarbital (n=13)</i>: Mean Age=24.9 yr; Mean GCS=4.2; <i>Mannitol (n=17)</i>: Mean Age=24.4 yr; Mean GCS=4.4.</p> <p>Intervention: Patients were randomized to receive either 20% mannitol (1 gm/kg) or pentobarbital (initial bolus of 10 mg/kg, then continuous infusion at 0.5-3 mg/kg/hr). The other treatment was initiated on top of initial one if ICP proved refractory to maximal doses of the original drug.</p> <p>Outcome Measures: Intracranial Pressure (ICP), Mortality.</p>	<ol style="list-style-type: none"> For patients with evacuated hematomas, no significant difference was observed in mortality at 3 mo between pentobarbital and mannitol groups (40% versus 43%). Nearly twice as many patients in the pentobarbital group required the other regimen (mannitol) to control raised ICP compared to those in the mannitol group (p=0.04). For patients without evacuated hematoma, significantly higher proportion of patients treated with pentobarbital died compared to those treated with mannitol initially (77% versus 41%, p=0.03). In these patients, there was a higher rate of failure to control ICP in the pentobarbital group than in the mannitol group (p<0.001).

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
Fried et al. (1989) USA PCT N=7	<p>Population: TBI; Mean Age=31 yr; Gender: Male=4, Female=3; Time Post Injury≤1 wk; Mean GCS=4.7.</p> <p>Intervention: Patients unresponsive to conventional therapy received pentobarbital administered as a bolus followed by a continuous infusion to achieve serum concentrations of 20-40mg/L (n=4). Patients responsive to conventional therapy formed the control group (n=7).</p> <p>Outcome Measures: Energy Expenditure, Urinary Nitrogen Excretion, Nitrogen Balance, Urinary 3-Methylhistidine Excretion.</p>	<ol style="list-style-type: none"> 1. Patients treated with pentobarbital had significantly lower energy expenditure (p<0.01), lower urinary total nitrogen excretion (p<0.01), and improved nitrogen balance (p<0.05) than the control group. 2. There was no significant difference in urinary 3-methylhistidine excretion between groups.
Multiple		
Perez-Barcena et al. (2008) Spain RCT PEDro=4 N=44	<p>Population: TBI; <i>Thiopental</i> (n=22): Median Age=26 yr; Gender: Male=19, Female=3; Median GCS=6.5. <i>Pentobarbital</i> (n=22): Median Age=32 yr; Gender: Male=19, Female=3; Median GCS=7.</p> <p>Intervention: Participants were randomized to receive thiopental or pentobarbital. Thiopental was delivered in an initial bolus of 2 mg/kg over 20s. A second bolus of 3-5 mg/kg was administered if ICP>20mmHg. Once ICP<20mmHg was achieved, a continuous infusion was administered (3 mg/kg/hr). Pentobarbital was delivered in an initial dose of 10 mg/kg for 30 min, followed by continuous infusion of 5 mg/kg/hr for 3 hr, and then a dose of 1 mg/kg/hr for the last hr.</p> <p>Outcome Measure: Intracranial Pressure (ICP).</p>	<ol style="list-style-type: none"> 1. Uncontrolled ICP was significantly lower with thiopental than pentobarbital (50% versus 82%, p=0.03). 2. Thiopental was more effective than pentobarbital for controlling ICP (OR=5.1, p=0.027). 3. Relative risk for good control of ICP between thiopental and pentobarbital was 2.26 in patients with focal lesions and 3.52 in patients with diffuse lesions.
Perez-Barcena et al. (2005) Spain RCT PEDro=5 N=20	<p>Population: TBI; Mean Age=33 yr; Gender: Male=16, Female=4; GCS≤8.</p> <p>Intervention: Participants were randomized to receive Thiopental (n=10) or Pentobarbital (n=10). Thiopental was delivered in an initial bolus of 2 mg/kg over 20s A second bolus of 3-5 mg/kg was administered if ICP>20mmHg, followed by continuous infusion of 3 mg/kg/hr once ICP<20 mmHg. Pentobarbital was delivered in an initial dose of 10 mg/kg for 30 min, followed by continuous infusion of 5 mg/kg/hr for 3hr. For the last hour a dose of 1 mg/kg/hr was administered. Outcomes were assessed at discharge and 6mo.</p> <p>Outcome Measures: Intracranial Pressure (ICP), Mortality.</p>	<ol style="list-style-type: none"> 1. Thiopental was able to control ICP in 50% of patients while pentobarbital was only able to control ICP in 20% (p=0.16). 2. 50% of patients in the thiopental group died at discharge while 80% died in the pentobarbital group (p=0.16).
Llompert-Pou (2007) Spain Case Control N=40	<p>Population: TBI; <i>Barbiturates</i> (n=17): Mean Age=35 yr; Gender: Male=16, Female=1; Mean GCS Score=7. <i>Control</i> (n=23): Mean Age=27 yr; Gender: Male=20, Female=3; Mean GCS=7.</p> <p>Intervention: Patients were included in retrospective analysis. Those with elevated</p>	<ol style="list-style-type: none"> 1. Within 24 hr, adrenal function was similar in both groups. 2. After treatment with barbiturates, patients demonstrated higher adrenal insufficiency compared to the control group (53% versus 22%, p=0.03).

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
	<p>Intracranial Pressure (ICP) refractory to first tier measures received thiopental (n=10) or pentobarbital (n=7). The remaining patients showed controlled ICP in response to first tier measures.</p> <p>Outcome Measure: Adrenal function.</p>	<ol style="list-style-type: none"> 3. 94% of patients treated with barbiturates received norepinephrine (NE), while only 39% of those without received NE (p<0.001). 4. Those treated with barbiturates had higher NE doses than those without (1.07 µg/kg/min versus 0.31 µg/kg/min, p=0.03). 5. There was a trend toward a higher incidence of adrenal insufficiency among patients treated with pentobarbital than those treated with thiopental (71% versus 40%, p=0.20).
Unspecified Barbiturates		
<p>Colton et al. (2014b) USA Case Series N=117</p>	<p>Population: TBI; Mean Age=40.0 yr; Gender: Male=93, Female=24; Median GCS=6.</p> <p>Intervention: Participants were included in retrospective analysis after having received one of the following ICP therapies: hypertonic saline (HTS), mannitol, propofol, fentanyl, and barbiturates.</p> <p>Outcome Measure: Intracranial Pressure (ICP).</p>	<ol style="list-style-type: none"> 1. Treatment with HTS resulted in the largest ICP decrease of the treatments examined. 2. Propofol and fentanyl escalations resulted in smaller but significant ICP reductions. 3. Mannitol resulted in statistically insignificant reductions in the first hr but rebounded by the second hr.
<p>Majdan et al. (2013) Slovakia Case Control N=1172</p>	<p>Population: TBI; <i>High Barbiturate Group (n=71):</i> Median Age=36 yr; Gender: Male=51, Female=20; Median GCS=6. <i>Low Barbiturate Group (n=140):</i> Median Age=41; Gender: Male=113, Female=27. <i>No Barbiturate Group (n=961):</i> Median Age=45 yr; Gender: Male=737, Female=224.</p> <p>Intervention: Participants were categorized into high barbiturate (≥2 g/day), low barbiturate (<2 g/day), or no barbiturate groups for retrospective analysis.</p> <p>Outcome Measures: Intracranial Pressure (ICP), Mean Arterial Pressure (MAP), Glasgow Outcome Scale (GOS), Mortality, Hospital days.</p>	<ol style="list-style-type: none"> 1. Patients treated with high doses of barbiturate had significantly longer intubation days, days on ICU, and days in hospital compared to patients treated with low doses or no barbiturate (all p<0.001). 2. Barbiturate administration was associated with a significant reduction in the daily hr of ICP>25 mmHg, but was also associated with a significant elevation in daily hr of MAP <70 mmHg (p<0.05). 3. The effect of barbiturate use to treat ICP was not associated with improved outcomes as rates of ICU death, hospital death, 6 mo death, and poor outcome were not significantly different between responders and non-responders.
<p>Thorat et al. (2008) Singapore Case Series N=12</p>	<p>Population: TBI; Mean Age=38.58 yr; Gender: Male=10, Female=2; Median GCS=6.</p> <p>Intervention: Patients received a 250 mg bolus of barbiturates followed by continuous infusion of 4-8 mg/kg/hr.</p> <p>Outcome Measures: Intracranial Pressure (ICP), Mean Arterial Pressure (MAP), Cerebral Perfusion Pressure (CPP), Brain Tissue Oxygen Pressure (P_{ti}O₂), Pressure Reactivity Index (PRx).</p>	<ol style="list-style-type: none"> 1. Mean duration of barbiturate coma was 61.25 hr. 2. No significant reductions in mean ICP, MAP, CPP, P_{ti}O₂, or PRx were reported. 3. Eight of 12 patients experienced reductions in ICP, but only 4 had levels below 20 mmHg and only 3 of them survived. 4. Improved P_{ti}O₂ was seen in 6 of the 8 patients with initial P_{ti}O₂ >10 mmHg.

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
		5. There were no significant differences in initial ICP or P_{iO_2} levels between survivors and non-survivors, but the difference became significant after treatment ($p=0.012$ and $p=0.042$, respectively). 6. Favourable and significant changes in PRx were observed among survivors ($p=0.020$), but not among non-survivors.

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002)

Discussion

Barbiturate administration is used in patients' refractory to conventional treatment to decrease elevated ICP, and the increased cellular metabolism and protein catabolism caused by an ABI. As a result, an early PCT studied the effects of pentobarbital on surrogate markers of metabolism (Fried et al., 1989). The researchers noted lower energy expenditure, lower total urinary nitrogen excretion, and improved nitrogen balance in patients' refractory to conventional therapy when compared to controls. The results brought forth suggest that pentobarbital effectively reduces cellular metabolism and protein catabolism post ABI, and as a result potentially improves patient survival. In order to fully elucidate the effects of pentobarbital on patients post ABI, follow up studies are required.

The findings of a RCT by Eisenberg et al. (1988) suggested that pentobarbital was an effective adjunctive therapy for the management of elevated ICP refractory to conventional therapeutic measures. However, this study only supported the use of the high dose barbiturate for a small subgroup of patients with severe ABI ($GCS \leq 7$). In contrast, the findings of a RCT by Ward et al. (1985) suggested that pentobarbital was no better than conventional ICP management measures; a finding which was corroborated by Schwartz et al. (1984) in a RCT and by Thorat et al. (2008) in a smaller case series.

While barbiturate use may decrease elevated ICP, it should be used with caution due to the many reports of adverse events. Schwartz et al. (1984) found that over half of those treated with pentobarbital developed arterial hypotension, an adverse effect that could worsen the condition of patients with severe ABI. Majdan et al. (2013) found that barbiturate administration was associated with a significant increase in the amount of time spent with low MAP, despite a decrease in the amount of time with elevated ICP. Furthermore, the authors reported that high doses of barbiturate were associated with increased intubation days, days in the ICU, and did not improve clinical outcomes.

In accordance with recommendations made by the Brain Trauma Foundation, Perez-Barcena et al. (2005; Perez-Barcena et al., 2008) compared the efficacy of pentobarbital and thiopental on the management of refractory ICP unmanageable by conventional measures. In two linked trials, they reported that thiopental was superior to pentobarbital in controlling refractory ICP. In the first report, thiopental was shown to help reduce refractory ICP in a greater number of patients, although these differences were not statistically different (Perez-Barcena et al., 2005). In a follow-up report, the authors found statistically significant results in favour of thiopental using multivariate logistic regression (Perez-Barcena et al., 2008).

In another study, Schalen et al. infused thiopental intravenously for at least 12 hours, and noted a decrease ICP, CPP, and MAP in 82%, 84%, and 58% of patients, respectively. The conclusions drawn from this study should be interpreted with caution, as the small sample size and lack of controls warrant larger studies to further investigate the effects of thiopental.

Llompert-Pou et al. (2007) found thiopental less likely to induce adrenal insufficiency when compared to pentobarbital, further supporting its use when barbiturate coma is indicated. It should be noted that in an earlier study, Stover et al. (1998) reported that use of thiopental significantly reduced white blood cell production and could induce reversible leukopenia and granulocytopenia. The authors also noticed interactions with bone marrow suppressing antibiotics, which further exacerbated the problem. Thus, in instances where barbiturate coma is indicated, monitoring of immunological response is recommended.

There is little evidence that barbiturate therapy contributes to improvements in long-term clinical outcomes. In a prospective trial by Nordby and Nesbakken (1984), the authors reported that thiopental combined with mild hypothermia resulted in better clinical outcomes one year post injury when compared with conventional ICP management measures (including hyperventilation, steroids and mannitol). However, since this study used a combination of thiopental and hypothermia, it is not possible to attribute the better clinical outcomes to thiopental alone.

Conclusions

There is level 2 evidence that thiopental is more effective than pentobarbital for controlling elevated intracranial pressure refractory to conventional treatment, and less likely to induce adrenal insufficiency post ABI.

There is level 2 evidence that thiopental in combination with mild hypothermia has better one-year clinical outcomes compared to conventional management post ABI.

There is level 3 evidence that thiopental induces leukopenia and granulocytopenia in patients post ABI.

There is level 4 evidence that thiopental decreases intracranial pressure, cerebral perfusion pressure, and mean arterial pressure post ABI.

There is conflicting (level 1b and level 2) evidence regarding whether or not pentobarbital improves intracranial pressure compared to conventional management measures post ABI. Level 1b evidence suggests there is no difference.

There is level 2 evidence that barbiturate use is associated with development of hypotension in patients post ABI.

There is level 2 evidence that pentobarbital decreases energy expenditure, total urinary nitrogen excretion, improves nitrogen balance, but has no effect on 3-methylhistidine excretion compared to controls in individuals with an ABI refractory to standard therapy.

There are conflicting reports regarding whether pentobarbital is superior to conventional management at improving intracranial pressure. The strongest evidence suggests there is no difference.

Thiopental may decrease intracranial pressure, cerebral perfusion pressure, and mean arterial pressure post ABI.

Thiopental may be more effective than pentobarbital at controlled refractory intracranial pressure, and less likely to develop adrenal insufficiency. However, thiopental may still be associated with leuko- and granulocytopenias. When used, combination with hypothermia may result in greater long-term outcomes.

Barbiturate therapy should be avoided until all other measures for controlling elevated intracranial pressure are exhausted; special attention should be paid to monitoring immunological function, adrenal function, and blood pressure status if used.

Pentobarbital might decrease energy expenditure and nitrogen metabolism in individuals with an ABI refractory to standard therapy.

15.1.3.5 Cannabinoids

Dexanabinol (HU-211) is a synthetic, non-psychotropic cannabinoid (Mechoulam et al., 1988). It is believed to act as a non-competitive N-methyl-D-aspartate receptor antagonist to decrease glutamate excitotoxicity (Feigenbaum et al., 1989). Dexanabinol is also believed to possess antioxidant properties and has shown encouraging neuroprotective effects in animal models of TBI (Shohami et al., 1995).

The AANS and the EBIC made no recommendations regarding cannabinoids in acute ABI.

Table 15.11 Dexanabinol for the Acute Management of Intracranial Pressure Post ABI

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Maas et al. (2006) Netherlands RCT PEDro=10 N=861	Population: TBI; Time Post Injury≤6 hr; GCS Range≤5. <i>Dexanabinol</i> (n=428): Median Age=32 yr; Gender: Male=344, Female=84. <i>Placebo</i> (n=418): Median Age=33 yr; Gender: Male=345, Female=73. Intervention: Patients were randomized to receive either a single intravenous injection of 150mg dexanabinol dissolved in cremophor-ethanol solution or placebo for 15 min. Monitoring occurred for the first 72 hr. Outcomes were assessed 3 mo and 6mo post treatment. Outcome Measures: Glasgow Outcome Scale Extended (GOSE), Intracranial Pressure (ICP),	<ol style="list-style-type: none"> GOSE scores at 6 mo did not differ between groups (p=0.78). Unfavourable outcome was found in 50% of the treatment group and 51% of controls (OR=1.07). There were no differences in mortality or neurological deterioration between groups. There were no differences in post-treatment ICP or CPP between groups.

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
	Cerebral Perfusion Pressure (CPP), Mortality, Neurological Deterioration.	
Knoller et al. (2002) Israel RCT PEDro=7 N=67	<p>Population: TBI; <i>Dexanabiol</i> (n=30): Mean Age=29 yr; Gender: Male=25, Female=5; Mean Time Post Injury=5 hr; Mean GCS=6.3. <i>Placebo</i> (n=37): Mean Age=31 yr; Gender: Male=32, Female=5; Mean Time Post Injury=4.9 hr; Mean GCS=6.2.</p> <p>Intervention: Patients were randomized to receive either intravenous injection of 50 mg dexanabiol in cremophor-ethanol solution or placebo for 15 min. Monitoring occurred for 10 days. Outcomes were assessed at 10 days 1 mo, 3 mo, and 6 mo post treatment.</p> <p>Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Glasgow Outcome Scale (GOS), Disability Rating Scale (DRS), Adverse Events (AEs), Mortality.</p>	<ol style="list-style-type: none"> 1. Mean percentage of time that ICP>25 mmHg was significantly lower in the treatment group compared to controls on day 2 and 3 (p<0.02 and p<0.005, respectively). 2. Mean percentage time that CPP<50 mmHg was significantly lower in the treatment group compared to controls on days 2 and 3 (p<0.05). 3. On the GOS, a significantly higher proportion of the treatment group had favourable outcomes compared to controls at 1 mo (20% versus 2.7%, p=0.04), with a trend remaining at 3mo (p=0.1). 4. On the DRS, a higher proportion of the treatment group achieved no disability compared to controls. 5. No significant differences were found in AEs or mortality between groups.
Dual Cannabinoid Agonist		
Firsching et al. (2012) Germany RCT PEDro=8 N=97	<p>Population: TBI; <i>High Dose (HD, n=31)</i>: Mean Age=35.6 yr; Gender: Male=21, Female=10. <i>Low Dose (LD, n=33)</i>: Mean Age=36.4 yr; Gender: Male=24, Female=9. <i>Placebo (n=33)</i>: Mean Age=38.5 yr; Gender: Male=27, Female=6.</p> <p>Intervention: Patients were randomized to receive either placebo, high dose (1000 ug), or low dose (500 ug) of a dual cannabinoid agonist. Outcomes were assessed at 7 days, 14 days, 1 mo, 3 mo, and 6 mo after drug administration.</p> <p>Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Survival.</p>	<ol style="list-style-type: none"> 1. ICP>20 mmHg duration was shorter in the HD and LD groups compared to the placebo group, but this difference was not significant (p>0.05). 2. CPP<60 mmHg duration was significantly lower in the HD group compared to the placebo group (p<0.05). 3. CPP at 7 days was significantly higher in the HD group (p=0.0471) compared to the placebo group, but not in the LD group (p=0.0765) compared to the placebo group. 4. Survival at 1 mo was significantly higher in the HD (p=0.043) and LD (p=0.011) groups compared to the placebo group, but this was not seen at 3mo and 6mo.

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

In an early RCT, Knoller et al. (2002) found that dexanabiol (50 mg) showed significant improvements in ICP and CPP over placebo in patients with TBI. Despite showing significant improvements on the GOS and Disability Rating Scale at 1-month post treatment, these benefits progressively lost significance over the 6-month follow-up. Maas et al. (2006) conducted a large-scale multicenter RCT to better establish the

efficacy of dexanabinol in the treatment of TBI. The authors reported that dexanabinol did not significantly improve outcomes on the GOSE, Barthel Index, or quality of life measures (SF-36, CIQ) at six months when compared to placebo. Moreover, dexanabinol failed to provide any acute control of ICP or CPP. These findings suggest that the initial benefits reported by Knoller et al. (2002) may have been due to their small sample size.

Firsching et al. (2012) utilized KN38-7271, a dual cannabinoid agonist, as means of reducing ICP. After administration of high-dose KN38-7271 (1000 μ), the authors reported significant increases in CPP and greater survival at one month, but non-significant decreases in ICP when compared to low-dose KN38-7271 (500 μ). These results suggest that the dual cannabinoid agonist may have an overall positive effect on patients post TBI, especially at high doses, and is worth exploring in future research.

Conclusions

There is conflicting (level 1b) evidence as to whether dexanabinol in cremophor-ethanol solution effectively lowers intracranial pressure, increases cerebral perfusion pressure, and improves long-term clinical outcomes post TBI when compared to placebo.

There is level 1b evidence that high-dose KN38-7271 (a dual cannabinoid agonist) may improve intracranial pressure and cerebral perfusion pressure and improves survival post TBI compared to low-dose KN38-7271.

It is unclear whether Dexanabinol in cremophor-ethanol solution is effective in controlling intracranial pressure and improving cerebral perfusion pressure, and clinical outcomes post TBI. The strongest evidence suggests no beneficial effects.

KN38-7271, a dual cannabinoid agonist, is likely effective at improving intracranial pressure, cerebral perfusion pressure and survival post TBI at high doses.

15.1.3.6 Progesterone

Progesterone has drawn interest as a potential neuroprotective agent. Animal studies have suggested that progesterone reduces cerebral edema, regulates inflammation, reconstitutes the blood brain barrier, modulates excitotoxicity, and decreases apoptosis (Stein, 2008). In the human population, Groswasser et al. (1998) observed that female patients with TBI recovered better than male patients and suggested progesterone as a possible cause of this disparity. Trials have since been undertaken to accurately assess the effects of progesterone in the ABI population.

The AANS and the EBIC made no recommendations regarding progesterone in acute ABI.

Table 15.12 Progesterone for the Acute Management of Intracranial Pressure Post ABI

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
<p>Skolnick et al. (2014b) Belgium RCT PEDro=7 N=1195</p>	<p>Population: TBI; <i>Progesterone</i> (n=591): Median Age=35 yr; Gender: Male=464, Female=127; Median Time Post Injury=7 hr 4 min; GCS Range≤8. <i>Placebo</i> (n=588): Median Age=34 yr; Gender: Male=463, Female=125; Median Time Post Injury=7 hr 2 min; GCS≤8. Intervention: Participants were randomized to receive either progesterone (0.71 mg/kg/hr loading dose, followed by a continuous maintenance infusion of 0.5 mg/kg/hr) or placebo for 120 hr. Outcomes were assessed at baseline and 6mo. Outcome Measures: <i>Glasgow Outcome Scale (GOS)</i>.</p>	<ol style="list-style-type: none"> 1. There was no significant difference in the GOS scores of patients with the worst prognosis between groups (n=393; p=0.36). 2. There was no significant difference in the GOS scores of patients with intermediate prognosis between groups (n=394; p=0.82). <p>There was no significant difference in the GOS scores of patients with the best prognosis between groups (n=392; p=0.38).</p>
<p>Wright et al. (2014) USA RCT PEDro=10 N=882</p>	<p>Population: TBI; Median Age=35 yr; Gender: Male=650, Female=232; Mean Time Post Injury=218.1 min; Severity: Moderate=254, Moderate to Severe=472, Severe=156. Intervention: Participants were randomized to receive one of intravenous infusions of progesterone (n=442) or placebo (n=440). Progesterone was administered continuously at 14.3 mL/hr for 1 hr, then at 10 mL/hr for 71 hr. The dose was tapered by 2.5 mL/hr every 8hr, for total treatment duration of 96hr. Outcomes were assessed at 6mo. Outcome Measures: <i>Glasgow Outcome Scale Extended (GOSE), Mortality, Adverse Effects</i>.</p>	<ol style="list-style-type: none"> 1. Favourable outcomes occurred in 51% of patients treated with progesterone and in 55.5% of the placebo group. Relative benefit was 0.95, meaning fewer favourable outcomes are expected in the progesterone group (RR: 0.95). 2. Mortality at 6mo did not differ significantly between the two groups. The frequency of adverse effects did not differ significantly between the two groups, with the exception of phlebitis or thrombophlebitis, which was higher in the progesterone group (17.2% versus 5.7%; relative risk, 3.03).
<p>Shakeri et al. (2013) Iran RCT PEDro=7 N=76</p>	<p>Population: TBI; Gender: Male=76, Female=0; Time Post Injury≤6 hr. <i>Progesterone Group</i> (n=38): Mean Age=33.97 yr; Mean GCS=5.74. <i>Control Group</i> (n=38): Mean Age=34.68 yr; Mean GCS=5.79. Intervention: Participants were randomized to receive either progesterone (1 mg/kg every 12 hr for 3 days) or no treatment (control). Outcomes were assessed at 3mo. Outcome Measures: Glasgow Coma Scale (GCS), Glasgow Outcome Scale (GOS).</p>	<ol style="list-style-type: none"> 1. Admission and discharge GCS were not significantly different between groups. 2. GOS scores at 3 mo follow-up showed no significant differences between groups in terms of favourable outcomes. In patients with GCS=5-8, there was a significant difference in favourable outcomes between treatment and controls (16.67% versus 10%, p=0.03); this was not seen in patients with GCS<5.
<p>Xiao et al. (2008) China RCT PEDro=7 N=159</p>	<p>Population: TBI; <i>Progesterone</i> (n=82): Mean Age=30 yr; Gender: Male=58, Female=24; Mean Time Post Injury=3.80 hr; Mean GCS=6.0. <i>Placebo</i> (n=77): Mean Age=31 yr; Gender: Male=57, Female=25; Mean Time Post Injury=3.65 hr; Mean GCS=6.1. Intervention: Patients were randomized to receive intramuscular progesterone or placebo. Progesterone was administered at 1.0 mg/kg twice a day for 5 days. Outcome Measures: <i>Intracranial Pressure (ICP), Glasgow Outcome Scale (GOS), Modified Functional Independence Measure (mFIM), Mortality</i>.</p>	<ol style="list-style-type: none"> 1. Progesterone group showed more favourable outcomes on the GOS than controls at 3 mo (47% versus 31%, p=0.034) and 6 mo (58% versus 42%, p=0.048). 2. Progesterone group had higher mean mFIM scores at 3 mo (8.02 versus 7.35, p<0.05) and 6 mo (9.87 versus 8.95, p<0.01). 3. Mortality at 6 mo was significantly lower in the treatment group than the control group (18% versus 32%, p<0.039). 4. No significant difference in ICP was noted between groups.

		No AEs were reported after treatment of progesterone.
Wright et al. (2007) USA RCT PEDro=10 N=100	Population: TBI; Mean Age=35.8yr; Gender: Male=71, Female=29; Mean Time Post Injury=379.2min; Severity: Mild/Moderate=28, Severe=72. Intervention: Patients were randomized in a 4:1 ratio to intravenous progesterone (n=77) or placebo (n=23). Progesterone was administered at a loading dose of 0.71 mg/kg at 14 mL/hr for 1 hr, then at 10 mL/hr for 11 hr, followed by five 12 hr maintenance infusions at 10 mL/hr over 3 days. Outcomes were assessed 30 days post injury. Outcome Measures: Glasgow Outcome Scale Extended (GOSE), Disability Rating Scale (DRS), Adverse Events (AE), Intracranial Pressure (ICP).	1. AE rates and physiological variables (e.g. ICP) were similar between groups. No serious AEs were associated with progesterone. 2. The placebo group had a higher 30 days mortality rate compared to the progesterone group (RR 0.43). 3. Patients with severe injury (GCS=4-8) were functioning at a relatively poor level, regardless of group. For patients with moderate injury (GCS 9-12), those in the progesterone group were more likely to have moderate or good recovery on GOSE (55.6% versus 0%, p=0.0202) and better score on DRS (5.0 versus 12.7) when compared to the placebo group.

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

In a RCT, Wright et al. (2007) evaluated patients receiving progesterone over three days and found no significant improvement in ICP levels over placebo. However, these patients showed a decreased 30-day mortality rate without an increased rate of complications. As well, less severe patients in this group additionally showed significantly greater rates of favourable outcomes on the GOSE. Noting limitations in group distribution within their study, the authors recommended a larger clinical trial. Xiao et al. (2008) conducted such a trial with patients receiving progesterone or placebo over five days. The researchers reported a lack of improvement in ICP over placebo, but significantly greater morbidity (GOS) and independence (FIM) scores at three months and six months. In addition, there was significantly lower incidence of mortality at six months associated with the progesterone group. Notably, there were no reported complications associated with progesterone administration. In contrast, other studies have reported no significant differences in favourable outcomes between those receiving progesterone or placebo after three months (Shakeri et al., 2013) or six months (Shakeri et al., 2013; Skolnick et al., 2014a; Wright et al., 2014). However, in a subgroup analysis of patients with initial GCS \geq 5, Shakeri et al. (2013) found a significant improvement in GOS scores associated with progesterone. As well, one study reported that progesterone was associated with increased rate of serious adverse event such as phlebitis and thrombophlebitis (Wright et al., 2014). Given the conflicting findings between studies, further studies investigating the use of progesterone in ABI are suggested.

Conclusions

There is level 1a evidence that progesterone treatment is no better than placebo at improving Glasgow outcome scale scores at 3 and 6 mo post TBI.

There is level 1b evidence that progesterone is superior to placebo at improving Glasgow outcome scale scores in patients with an initial Glasgow coma scale score \geq 5 post TBI.

There is level 1b evidence that progesterone treatment may be associated with adverse events such as phlebitis and thrombophlebitis.

There is level 1a evidence that progesterone does not improve intracranial pressure compared to placebo post ABI.

There is level 1a evidence that progesterone improves mortality and Glasgow outcome scale scores compared to placebo in patients post ABI.

Progesterone does not improve functional outcomes post TBI, with the potential exception of patients who are not severely ill upon admission (Glasgow coma scale score ≥ 5)

Progesterone is likely associated with the development of phlebitis and thrombophlebitis.

Progesterone has no effect on intracranial pressure, but does reduce mortality, and improves functional and neurological outcomes post ABI.

15.1.3.7 Bradykinin Antagonists

Any type of tissue injury or cell death following brain injury acts as a strong stimulus for initiation of an inflammatory response. An important player in the acute inflammatory cascade is the kinin-kallikrein pathway; a pathway which generates the compound bradykinin. (Marmarou et al., 1999; Narotam et al., 1998). The binding of bradykinin to its BK₂ receptor leads to a cascade of events, ultimately yielding altered vascular permeability and tissue edema (Francel, 1992). Upregulation of kinins following blunt trauma has been reported, emphasizing their importance in the pathophysiology of brain injury (Hellal et al., 2003). Animal research using BK₂ receptor knockout mice has demonstrated direct involvement of this receptor in the development of the inflammatory-induced secondary damage and subsequent neurological deficits resulting from diffuse TBI (Hellal et al., 2003). These findings strongly suggest that specific inhibition of the BK₂ receptor could prove to be an effective therapeutic strategy following brain injury.

Bradycor is a bradykinin antagonist that acts primarily at the BK₂ receptor (Marmarou et al., 1999; Narotam et al., 1998), making it attractive for the management of post-ABI inflammation. Anatibant is another BK₂ receptor antagonist that is believed to more strongly bind the BK₂ receptor compared to Bradycor (Marmarou et al., 2005). Animal research has suggested that Anatibant dampens acute inflammation, reduces brain edema, and improves long-term neurological function (Hellal et al., 2003; Kaplanski et al., 2002; Pruneau et al., 1999; Stover et al., 2000).

The AANS and EBIC made no recommendations regarding bradykinin antagonists in acute ABI.

Table 15.13 Bradycor for the Acute Management of Intracranial Pressure Post ABI

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Anatibant		
<p>Shakur et al. (2009) UK RCT PEDro=9 N=228</p>	<p>Population: TBI; Mean Age=36 yr; Gender: Male=203, Female=25; Mean Time Post Injury=6 hr; Mean GCS=8. Intervention: Patients were randomized to receive placebo (n=57), high-dose Anantibant (n=57; 15mg/dY), medium-dose Anantibant (n=56; 10 mg/day) or low-dose Anantibant (n=58; 5 mg/day). Maintenance doses were administered for 4 days. Outcomes were assessed at 2 wk post injury. Outcome Measures: Glasgow Coma Scale (GCS), Disability Rating Scale (DRS), Modified Oxford Handicap Scale (HIREOS), Serious Adverse Event (SAE), Mortality.</p>	<ol style="list-style-type: none"> 1. The trial was ended early due to concerns with patient safety. 2. Mortality was slightly higher in patients treated with Anatibant than those with placebo (19.0% versus 15.8%), but the risk was not significant (RR=1.20, p=0.38). 3. There was a greater proportion of SAEs in patients treated with Anatibant than those with placebo (26.4% versus 19.3%), but the risk was not significant (RR=1.37, p=0.19). 4. Mean GCS was higher in the Anatibant group than the placebo group, but the difference was not significant (12.48 versus 9.73, $\delta=-0.55$, p>0.05). 5. Mean DRS was higher in the Anatibant group than the placebo group, but the difference was not significant (11.18 versus 9.73, $\delta=1.61$, p>0.05). 6. Mean HIREOS was slightly higher in the Anatibant group than the placebo group, but the difference was not significant (3.94 versus 3.54, $\delta=0.42$, p>0.05).
<p>Marmarou et al. (2005) USA RCT PEDro=4 N=25</p>	<p>Population: TBI; GCS Range\leq8. <i>Low Dose (n=10):</i> Mean Age=31.2 yr; Gender: Male=9, Female=1; Mean Time Post Injury=10.6 hr. <i>High Dose (n=10):</i> Mean Age=39.1 yr; Gender: Male=9, Female=1; Mean Time Post Injury=11.3 hr. <i>Placebo (n=4):</i> Mean Age=33.5 yr; Gender: Male=2, Female=2; Mean Time Post Injury=8.2 hr. Intervention: Participants were randomized to receive placebo, low-dose Anatibant (3.75 mg), or high dose Anatibant (22.5 mg). Monitoring occurred for 5 days and outcomes were assessed at 1 mo, 3 mo, and 6 mo. Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Glasgow Outcome Scale (GOS).</p>	<ol style="list-style-type: none"> 1. A greater proportion of patients treated with high dose Anatibant showed favourable outcomes on GOS at 3 mo and 6 mo than those with low dose or placebo. 2. Given small sample size and heterogeneity between groups, conclusions could not be drawn regarding ICP or CPP.
<p>Marmarou et al. (1999) USA RCT PEDro=8 N=136</p>	<p>Population: TBI; <i>Bradycor (n=66):</i> Mean Age=30 yr; Gender: Male=47, Female=19; Mean Time Post Injury=10 hr; Mean GCS=6.0. <i>Placebo (n=67):</i> Mean Age=34 yr; Gender: Male=55, Female=12; Mean Time Post Injury=10 hr; Mean GCS=6.1. Intervention: Participants were randomized to receive continuous intravenous infusion of either Bradycor (3.0 μg/kg/min) or placebo for 5 days. Monitoring occurred for 5 days and outcomes were</p>	<ol style="list-style-type: none"> 1. Percentage of time ICP>15 mmHg on 4-5 days was significantly lower in the Bradycor group compared with placebo (p=0.035). 2. There were fewer deaths in the Bradycor group than placebo (20% versus 27%). 3. The Bradycor group showed a 10.3% and 12% improvement in GOS at 3mo and 6mo respectively (p=0.26).

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
	assessed at 3 mo and 6 mo. Outcome Measures: Intracranial Pressure (ICP), Glasgow Outcome Scale (GOS), Therapeutic Intensity Levels (TIC), Mortality.	4. The Bradycor group had significantly lower TIC than placebo ($p<0.05$).
Narotam et al. (1998) South Africa RCT PEDro=6 N=20	Population: TBI; Time Post-Injury=24-96 hr; GCS Range=9-14. Intervention: Participants were randomized to receive continuous intravenous infusion of Bradycor (3.0 $\mu\text{g}/\text{kg}/\text{min}$) or placebo for 7 days. Outcome Measures: Intracranial Pressure (ICP), Glasgow Coma Scale (GCS), Therapeutic Intensity Levels (TIL).	1. Bradycor group had a longer interval from time of injury to initiation of drug infusion ($p=0.027$). 2. The mean increase in peak ICP from baseline was greater in the placebo group than Bradycor group (21.9 mmHg versus 9.5 mmHg, $p=0.018$). 3. The mean reduction in GCS score in the placebo group was significantly greater than in the Bradycor group (4 versus 0.6, $p=0.002$). 4. Bradycor had a significant effect in preventing elevation of ICP>20 mmHg compared to placebo (91% versus 78%, $p=0.005$). 5. Bradycor group had significantly lower TIL than placebo ($p<0.05$).

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

Shakur et al. (2009) conducted a large-scale multicenter trial of Anatibant. The authors reported a non-significant elevated risk of serious adverse events among patients receiving the medication, without improvements in morbidity (DRS, GCS) or mortality. As such, the trial was terminated early on by the investigators, leading to a legal dispute with its sponsors.

Anatibant is believed to be a more potent bradykinin antagonist than Bradycor, and was evaluated by Marmarou et al. (2005) to study its effects on ICP and morbidity outcomes. Due to a small sample size and lack of baseline comparability between groups, the authors were unable to draw any significant conclusions regarding the efficacy of Anatibant in preventing brain edema or deteriorations in ICP and CPP. However, patients who received a higher dose of the medication had more favourable outcomes on the GOS at three months and six months when compared to a lower dose and placebo.

Two trials evaluated the efficacy of Bradycor in the acute treatment of ABI. Both trials reported that treatment with Bradycor resulted in a significant reduction in ICP elevations when compared to placebo - as indicated by the time spent under intracranial hypertension (Narotam et al., 1998). In the smaller of the two trials, Narotam et al. (1998) found that patients in the placebo group experienced a greater deterioration in GCS scores over the course of the study. These findings were not replicated in Marmarou et al., as the researchers reported no significant differences between groups in mortality rates, improvements in GOS scores at three months and six months, or the intensity of additional therapeutic interventions needed to control ICP.

Conclusions

There is level 1b evidence that Anatibant, regardless of dose, has no effect on serious adverse events, mortality, Glasgow Coma Scale, Modified Oxford Handicap Scale, or Disability Rating Scale scores in individuals post ABI.

There is level 2 evidence that high-dose anatibant is superior to low-dose anatibant and placebo at improving Glasgow outcome scale scores at 3 and 6 mos post TBI.

There is level 1a evidence that Bradycor is effective at preventing acute elevations intracranial pressure and reducing therapeutic intensity levels post ABI when compared to placebo.

There is conflicting (level 1b) evidence that Bradycor improves mortality and Glasgow outcome scale scores in patients post ABI.

Anatibant, regardless of dose, likely does not cause serious adverse events, affect morbidity, mortality or disability in patients post ABI.

It is unclear if a higher dose of anatibant is superior to a lower dose at improving intracranial pressure, however it may improve functional outcomes up to 6 months post injury.

Bradycor can prevent acute elevations in intracranial pressure and reduce therapeutic intensity levels post ABI; however, its effect on morbidity and mortality outcomes is not clear.

15.1.3.8 Dimethyl Sulfoxide

Dimethyl Sulfoxide (DMSO) is an organic sulfur-containing compound that has been shown to stabilize cell membranes, protect cells from mechanical damage and reduce edema in tissue (Kulah et al., 1990). Furthermore, DMSO is believed to act as an antioxidant and has been credited with the ability to increase tissue perfusion, neutralize metabolic acidosis, and to decrease intracellular fluid retention (Kulah et al., 1990). As a result, DMSO has been suggested for the treatment of elevated ICP following ABI.

The AANS and the EBIC made no recommendations regarding DMSO in acute ABI.

Table 15.14 Dimethyl Sulfoxide for the Acute Management of Intracranial Pressure Post ABI

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Karaca et al. (1991) Turkey & Canada Case Series	Population: TBI; Mean GCS=6. Intervention: Patients received intravenous infusion of 28% DMSO (1.2 g/kg), every 6 hr for 1-10 days. Monitoring occurred for 10 days and outcomes were	1. All patients showed a reduction in ICP after 24 hr and 7 had normal ICP after 6 days.

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
N=10	assessed at 6 days and 3 mo. Outcome Measures: Intracranial Pressure (ICP), Neurological assessment.	<ol style="list-style-type: none"> 2. Reductions in ICP were seen within the first 30 min, however the effect was not sustained, and most patients required maintenance doses for 2-10 days to minimize fluctuations in ICP. 3. Neurological assessment at 6d days showed 2 patients with severe neurological deficits, 2 with moderate impairments, and 6 patients with mild to no deficit. 4. At 3 mo, 1 patient remained severely impaired and 7 patients showed mild to no deficit.
Kulah et al. (1990) Turkey Case Series N=10	Population: TBI; Mean Time Post Injury=6hr; GCS Range≤6. Intervention: Patients received intravenous infusion of DMSO up to 7 days. Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Mean Arterial Pressure (MAP).	<ol style="list-style-type: none"> 1. Three patients died due to uncontrolled ICP. 2. In most cases DMSO reduced ICP within 10min with a parallel increase CPP but had no effect on MAP. 3. DMSO caused only a temporary decrease in ICP, as continuous infusions did not prevent the ICP from returning to elevated baseline levels.
Marshall et al. (1984) USA Case Series N=5	Population: ABI; GCS<7. Intervention: Patients received rapid intravenous infusion of 10% or 20% DMSO at a dose of 1 g/kg, with an upper dose limit of 8 g/kg/day. Outcome Measures: Intracranial Pressure (ICP), Complications.	<ol style="list-style-type: none"> 1. All patients showed satisfactory control of elevated ICP (ICP<25 mmHg, >15 min) within min (2-24 min). 2. Despite initial improvements in ICP, an ultimate loss of ICP control occurred. 3. Most patients experienced significant hyponatremia as a side effect.

Discussion

Three studies have examined the effects of DMSO in the management of ICP post ABI. In a study by Kulah et al. (1990), the authors reported that in the majority of cases DMSO was effective in controlling ICP elevations within minutes of injection, which was followed by a concomitant increase in CPP. However, continuous infusions of DMSO for up to seven days failed to control elevations in ICP and values returned to baseline. In a similar study conducted by Karaca et al. (1991), patients were treated with repeated injections of DMSO for up to 10 days. Although reductions in ICP were observed within the first 30 minutes after administration, the effect was not sustained, and most patients required maintenance doses to minimize fluctuations in ICP. The results from both of these retrospective studies suggest that DMSO may acutely reduce ICP, however it is not an appropriate agent when attempting to maintain long-term ICP control.

Marshall et al. (1984) observed the effects of using DMSO on patients with ABI. Originally, patients received 10% DMSO and temporary ICP decreases were observed; however, ICP quickly returned to baseline (2-24 min) and electrolyte imbalances such as hyponatremia were observed. Subsequently, the

remaining patients received 20% DMSO and while ICP reduction was maintained longer, electrolyte imbalances continued to develop despite close patient monitoring.

Conclusions

There is level 4 evidence that dimethyl sulfoxide temporarily reduces intracranial pressure elevations and increases cerebral perfusion pressure post ABI.

There is level 4 evidence that increasing concentrations of DMSO provide longer intracranial pressure reduction but are accompanied by an increase in electrolyte imbalances post ABI.

Dimethyl sulfoxide may cause temporary improvements in intracranial pressure and cerebral perfusion pressure post ABI; however, these improvements may not be sustained long-term.

DMSO might be able to transiently lower intracranial pressure; however, it is associated with the development of electrolyte imbalances. Both responses appear to be dose-dependent.

15.1.3.9 Corticosteroids

Corticosteroids are steroid hormones produced by within the body and can be classified as either a glucocorticoid (anti-inflammatory, metabolic), or a mineralocorticoid (regulate electrolyte and water balance). Numerous glucocorticoids have been used in brain injury care including dexamethasone, methylprednisolone, prednisolone, prednisone, betamethasone, cortisone, hydrocortisone, and triamcinolone (Alderson & Roberts, 2005). Using such a broad spectrum of agents within diverse patient groups has made understanding corticosteroid efficacy difficult. Adding to this difficulty is a lack of understanding regarding the mode of action of steroids in ABI treatment. Grumme et al. (1995) reported that laboratory studies have associated corticosteroid use with reductions in net brain weight, facilitation of synaptic transmission, reduction of lipid peroxidation, preservation of electrolyte distribution, enhanced blood flow, and membrane stabilization (Grumme et al., 1995). While it had previously been thought that the benefits of corticosteroids could arise from reductions in ICP, several studies have suggested limitations in their usage for that purpose. For example, focal lesions seem to respond well to corticosteroid therapy, while diffuse intracerebral lesions and hematomas are less responsive (Cooper et al., 1979; Grumme et al., 1995).

In the wake of several large-scale trials, questions were brought forth regarding the safety of corticosteroid administration. Alderson and Roberts (1997) conducted a systematic review of the existing literature and concluded that there was a 1.8% improvement in mortality associated with corticosteroid use. However, their 95% confidence interval ranged from a 7.5% reduction to a 0.7% increase in deaths. Roberts et al. (2004) studied corticosteroid use in ABI with the goal of recruiting 20,000 patients with TBI; after 10,008 patients were recruited it became clear that corticosteroid use caused significant increases in mortality and the trial was halted. The authors also conducted a systematic review and meta-analysis of existing trials using corticosteroids for head injury. Before the CRASH trial, a 0.96 relative risk of death was seen in the corticosteroid group. Once the patients from the CRASH trial were added, the relative risk changed to 1.12. The authors suggest that based on this large multinational trial, corticosteroids should not be used in head injury care no matter the severity of injury.

The AANS stated that steroid use was not recommended for reducing ICP or improving outcomes, and that high-dose methylprednisolone was associated with increased mortality (Carney et al., 2017). The earlier EBIC stated that there was no established indication for the use of steroids in acute head injury management (Maas et al., 1997).

Table 15.15 Miscellaneous Outcomes - Corticosteroids for Acute Management Post ABI

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Methylprednisolone		
Roberts et al. (2004) International RCT PEDro=10 N=10,008	Population: ABI; Mean Age=37 yr; Gender: Male=6104, Female=1904; Median Time Post Injury=3 hr; Severity: Mild=3002, Moderate=3040, Severe=3966. Intervention: Patients were randomized to receive either methylprednisolone (n=5007) or placebo (n=5001). Methylprednisolone was administered intravenously at a loading dose of 2 g/hr in a 100 mL infusion and maintained at 0.4 g/hr for 48 hr in a 20 mL/hr infusion. Outcomes were assessed at 2 wk post treatment. Outcome Measure: Mortality.	<ol style="list-style-type: none"> 1. Compared with the placebo group, the risk of death was higher in the methylprednisolone group (RR=1.18; p=0.0001). 2. Relative risk of death did not differ by injury severity (p=0.22) or time post injury (p=0.05).
Giannotta et al. (1984) USA RCT PEDro=7 N=88	Population: TBI; Time Post Injury≤6 hr; GCS Ranges≤8. Intervention: Patients were randomized to receive high-dose methylprednisolone (n=38; 30 mg/kg/6 hr for 2 doses, 250 mg/6 hr for 8 doses, then tapered), low-dose methylprednisolone (n=34; 1.5mg/kg/6hr for 2 doses, 25 mg/6 hr for 8 doses, then tapered), or placebo (n=16) over 8 days. Outcome Measures: Glasgow Outcome Scale (GOS), Mortality.	<ol style="list-style-type: none"> 1. At 6 mo, there was no significant difference in mortality or morbidity between groups. 2. For patients younger than 40 yr, there was a combined 43% mortality in the low dose and placebo groups compared to a 6% mortality in the high dose group (p<0.05).
Saul et al. (1981) USA RCT PEDro=4 N=100	Population: TBI; Mean Age=31 yr; Time Post Injury≤6 hr; GCS Ranges≤7. Intervention: Patients were randomized receive to either intravenous methylprednisolone (250 mg bolus followed by a continuous 125 mg/6 hr infusion) or no drug. Outcome Measure: Glasgow Outcome Scale (GOS).	<ol style="list-style-type: none"> 1. At 6mo, no significant difference was seen in proportion of GOS=3-5 compared to GOS=1-2 between groups (p=0.22).
Oliynyk et al. (2016) Ukraine & Poland Case Series N=267	Population: Severe TBI. Intervention: Retrospective analysis of patients with sepsis and acute respiratory distress syndrome (ARDS) secondary to severe TBI who were administered Solu-Medrol (methylprednisolone) for 3 days (500 mg/ day), followed by reductions in dosage by one-half every 3 days after. Patients were further analysed based on the type of respiratory support they received to treat their ARDS: controlled volume forced expiration, or Biphasic Positive Airway Pressure [BiPAP]).	<ol style="list-style-type: none"> 1. Patient mortality decreased by 1.24x when BiPAP mechanical ventilation was used compared to volume-controlled forced ventilation (5-7mL/kg) (p=0.01). For the patients who survived, the duration of BiPAP ventilation was 1.32x shorter than forced ventilation with volume control duration. 2. Corticosteroids improved mortality rate with both ventilation systems. For dead patients, corticosteroids prolonged

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
	Outcome Measure: Mortality.	ventilation time (all $p < 0.01$) and for surviving patients, the ventilation period was shortened (both $p < 0.01$).
Dexamethasone		
Dearden et al. (1986) UK RCT PEDro=4 N=130	Population: TBI; Age Range=3-79 yr; Gender: Male=93, Female=37; Time Post Injury: ≤ 8 hr=93, > 8 hr=37; Severity: Mild/Moderate=23, Severe=107. Intervention: Patients randomized to receive either IV bolus of dexamethasone (n=68) or placebo (n=62). Dexamethasone was administered intravenously at 100 mg/ days on days 1-3, 50 mg/ days on day 4, and 25 mg on day 5. Outcome Measure: Glasgow Outcome Scale (GOS).	<ol style="list-style-type: none"> GOS score at 6 mo was worse in the steroid group than the placebo group (49% versus 35.5% dead or vegetative), but the difference was not significant ($p > 0.05$). Patients in the steroid group with ICP > 20 mmHg and > 30 mmHg showed significantly poorer outcomes on GOS compared to similar patients in the placebo group ($p < 0.05$).
Braakman et al. (1983) Netherlands RCT PEDro=4 N=161	Population: TBI; Time Post Injury < 6 hr; Severity: Severe. Intervention: Patients were randomized to receive either high-dose dexamethasone (n=81) or placebo (n=80). After a 100 mg intravenous (IV) dose, Dexamethasone was administered IV at 100 mg/ day from days 1-4, at 16 mg/ day IV or intramuscularly (IM) from days 5 to 7, and at 12 mg, 8 mg, 4 mg IV or IM on day 8, 9, and 10, respectively. Outcome Measures: Glasgow Outcome Scale (GOS), Mortality.	<ol style="list-style-type: none"> No significant differences were seen in 1mo mortality rates or in 6 mo GOS scores between groups.
Kaktis & Pitts et al. (1980) USA RCT PEDro=4 N=115	Population: ABI. Intervention: Patients were randomized to receive one of "mega dose" dexamethasone (50 mg, then 25 mg/ 6hr), conventional dose dexamethasone (10 mg, then 4 mg/6 hr) or saline placebo for a maximum of 7 days or until awakening. Outcome Measures: Infections of Cerebrospinal Fluid (CSF), Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH), Hyperglycemia.	<ol style="list-style-type: none"> Infections of the cerebrospinal fluid was significantly higher in the mega dose group than conventional dose and placebo groups (8% versus 0% versus 0%, $p < 0.025$). SIADH was significantly more prevalent in the conventional dose group than the mega dose and placebo groups (19% versus 10% versus 0%, $p < 0.05$). Hyperglycemia was more prevalent in the mega and conventional dose groups than the placebo (35% versus 34% versus 11%, $p = 0.05$).
Cooper et al. (1979) USA RCT PEDro=8 N=76	Population: TBI; Mean Age=25.6 yr; Gender: Male=59, Female=17; Mean GCS=5.23. Intervention: Patients were randomized to receive one of low-dose dexamethasone (n=25; 10 mg initially, then 4 mg every 6 hr), high-dose dexamethasone (n=24; 60 mg initially, then 24 mg every 6 hr), or placebo (n=27). Outcome Measures: Intracranial Pressure (ICP), Glasgow Outcome Scale (GOS).	<ol style="list-style-type: none"> No significant difference was seen between groups in terms of ICP or 6 mos GOS score.

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Glucocorticoids		
Watson et al. (2004) USA Cohort N=404	Population: TBI; <i>Glucocorticoid</i> (n=125): Mean Age=33 yr; Gender: Male=100, Female=25. <i>Control</i> (n=279): Mean Age=35 yr; Gender: Male=209, Female=70. Intervention: Patients treated with glucocorticoids were compared to those not receiving them (control). Outcome Measures: Incidence of Post-Traumatic Seizures (PTS).	<ol style="list-style-type: none"> 1. One hundred and five patients received glucocorticoids within 1 day of their injury, and 20 received them ≥ 2 days. 2. Patients receiving glucocorticoids within 1 day were more likely to develop first late PTS than were those without (HR=1.74, p=0.04). 3. Those receiving glucocorticoids ≥ 2 days post injury had no similar associations with PTS (HR=0.77, p=0.66). 4. Glucocorticoid administration was not associated with second late PTS development in any group.
Triamcinolone		
Grumme et al. (1995) Germany RCT PEDro=9 N=396	Population: TBI; <i>Triamcinolone</i> (n=187): Mean Age=31 yr; Gender: Male=154, Female=33. <i>Placebo</i> (n=209): Mean Age=31 yr; Gender: Male=168, Female=41. Intervention: Patients were randomized to receive either triamcinolone or placebo. Triamcinolone was administered intravenously at 200 mg within 4 hr of injury, followed by 3x40 mg/day for 4 days and 3x20 mg/ day for 4 days. Outcome Measure: Glasgow Outcome Scale (GOS).	<ol style="list-style-type: none"> 1. No significant difference was observed between groups in GOS at discharge or at 1 yr follow-up. 2. A significantly greater proportion of patients with GCS<8 and focal lesions treated with triamcinolone achieved good outcomes on GOS compared to those treated with placebo (16/46 versus 10/47, p=0.0145).

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

Two studies assessed methylprednisolone in ABI management. The studies reported either no difference in morbidity (Giannotta et al., 1984; Saul et al., 1981), or a decrease in mortality (Giannotta et al., 1984) when compared to controls. It is important to note that the decrease in mortality in the study by Giannotta et al. was only observed in patients under 40 years of age receiving high dose methylprednisolone, and not any other group. In light of a series of inconclusive studies concerning the effectiveness and safety of corticosteroid use, a very large multinational randomized collaboration for assessment of early methylprednisolone administration was initiated in 1999 (Roberts et al., 2004). The study never reached its conclusion and was stopped early due to increased mortality in the methylprednisolone group. A relative mortality risk of 1.8 (P=0.0001) was reported in the treatment group and as a result the authors suggest that corticosteroids should not be used for the treatment of ABI regardless of injury severity, or refractoriness to first line treatments. Despite the recommendations put forth by this study, a group analyzed the effects of Solu-Medrol (methylprednisolone) in patients with ARDS secondary to sepsis post ABI (Oliynyk et al., 2016). It was found that both the type of mechanical ventilation received (BiPAP) and methylprednisolone reduced mortality rates in the patient population. The findings of this study suggest that while methylprednisolone is contraindicated as a first line ABI treatment, it might be effective in improving specific complications that develop post-ABI. In light of the overwhelming evidence warning

against methylprednisolone use however, extreme caution should be applied when trying to interpret this finding outside of the specific setting in which it was studied.

Four RCTs were found that assessed dexamethasone in ABI. While one study reported no difference in morbidity or mortality (Braakman et al., 1983), other studies reported non-significant decreases in morbidity (Dearden et al., 1986) and an increase in dose-specific complications such as CSF infections, SIADH, and hyperglycemia (Kaktis & Pitts, 1980) when compared to placebo. Lastly, Cooper et al. (1979) compared doses of dexamethasone and their effects on lowering ICP and neurological outcomes (GOS). They found that regardless of the dose of dexamethasone received (low or high), there were no significant differences in ICP or neurological outcomes at 6 months between groups. Given the results of this study, and the guideline recommendations against the use of corticosteroids for ICP management, corticosteroids may not be effective agents in lowering ICP post ABI.

In a cohort study conducted by Watson et al. (2004) patients receiving any form of glucocorticoid therapy (dexamethasone 98%, prednisone 2.4%, methylprednisone 1.6%, or hydrocortisone 1.6%) were compared to patients treated without corticosteroids for the risk of development of post-traumatic seizures (PTS). The researchers noted that patients receiving glucocorticoid treatment on the first day post injury were at increased risk of developing first late seizures compared to patients receiving no treatment. There was no increased risk of PTS in patients receiving treatment after the first day. The authors suggest that this adds further strength to the argument against routine corticosteroid use in TBI (Watson et al., 2004).

Grumme et al. (1995) conducted a RCT in which GOS scores were assessed one year after injury in patients treated with the synthetic corticosteroid triamcinolone. While no overall effect was found between groups, a significant increase in beneficial outcomes was seen in patients who had both a GCS<8 and a focal lesion. The authors suggest that in light of this evidence, patients with both GCS<8 and a focal lesion would benefit from steroid administration immediately after injury.

Conclusions

There is conflicting (level 1b) evidence that methylprednisolone increases mortality rates compared to placebo in individuals post ABI. The largest trial strongly recommends against its use due to increased mortality.

There is level 1b evidence that high (60 mg loading dose, 24 mg every 6 hr) and low (10 mg loading dose, 4 mg every 6 hr) dose dexamethasone are the same as placebo at improving intracranial pressure, and neurological outcomes (6 mo) post TBI.

There is conflicting (level 2) evidence that dexamethasone increases mortality and the rate of complications (hyperglycemia, cerebral spinal fluid infections) when compared to placebo post ABI.

There is level 1b evidence that triamcinolone may improve outcomes compared to placebo in individuals post ABI with a Glasgow Coma Scale score less than 8 and a focal lesion.

There is level 2 evidence that glucocorticoid administration on the first day post-injury may increase the risk of developing first late seizures compared to placebo.

There is level 4 evidence that methylprednisolone improves mortality rates in patients with acute respiratory distress syndrome secondary to sepsis post ABI.

Corticosteroids such as methylprednisolone, dexamethasone, and other glucocorticoids may worsen outcomes, and should not be used. However, methylprednisolone may be effective at improving mortality when specific complications, such as acute respiratory distress syndrome secondary to sepsis, arise.

Triamcinolone may improve outcomes in individuals post ABI with a Glasgow Coma Scale score less than 8 and a focal lesion.

15.1.3.10 Other Medications

In addition to the aforementioned medications, other pharmacological interventions have been evaluated for effectiveness in reducing elevated ICP post ABI, including analgesics, hormones, and selective inhibitors.

Table 15.16 Other Medications for the Acute Management of Intracranial Pressure Post ABI

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Van Haren et al. (2013) USA RCT PEDro=6 N=35	Population: TBI; <i>Vasopressin</i> (n=42): Mean Age=40 yr; Gender: Male=34, Female=6; Mean Time Post Injury=16 hr; GCS Severity: Severe=71%. <i>Catecholamine</i> (n=54): Mean Age=38 yr; Gender: Male=44, Female=10; Mean Time Post Injury=56 hr; GCS Severity: Severe=87%. Intervention: Participants were randomized to receive vasopressin (1.2 U/hr, increased to a maximum of 4 U/hr) or catecholamine. Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Length of Stay (LOS), Mortality.	<ol style="list-style-type: none"> 1. There was no significant difference between groups in improvements to ICP monitoring (p=0.695), CPP minimum (p=0.642), CPP<60 mmHg duration (p=0.365), ICP maximum (p=0.091), or ICP>20mmHg duration (p=0.095). 2. There was no significant difference between groups in LOS in ICU (p=0.747) or hospital (p=0.230). 3. There was no significant difference between groups in mortality (p=0.641).
Galton et al. (2011) USA RCT PEDro=6 N=10	Population: TBI; <i>Conivaptan</i> (n=5): Mean Age=47.8 yr; Gender: Male=4, Female=1; Time Post Injury>24 hr; Mean GCS=4.4. <i>Control</i> (n=5): Mean Age=50.2 yr; Gender: Male=3, Female=2; Time Post Injury>24 hr; Mean GCS=5.0. Intervention: Participants were randomized to receive a single 20 mg dose of conivaptan or standard acute care (control). Outcome Measures: Intracranial Pressure (ICP), Serum Sodium.	<ol style="list-style-type: none"> 1. Conivaptan group had significantly lower ICP (p=0.046) and higher serum sodium (p=0.020) at 4 hr compared to control.
Picetti et al. (2014) Italy	Population: TBI=10, SAH=18, ICH=2, Stroke=2; Mean Age=54.2 yr; Gender: Male=14, Female=18; Median GCS=8.	<ol style="list-style-type: none"> 1. There was a significant reduction in ICP at 2 hr after paracetamol infusion (p=0.0002).

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Case Series N=32	Intervention: Participants who received paracetamol were retrospectively analyzed. Outcome Measures: Intracranial Pressure (ICP), Core Body Temperature (Tc), Mean Arterial Pressure (MAP), Cerebral Perfusion Pressure (CPP).	2. There were significant decreases in Tc (p=0.0001), MAP (p=0.0006), and CPP (p=0.0033) after paracetamol infusion.

Discussion

In a small clinical trial, conivaptan demonstrated decreased ICP and increased serum sodium post ABI when compared to standard acute care, which included osmolar therapy, sedation, analgesia, and/or head/body positioning (Galton et al., 2011). In a later trial, it was reported that vasopressin and catecholamine treatment yielded similar improvements to ICP and CPP post TBI (Van Haren et al., 2013). In addition, there was no significant differences in morbidity and mortality between treatments as demonstrated by similar hospital LOS, and mortality between groups. Given the limited research on each of these medications, additional clinical trials are required to make firm conclusions.

In a retrospective study, paracetamol (acetaminophen) was found to significantly reduce ICP, CPP, MAP, and core body temperature post TBI (Picetti et al., 2014). Despite the improvement in ICP, the decrease in CPP and MAP caused by paracetamol could further exacerbate the injury and thus nullify any potential improvements made by reducing ICP. Given the limited research of paracetamol use in ICP management, additional clinical trials are required to make firm conclusions.

Conclusions

There is level 1b evidence that conivaptan is superior to standard care (e.g. osmolar therapy, sedation, analgesia) in lowering elevated intracranial pressure post ABI.

There is level 1b evidence that vasopressin and catecholamine treatment are likely similar in lowering elevated intracranial pressure, improving hospital length of stay and mortality post ABI.

There is level 4 evidence that paracetamol may lower elevated intracranial pressure, cerebral perfusion pressure, mean arterial pressure, and core body temperature post ABI.

Conivaptan is likely superior to standard therapy at lowering intracranial pressure post ABI.

Vasopressin and catecholamine treatment may be similar for improving intracranial pressure, morbidity and mortality outcomes post ABI.

Elevated intracranial pressure may be effectively reduced by paracetamol, however concurrent decreases in cerebral perfusion, mean arterial pressure, and core body temperature can be expected.

15.1.4 Osmolar Interventions

Osmolar therapy is a major treatment approach in controlling intracranial hypertension and edema following ABI. Although mannitol is the drug most widely used in this regard, saline has gained popularity and some studies have called for examination of it as a primary measure for ICP control (Horn et al., 1999; Ware et al., 2005). Although no longer used as a first-line treatment, studies have begun to investigate the use of urea in specific ABI cases where the common therapies - mannitol, HTS - are not appropriate.

15.1.4.1 Hypertonic Saline

Hypertonic saline (HTS) exerts its effect mainly by increasing serum sodium concentrations and plasma osmolality, thereby increasing the osmotic gradient between the intracellular and extracellular compartments. The increased osmotic gradient allows water to passively diffuse from the cerebral intracellular and interstitial space into blood capillaries, causing a reduction in water content and ICP (Khanna et al., 2000). While mannitol works in a similar manner, HTS has a better reflection coefficient (1.0 versus 0.9) making HTS less likely to cross the Blood Brain Barrier (BBB) and allowing it to act as a more effective osmotic agent (Suarez, 2004). In addition, it has also been proposed that HTS normalizes resting membrane potential and cell volume by restoring normal intracellular electrolyte balance in injured cells (Khanna et al., 2000).

Despite increasing use of HTS in individuals with ABI, the AANS concluded that there was insufficient evidence available to support a formal recommendation (Carney et al., 2017). The EBIC made no recommendations for the use of HTS.

Table 15.17 Hypertonic Saline for the Acute Management of Intracranial Pressure Post ABI

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Jagannatha et al. (2016) India RCT PEDro=5 N=38	<p>Population: TBI; <i>Hypertonic Saline (HTS, n=18)</i>: Mean Age=27 yr; Gender: Male=16, Female=2; Mean Time Post Injury=6.1 hr; Median GCS=4. <i>Mannitol (MAN, n=20)</i>: Mean Age=31 yr; Gender: Male=18, Female=2; Mean Time Post Injury=6.7 hr; Median GCS=5.</p> <p>Intervention: Participants were randomized to receive HTS (3%) or MAN (20%). Outcomes were assessed daily for 6 days.</p> <p>Outcome Measures: Intracranial Pressure (ICP), Mean Arterial Pressure (MAP), Heart Rate (HR), Blood Glucose, Fluid Balance, Serum Osmolality, Serum Sodium.</p>	<ol style="list-style-type: none"> 1. There was no significant difference between groups in reduction in ICP (p=0.135). 2. Blood Glucose significantly decreased over 6 d in the HTS group (p=0.003). 3. There was no significant difference in Blood Glucose over 6 d in the MAN group (p=0.36). 4. There was no significant difference in HR, MAP, Fluid Balance, Serum Osmolality, or Serum Na+ (all p>0.05) for both MAN and HTS groups over 6 days.

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Jagannatha et al. 2018 India Post-Hoc Analysis N= 38	Intervention: A post-hoc analysis of the study conducted by Jagannatha et al. (2016), focusing on comparing urinary sodium and urine osmolarity in the HTS and Mannitol groups. Outcome Measures: Urinary Sodium, Urinary Osmolarity.	<ol style="list-style-type: none"> 1. Urinary sodium excretion was significantly higher in the HTS group compared to the Mannitol group ($p=0.02$) 2. Urinary Osmolarity was not different between groups ($=0.63$)
Bourdeaux et al. (2011) UK RCT PEDro=6 N=11	Population: TBI; Age>16 yr. Intervention: Participants were randomized to receive 5% hypertonic saline (HTS, $n=10$) or 8.4% sodium bicarbonate (SBC, $n=10$). Outcome Measure: Intracranial Pressure (ICP).	<ol style="list-style-type: none"> 1. Overall, there was a significant decrease in ICP at all time points ($p<0.001$). 2. There was no significant difference in ICP with time between HTS and SBC ($p=0.504$). 3. After 150 min, the mean ICP was higher in HTS group compared to SBC group ($p<0.05$).
Cottenceau et al. (2011) Israel RCT PEDro=6 N=47	Population: TBI; <i>Hypertonic Saline (HTS, $n=22$):</i> Mean Age=42.7 yr; Median GCS=5. <i>Mannitol (MAN, $n=25$):</i> Mean Age=36.1 yr; Median GCS=7. Intervention: Participants were randomized to receive HTS (7.5%, 2 mL/kg) or MAN (20%, 4 mL/kg). Outcomes were assessed at baseline, 30 min, 120 min, and 6 mo. Outcome Measures: Intracranial Pressure (ICP), Mean Arterial Pressure (MAP), Cerebral Perfusion Pressure (CPP), Global Cerebral Blood Flow Oxygen (CBF), Arterial Jugular Difference for Oxygen Content (AVDO ₂), Global Cerebral Metabolic Rate of Oxygen (CMRO ₂).	<ol style="list-style-type: none"> 1. The HTS group had significantly greater CBF when compared to the MAN group ($p=0.0087$) over time. 2. There was no significant difference between groups over time in ICP, MAP, CPP, AVDO₂, or CMRO₂ (all $p>0.05$).
Battison et al. (2005) UK RCT Crossover PEDro=5 N=9	Population: TBI=6, SAH=3. Intervention: Participants received intravenous infusions of 20% mannitol (200 mL), a solution of 7.5% hypertonic saline (100mL) and 6% dextran-70 (HSD) over 5 min in a randomized order. Outcomes were assessed before and after treatment. Outcome Measure: Intracranial Pressure (ICP).	<ol style="list-style-type: none"> 1. Both mannitol and HSD were effective in reducing ICP. 2. HSD caused a significantly greater decrease in median ICP than mannitol (13 mmHg versus 7.5 mmHg, $p=0.044$). 3. HSD had a longer duration of effect than mannitol ($p=0.044$).
Harutjunyan et al. (2005) Germany RCT PEDro=5 N=40	Population: TBI; <i>Hypertonic Saline group (HTS; $n=17$):</i> Mean Age=47 yr; Gender: Male=9, Female=8; Mean GCS=6. <i>Mannitol group (MAN; $n=15$):</i> Mean Age=47 yr; Gender: Male=8, Female=7; Mean GCS=5.8. Intervention: Patients at risk of increased ICP were randomized to receive either 7.2% hypertonic saline or 15% mannitol. Treatment was stopped when ICP was <15 mmHg. Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Heart Rate (HR), Mean Arterial Pressure (MAP).	<ol style="list-style-type: none"> 1. There was no significant difference over time or between groups for HR (all $p>0.05$). 2. There was no significant difference in MAP between groups ($p>0.05$). 3. There was a significant reduction in ICP over time for both the HTS and MAN groups (all $p<0.0001$), however, there was no significant difference between groups ($p>0.05$). 4. There was a significant increase in CCP over time for both the HTS and MAN groups (all $p<0.0001$); with the HTS group

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
		significantly higher than the MAN group (p<0.05).
Cooper et al. (2004) Australia RCT PEDro=9 N=229	<p>Population: TBI; <i>Hypertonic Saline (HTS, n=114)</i>: Mean Age=38 yr; Gender: Male=75, Female=39; Mean GCS=4. <i>Ringer's Lactate Solution (RLS, n=115)</i>: Mean Age=37 yr; Gender: Male=76, Female=39; Mean GCS=4.</p> <p>Intervention: Participants were randomized to receive intravenous infusion of 7.5% HTS (250 mL) or RLS (250 mL). Outcomes were assessed at discharge, 3 mo, and 6 mo.</p> <p>Outcome Measures: Glasgow Coma Scale (GCS), Glasgow Outcome Scale (GOS), GOS Extended (GOSE), Length of Stay (LOS), Functional Independence Measure (FIM), Rancho Los Amigos Scale (RLAS), Return to Work (RTW), Survival, Intracranial Pressure (ICP).</p>	<ol style="list-style-type: none"> Survival rate was similar in HTS and RLS at discharge (55% versus 50%, p=0.32), 3 mo (55% versus 48%, p=0.26), and 6 mo (55% versus 47%, p=0.23). LOS was similar in HTS and TLS at discharge (12 days versus 11 days, p=0.52). Median GCS was similar in both groups at 3 mo (15, p=0.62) and 6 mo (15, p=0.96). Median GOS was similar in both groups at 3 mo (4, p=0.64) and 6 mo (4, p=0.43). Median GOSE was similar in both groups at 3 mo (5, p=0.65) and 6 mo (5, p=0.45). Median FIM was similar in HTS and RLS at 3 mo (97.5 versus 99.6, p=0.76) and 6 mo (109 versus 109, p=0.96). Median RLAS was similar in HTS and RLS at 3 mo (6.82 versus 7.15, p=0.24) and 6 mo (7.32 versus 7.57, p=0.22). RTW was similar in HTS and RLS at 3 mo (51% versus 48%, p=0.35) and 6 mo (62% versus 53%, p=0.17). There was no significant difference between groups in those with baseline GCS\geq5 (n=101, p=0.48), shorter time to treatment (<60 min; n=95, p=0.26), or longer time to treatment (>60 min; n=96, p=0.85). Median ICP after treatment was not significantly different between groups
Violet et al. (2003) France RCT PEDro=7 N=20	<p>Population: TBI; <i>Hypertonic Saline (HTS, n=10)</i>: Mean Age=35 yr; Gender: Male=5, Female=5; Mean GCS=4.7. <i>Mannitol (MAN, n=10)</i>: Mean Age=31 yr; Gender: Male=4, Female=6; Mean GCS=6.0.</p> <p>Intervention: Participants were randomized to receive intravenous infusions of 7.5% HTS or 20% MAN. Infused volume was the same for both medications: 2 ml/kg of body weight in 20min. Outcomes were assessed over a mean of 7 days.</p> <p>Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Glasgow Outcome Scale (GOS), Mortality.</p>	<ol style="list-style-type: none"> HTS had significantly fewer mean episodes of ICP>25 mmHg per day (6.9 versus 14.6, p<0.01) and shorter mean daily duration of these episodes (67 min versus 131 min, p<0.01) than MAN. There was no significant difference between HTS and MAN in mean episodes of CPP<70 mmHg (4.0 versus 3.1, p>0.05) or mean daily duration of these episodes (58 min versus 62 min, p>0.05). Failure of treatment was significantly greater in MAN than HTS (70% versus 10%, p=0.01). There was no significant difference between HTS and MAN in poor GOS (60% versus 50%, p>0.05) or mortality (40% versus 50%, p>0.05).

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Shackford et al. (1998) USA RCT PEDro=5 N=34	<p>Population: TBI. <i>Hypertonic Saline (HTS, n=18)</i>: Mean Age=33 yr; Gender: Male=17, Female=1; Mean GCS=4.7. <i>Ringer's Lactate Solution (RLS, n=16)</i>: Mean Age=31 yr; Gender: Male=10, Female=6; Mean GCS=6.7.</p> <p>Intervention: Participants were randomized to receive intravenous infusions of 1.6% HTS or RLS.</p> <p>Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Glasgow Outcome Scale (GOS).</p>	<ol style="list-style-type: none"> 1. Mean ICP was significantly greater in the HTS than RLS at baseline ($p<0.05$). 2. Mean ICP decreased in both groups, and there were no significant differences between groups in ICP at any time after entry ($p>0.05$). 3. Average total number of interventions to control ICP was significantly greater in the HTS than in the RLS ($p<0.01$). 4. Change in maximum ICP was positive in the RLS group but negative in the HTS group (-9.1 mmHg versus +2.5 mmHg, $p<0.05$). 5. There were no significant differences between the HTS and RLS in mean GOS at discharge (2.7 versus 2.5, $p>0.05$).
Tan et al. (2016b) Canada Case Control N=231	<p>Population: TBI; <i>Hypertonic Saline (HTS, n=124)</i>: Mean Age=31 yr; Gender: Male=99, Female=25; Mean GCS=5. <i>Control (n=107)</i>: Mean Age=40 yr; Gender: Male=82, Female=25; Mean GCS=6.</p> <p>Intervention: Participants who received HTS or did not (controls) were compared in retrospective analysis.</p> <p>Outcome Measures: Mortality, Intracranial Pressure (ICP), Length of Stay (LOS), Additional Treatments.</p>	<ol style="list-style-type: none"> 1. HTS and control groups were significantly different in mean age ($p<0.001$). 2. There was no significant difference in hospital mortality between HTS and control groups (28 versus 31, $p=0.34$), and HTS was not an independent predictor of hospital mortality (HR 1.07, $p=0.84$). 3. HTS group showed a significant decrease in ICP (4 mmHg, $p<0.001$), while controls did not (<2 mmHg, $p=0.14$). 4. Mean values were significantly higher in the HTS group than in the controls for LOS in ICU (15 versus 8, $p<0.001$), desmopressin use (24 versus 9, $p=0.03$), and mannitol use (63 versus 20, $p<0.001$). 5. There was significant association between HTS use and hypernatremia ($p<0.001$). 6. There was no association between hypernatremia and mortality ($P=0.53$). 7. In the HTS group, desmopressin use was associated with increased hospital mortality (HR 4.27, $p<0.001$), but mannitol use (HR 1.13, $p=0.58$) was not.
Major et al. (2015) UK Case Series N=15	<p>Population: TBI; Mean Age=36 yr; Gender: Male=11, Female=4.</p> <p>Intervention: Participants who received a single bolus of 30% hypertonic saline (HTS) were included in retrospective analysis.</p> <p>Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Mean Arterial Pressure (MAP), Heart Rate (HR).</p>	<ol style="list-style-type: none"> 1. There was a rapid and significant reduction in ICP over 8 hr ($p=0.0004$). 2. There was no significant difference in CPP, MAP, or HR (all $p>0.05$).

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Mangat et al. (2015) USA Case Control N=1238	<p>Population: TBI; <i>Hypertonic Saline (HTS, n=45)</i>: Mean Age=38.37 yr; Mean GCS=5.46. <i>Mannitol (MAN, n=477)</i>: Mean Age=36.13 yr; Mean GCS=4.75. <i>Hypertonic Saline & Mannitol (HTS+MAN; n=137)</i>: Mean Age=31.42 yr; Mean GCS=4.82. <i>Control (n=589)</i>: Mean Age=42.63 yr; Mean GCS=4.96.</p> <p>Intervention: Patients who received HTS, MAN, or neither (control) were retrospectively analyzed.</p> <p>Outcome Measures: Intracranial Pressure (ICP) Length of Stay (LOS), Mortality.</p>	<ol style="list-style-type: none"> 1. There was no significant difference in total number of ICP recording days between the HTS and MAN groups (p=0.09). 2. The cumulative and daily ICP burdens were significantly lower in patients who received HTS compared to patients who received MAN (p=0.003 and p=0.001, respectively). 3. LOS was significantly lower in the HTS compared to MAN with a 1:1 match (p=0.004); however, this became insignificant with a 1:2 match (p=0.06). 4. There was no significant difference between HTS and MAN in mortality rate (p=0.53).
Colton et al. (2014b) USA Case Series N=117	<p>Population: TBI; Mean Age=40.0 yr; Gender: Male=93, Female=24; Median GCS=6.</p> <p>Intervention: Participants were included in retrospective analysis after having received one of the following ICP therapies: hypertonic saline (HTS), mannitol, propofol, fentanyl, and barbiturates.</p> <p>Outcome Measure: Intracranial Pressure (ICP).</p>	<ol style="list-style-type: none"> 1. Treatment with HTS resulted in the largest ICP decrease of the treatments examined. 2. Propofol and fentanyl escalations resulted in smaller but significant ICP reductions. 3. Mannitol resulted in statistically insignificant reductions in the first hr but rebounded by the second hr.
Colton et al. (2014c) USA Case Series N=46	<p>Population: TBI; Mean Age=34.4 yr; Gender: Male=37, Female=9; Median GCS=6.</p> <p>Intervention: Participants who received hypertonic saline (HTS) were included in retrospective analysis.</p> <p>Outcome Measures: Intracranial Pressure (ICP), Mean Arterial Pressure (MAP), Cerebral Perfusion Pressure (CPP).</p>	<ol style="list-style-type: none"> 1. ICP was significantly reduced from 21.5 mmHg to 14.4 mmHg immediately after HTS (p<0.05) and to 12.5mmHg 2 hr after HTS (p<0.05). 2. There was no significant difference in MAP or CPP after HTS.
Dias et al. (2014) Portugal Pre-Post N=11	<p>Population: TBI; Mean Age=40 yr; Gender: Male=9, Female=2; Mean GCS=6.</p> <p>Intervention: Participants received 20% hypertonic saline (HTS). Outcomes were assessed before and after treatment.</p> <p>Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Cerebral Blood Flow index (CBFx), Cerebrovascular Pressure Reactivity Index (PRx).</p>	<ol style="list-style-type: none"> 1. Mean ICP decreased significantly from 20.5 to 14.3 mmHg at 128 min (p<0.001), with a final value of 16.8mmHg at 210 min. 2. Mean CPP increased significantly from 85.1 to 88.2 mmHg at 119 min (p<0.001), with a final value of 86.3mmHg at 210 min. 3. Significant improvements in CBFx (p=0.04) and PRx (p=0.01) were found after treatment.
Lewandowski-Belfer et al. (2014) USA Case Series N=55	<p>Population: TBI; Mean Age=50.1 yr; Gender: Male=24, Female=31.</p> <p>Intervention: Participants who received hypertonic saline (HTS) were included in retrospective analysis. Patients were divided based on HTS concentration (14.6% or 23.4%).</p> <p>Outcome Measures: Intracranial Pressure (ICP), Serum Sodium.</p>	<ol style="list-style-type: none"> 1. There was a significant increase in mean serum sodium after HTS administration (p<0.0001). 2. There was a significant decrease in ICP after HTS administration (p<0.0001). 3. The efficacy of 23.4% HTS in decreasing ICP was not found to be significantly different than 14.6% HTS (p=0.23).

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Eskandari et al. (2013) USA Pre-Post N=11	<p>Population: TBI; Mean Age=33.7yr; Gender: Male=10, Female=1; Mean GCS=7.18.</p> <p>Intervention: Participants received repeated 15min intravenous infusions of 14.6% hypertonic saline (HTS) over 12 hr. If after 60mins the patient once again met the criteria of having refractory ICP, then repeated boluses were administered. Outcomes were assessed for 60 min after each bolus and at 12 hr.</p> <p>Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Heart Rate (HR), Systolic Blood Pressure (SBP).</p>	<ol style="list-style-type: none"> 1. Mean ICP was reduced from 40mmHg at baseline to 33 mmHg after 5 min ($p<0.05$), to 28 mmHg after 10min ($p<0.05$), and to 23mmHg after 12hr ($p<0.05$). 2. Mean CPP increased from 60 mmHg at baseline to 63 mmHg after 5 min ($p<0.05$) and to 77 mmHg after 20 min ($p<0.05$); it was 70 mmHg by 12 hr. 3. There was no significant difference in HR or SBP after HTS treatment.
Paredes-Andrade et al. (2012) USA Case Series N=18	<p>Population: TBI; Mean Age=35 yr; Gender: Male=16, Female=2; Median GCS=6.</p> <p>Intervention: Patients who received hypertonic saline (HTS) were retrospectively analyzed.</p> <p>Outcome Measure: Intracranial Pressure (ICP).</p>	<ol style="list-style-type: none"> 1. There was a significant reduction of 8.8 mmHg in ICP ($p<0.0001$) following HTS treatment.
Roquilly et al. (2011) France Case Series N=50	<p>Population: TBI; Mean Age=36 yr; Gender: Male=46, Female=4; Mean GCS=6.</p> <p>Intervention: Patients who received hypertonic saline (HTS) were retrospectively analyzed.</p> <p>Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Plasma Osmolarity, Natremia.</p>	<ol style="list-style-type: none"> 1. ICP significantly decreased after HTS administration ($p<0.05$). 2. CPP significantly increased after HTS administration ($p<0.05$). 3. Natremia significantly increased after HTS administration ($p<0.05$). 4. Plasma Osmolarity significantly increased after HTS administration ($p<0.05$).
Sakellariadis et al. (2011) Greece Case Control N=29	<p>Population: TBI; Mean Age=36 yr; Mean GCS=5.4.</p> <p>Intervention: Participants who received hypertonic saline (HTS) or mannitol were retrospectively analyzed.</p> <p>Outcome Measures: Intracranial Pressure (ICP), Duration of effectiveness.</p>	<ol style="list-style-type: none"> 1. There was no significant difference between HTS and mannitol in reducing ICP. 2. There was no significant difference between HTS and mannitol in duration of effectiveness.
Kerwin et al. (2009) USA Cohort N=22	<p>Population: TBI; Mean Age=35.7 yr; Gender: Male=16, Female=6; Mean GCS=6.9.</p> <p>Intervention: Patients received intravenous infusions of 23.4% hypertonic saline (HTS) or mannitol (15-75 g, at the discretion of the neurosurgeon).</p> <p>Outcome Measure: Intracranial Pressure (ICP).</p>	<ol style="list-style-type: none"> 1. Mean ICP reduction was significantly greater by HTS than mannitol (9.3mmHg versus 6.4 mmHg, $p=0.0028$). 2. Patients with initial ICP>30 mmHg had a significantly greater mean ICP reduction by HTS than mannitol (12.6 mmHg versus 8 mmHg, $p=0.0105$). 3. More patients responded to HTS than mannitol (93% versus 74%, $p=0.002$). 4. HTS was more likely to yield an ICP reduction of >10 mmHg, while mannitol was more likely to yield a reduction of <5 mmHg. 5. There was no significant difference between HTS and mannitol in amount of time ICP>20 mmHg (9.7 hr versus 7.4 hr,

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
		p=0.236) or duration of response (4.1 hr versus 3.8hr, p=0.854).
Odo et al. (2009) USA Cohort N=12	<p>Population: TBI; Mean Age=36 yr; Gender: Male=9, Female=3; Mean GCS=3; Mean Time Post Injury=8 hr.</p> <p>Intervention: Participants received intravenous infusions of 7.5% hypertonic saline (HTS) or 25% mannitol.</p> <p>Outcome Measures: Intracranial Pressure (ICP), Mean Arterial Pressure (MAP), Cerebral Perfusion Pressure (CPP), Brain Tissue Oxygen Tension ($P_{bt}O_2$), Central Venous Pressure (CVP), Cardiac Output (CO).</p>	<ol style="list-style-type: none"> 1. Mean ICP was more significantly reduced ($p<0.001$) by HTS than mannitol after 60min (15 mmHg versus 23 mmHg) and 120min (15 mmHg versus 24 mmHg). 2. Mean CPP was more significantly increased by HTS than mannitol after 120min (76 mmHg versus 65 mmHg, $p=0.02$). 3. Mean CO was more significantly increased by HTS than mannitol after 30 min (7.5 L/min versus 5.3 L/min, $p=0.003$), 60 min (7.8 L/min versus 6.6 L/min, $p=0.007$), and 120min (7.5 L/min versus 6.1 L/min, $p=0.002$). 4. Mean $P_{bt}O_2$ was significantly increased by HTS ($p<0.01$) and decreased by mannitol ($p>0.05$) over time, with significant differences at 60min (37 mmHg versus 28 mmHg, $p<0.05$) and 120 min (41 mmHg versus 27.5 mmHg, $p<0.01$). 5. There were no significant differences in MAP or CVP between groups.
Rockswold et al. (2009) USA Pre-Post N=25	<p>Population: TBI; Mean Age=33.5 yr; Gender: Male=21, Female=4; Mean GCS=5.7.</p> <p>Intervention: Participants received intravenous infusions of 23.4% hypertonic saline (HTS) over 15 min. Patients were stratified into 3 different risk categories according to their presenting ICP, MAP, and CPP values at treatment time. These 3 groups represent low, medium, and high risk for being refractory to ICP management</p> <p>Outcome Measures: Intracranial Pressure (ICP), Mean Arterial Pressure (MAP), Cerebral Perfusion Pressure (CPP), Brain Tissue Oxygen Tension ($P_{bt}O_2$), Glasgow Outcome Scale (GOS), Mortality.</p>	<ol style="list-style-type: none"> 1. Mean ICP decreased by 8.3 mmHg over time ($p<0.0001$). ICP level was positively affected for all 3 groups ($P<0.05$). 2. Mean ICP reduction was positively correlated with initial ICP ($p<0.05$): 14.2 mmHg in those with ICP>31 mmHg, 9.3mmHg in those with ICP=26-30 mmHg, and 6.4 mmHg in those with ICP=20-25. 3. Mean CPP increased in those with initial CPP=60-69 mmHg ($p<0.05$) and increased even more in those with CPP>70 mmHg ($p<0.05$). 4. Mean MAP increased in those with initial MAP<79 mmHg ($p<0.05$) and decreased in those with initial MAP>100 mmHg ($p<0.05$). 5. $P_{bt}O_2$ was significantly improved at 1, 3, and 4 hrs post treatment, but not at 2, 5, and 6 hrs. 6. At 6 mos, mortality was 28% and favourable outcome (GOS).
Pascual et al. (2008) USA Pre-Post	<p>Population: TBI; Mean Age=36.5 yr; Gender: Male=9, Female=3; Mean GCS=4.5.</p> <p>Intervention: Participants received intravenous infusions of 7.5% hypertonic saline (HTS).</p>	<ol style="list-style-type: none"> 1. ICP significantly decreased after HTS (>40%, $p<0.01$) and remained significantly lower than baseline up to 4 hr (~20%, $p<0.05$).

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
N=12	Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Brain Tissue Oxygen Tension (P_{btO_2}), Mean Arterial Pressure (MAP), Central Venous Pressure (CVP), Heart Rate (HR), Cardiac Output (CO).	<ol style="list-style-type: none"> 2. CPP significantly increased after HTS (>25%, $p<0.01$) and remained significantly greater than baseline up to 6 hrs (~30%, $p<0.01$). 3. P_{btO_2} significantly increased over time after HTS ($p<0.05$). 4. There was no significant difference in MAP, CVP, HR, or CO after HTS.
Lescot et al. (2006) France Pre-Post N=14	<p>Population: TBI; Mean Age=36 yr; Gender: Male=12, Female=2; Median GCS=7.</p> <p>Intervention: Participants received intravenous infusions of 20% hypertonic saline (HTS, 40 mL) for 20 min.</p> <p>Outcome Measures: Intracranial Pressure (ICP), Contused Brain Tissue (Specific Gravity, Volume), Non-Contused Brain Tissue (Specific Gravity, Volume), Natremia.</p>	<ol style="list-style-type: none"> 1. HTS significantly increased natremia from 143 mmol/L to 146 mmol/L. 2. HTS significantly decreased ICP from 23 mmHg to 17 mmHg. 3. Volume of non-contused brain tissue decreased by 13 mL whereas the specific gravity increased by 0.029%. 4. Volume of contused brain tissue increased by 5 mL without any concomitant change in density. 5. There was wide individual variability in the response of the non-contused brain tissue, with changes in specific gravity varying between -0.0124% and 0.0998%.
Ware et al. (2005) USA Case Control N=13	<p>Population: TBI; Mean Age=42.0 yr; Gender: Male=10, Female=3; Time Post Injury<12 hr; Mean GCS=7.7.</p> <p>Intervention: Participants received intravenous infusions of 23.4% hypertonic saline (HTS) and mannitol.</p> <p>Outcome Measure: Intracranial Pressure (ICP).</p>	<ol style="list-style-type: none"> 1. Both HTS and mannitol significantly reduced ICP ($p<0.001$) and there was no significant difference between them ($p=0.174$). 2. Mean duration of ICP reduction by HTS was significantly longer than mannitol (96 min versus 59 min, $p=0.016$).
Horn et al. (1999) Germany Case Series N=10	<p>Population: TBI=6, SAH=4; Mean Age=41 yr; Gender: Male=5, Female=5; Mean GCS=5.4.</p> <p>Intervention: Participants received intravenous infusions of 7.5% hypertonic saline (HTS, 20 mL/min, 2 mL/kg) after the failure of standard agents.</p> <p>Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP).</p>	<ol style="list-style-type: none"> 1. Mean ICP significantly decreased ($p<0.05$) from 33 mmHg to 18mmHg at the time of maximum effect (~100 min). 2. Mean CPP significantly increased ($p<0.05$) from 68 mmHg to 79 mmHg after 1hr and to 81 mmHg at maximum effect.
Schatzmann et al. (1998) Germany Case Series N=6	<p>Population: TBI=5, SAH=1; Mean Age=40 yr; Gender: Male=4, Female=2; Median GCS=6.</p> <p>Intervention: Participants received intravenous infusions of 10% hypertonic saline (HTS, 100 mL) after the failure of standard agents.</p> <p>Outcome Measure: Intracranial Pressure (ICP).</p>	<ol style="list-style-type: none"> 1. ICP decreased by an average of 43% (18 mmHg) after HTS. 2. Reduction in ICP lasted for an average of 93min and minimum ICP was reached at an average of 26 min after infusion.
Qureshi et al. (1998) USA Case Series N=10	<p>Population: TBI; Mean Age=44.4 yr; Mean GCS=7.1.</p> <p>Intervention: Participants received intravenous infusion of 3% hypertonic saline/acetate solution (75-150 mL/hr).</p> <p>Outcome Measures: Intracranial Pressure (ICP), Glasgow Outcome Scale (GOS), Serum Sodium.</p>	<ol style="list-style-type: none"> 1. ICP reduction correlated with increasing serum sodium concentration ($r^2=0.91$, $p=0.03$). 2. Mean ICP was reduced from 14.2mmHg to 7.3 mmHg after treatment.

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
		3. Mean GCS improved from 7.1 to 7.4 after treatment. 4. GOS was 3.6 1 mos after treatment.

Discussion

An abundance of retrospective studies have found that HTS treatment following ABI yields a significant decrease in ICP (Colton et al., 2014a; Colton et al., 2016; Colton et al., 2014c; Horn et al., 1999; Lewandowski-Belfer et al., 2014; Li et al., 2015; Major et al., 2015; Paredes-Andrade et al., 2012; Qureshi et al., 1998; Roquilly et al., 2011; Schatzmann et al., 1998). Prospective studies have supported these findings as well, demonstrating that HTS was responsible for significant reductions in ICP and increases in CPP (Dias et al., 2014; Eskandari et al., 2013; Lescot et al., 2006; Pascual et al., 2008; Rockswold et al., 2009). While most of these studies reported on short-term outcomes, one found that the effects lasted up to 12 hours (Eskandari et al., 2013).

Hypertonic saline administration was found to have improved cerebral blood flow in one study (Dias et al., 2014) with subsequent increases in cerebral oxygenation in another (Oddo et al., 2009; Pascual et al., 2008). Thus, HTS may be a valuable component in resuscitation of patients with ABI, although further research into this matter is required. Using CT technology, Lescot et al. (2006) assessed the effectiveness of HTS on volume, weight, and specific gravity of contused and non-contused brain tissue. Three days after TBI, contused tissue was shown to increase in volume after administration of HTS. The authors recommended further research assessing the effects of HTS on different tissue types, so that the contusion site and size might be appropriately factored into clinical decisions.

While complications were largely not reported, a number of studies noted significant increases in serum sodium (Lescot et al., 2006; Lewandowski-Belfer et al., 2014; Qureshi et al., 1998; Rockswold et al., 2009; Roquilly et al., 2011; Tan et al., 2016a), and days spent in the ICU (Tan et al., 2016a) after HTS treatment. While technically considered a complication of HTS treatment, Tan et al. (2016b) reported that the hypernatremia was not associated with an increase in mortality.

Several studies have compared HTS to mannitol in terms of efficacy in lowering elevated ICP and improving long-term outcomes. While one case-control study found no significant difference between the treatments in the level or duration of ICP reduction (Sakellaridis et al., 2011), another found that HTS had a longer lasting effect (Ware et al., 2005). Two cohort studies reported significantly greater reductions in ICP from HTS than mannitol (Kerwin et al., 2009; Oddo et al., 2009), with one noting that these ICP reductions were associated with greater increases in CPP (Oddo et al., 2009). The benefits of HTS were also reported in 2 retrospective studies where HTS was compared to mannitol (Mangat et al., 2015), and mannitol, propofol, fentanyl and barbiturates (Colton et al., 2014a). Both studies described improvements in either acute (Colton et al., 2014a) or sustained (Mangat et al., 2015) ICP management, with the latter also reporting a decrease in length of hospitalization compared to mannitol.

In an RCT, Vialet et al. (2003) found that patients receiving HTS had fewer episodes of ICP hypertension and fewer clinical failures than those receiving mannitol, although clinical outcomes at three months did not differ between groups. Another small RCT demonstrated that HTS yielded a significantly greater decrease in ICP over a longer period of time when compared to mannitol (Battison et al., 2005). However, three other RCTs were identified that found no benefit of HTS over mannitol in controlling elevated ICP, despite improvements in CPP (Harutjunyan et al., 2005), Cerebral Blood Flow (Cottenceau et al., 2011), and blood glucose control (Jagannatha et al., 2016). A secondary analysis of the Jagannatha et al. (2006) study attempted to explain the lack of efficacy of HTS over mannitol and found that urinary sodium concentrations were greater in patients receiving HTS (Jagannatha et al., 2018). The authors suggested that unless sodium excretion could be reduced, the efficacy of HTS would continue to be equivalent to that of mannitol in reducing ICP.

The comparison of HTS and mannitol was not just limited to the treatment's ICP-lowering potential, but also the morbidity and mortality associated with each. Hypertonic Saline was associated with a decrease in hospital length of stay (Mangat et al., 2015); however, no differences were observed in mortality or GOS/GOSE scores when compared to mannitol (Baker et al., 2009; Cooper et al., 2004; Mangat et al., 2015; Vialet et al., 2003)

Hypertonic saline has also been compared to Ringer's lactate solution for acute management of ABI. In an early RCT, Shackford et al. (1998) reported that both treatments lead to reductions in ICP and improvements in GOS, without any significant differences between them. The authors also found that those treated with HTS required a significantly greater number of additional medical interventions to lower ICP. However, it should be noted that they had a significantly greater number of patients with severe ABI. In a later RCT, Cooper et al. (2004) found that patients receiving either treatment were similar in terms of survival, favourable outcome, cognitive functioning, functional independence, and return to work at three to six months.

Furthermore, sodium bicarbonate solutions have been compared to HTS for managing acute ABI. In a small trial, Bourdeaux et al. (2011) reported that sodium bicarbonate yielded similar ICP reductions to HTS, but that these reductions were longer lasting. Additional studies are required to determine the efficacy of albumin and sodium bicarbonate in controlling elevated ICP and improving long-term outcomes post ABI.

Conclusions

There is level 3 evidence that hypertonic saline lowers elevated intracranial pressure post ABI.

There is level 3 evidence that hypertonic saline causes an increase in serum sodium, days spent in the ICU, but not mortality in patients post ABI

There is level 4 evidence that hypertonic saline lowers elevated intracranial pressure up to 12 hours post ABI.

There is level 4 evidence that hypertonic saline increases cerebral perfusion pressure and cerebral blood flow post ABI.

There is level 4 evidence that 3 days post TBI contused brain tissue increases in volume after administration of hypertonic saline.

There is level 1a evidence that hypertonic saline is similar to mannitol in terms of mortality or Glasgow outcome scale (extended) scores in patients post TBI.

There is conflicting (level 1b) evidence as to whether hypertonic solution lowers elevated intracranial pressure more effectively than mannitol post ABI.

There is level 1b evidence that the use of hypertonic solution results in similar intracranial pressure control and clinical outcomes (cognition, mortality, functional independence, return to work) when compared to Ringer's lactate solution post ABI.

There is level 1b evidence that sodium bicarbonate is the same as hypertonic saline at lowering intracranial pressure; however, it sustains this improvement longer in patients post ABI.

There is conflicting (level 2 and level 3) evidence that hypertonic saline lowers intracranial pressure for longer compared to mannitol post ABI. The level 2 evidence suggest that it does.

There is level 2 evidence that hypertonic saline is superior to mannitol at improving cerebral perfusion pressure, cerebral blood flow, and blood-glucose control in patients post ABI.

There is level 2 evidence that urinary sodium excretion is higher in hypertonic saline patients compared to those receiving mannitol post ABI.

There is level 4 evidence that hypertonic saline is superior to barbiturates, propofol, and fentanyl at lowering intracranial pressure post ABI.

Hypertonic saline may lower elevated intracranial pressure and potentially increases cerebral perfusion pressure and blood flow post ABI. The improvement in intracranial pressure may last up to 12 hours, though short-term improvements are more common.

Hypertonic saline may increase serum sodium, time spent in the ICU, but not mortality post ABI.

Contused brain tissue may increase in volume after administration of hypertonic saline post ABI.

It is unclear whether hypertonic saline is more effective than mannitol at lowering intracranial pressure or reducing hospital length of stay.

Hypertonic saline can improve cerebral perfusion pressure, cerebral blood flow, and brain tissue oxygenation more effectively than mannitol. However, hypertonic solution is not different than mannitol in terms of morbidity and mortality associated with treatment.

Hypertonic saline is superior to barbiturates, propofol, and fentanyl at lowering intracranial pressure post TBI.

Hypertonic saline may be similar to Ringer’s lactate at improving intracranial pressure and clinical outcomes post TBI.

Hypertonic saline may have similar effects on intracranial pressure when compared to sodium bicarbonate; however, sodium bicarbonate sustains the improvement for longer periods of time.

15.1.4.2 Mannitol

Rapid administration of mannitol is among the first-line treatments recommended for the management of increased ICP. However, this treatment is reported to be associated with significant diuresis and can precipitate acute renal failure, hyperkalemia, hypotension, and in some cases rebound increments in ICP (Battison et al., 2005; Doyle et al., 2001). For these reasons, the Brain Trauma Foundation recommends that mannitol only be used if a patient has signs of elevated ICP or deteriorating neurological status. Under such circumstances the benefits of mannitol for the acute management of ICP outweigh any potential complications or adverse effects. There is also some evidence that with prolonged administration mannitol may penetrate the blood brain barrier, thereby exacerbating the elevation in ICP (Wakai et al., 2013). Despite the effectiveness of mannitol in ICP management, evidence points to HTS as a potentially more effective hyperosmotic agent.

The AANS concluded that there was insufficient evidence available to support a formal recommendation for the use of mannitol in managing patients with ABI (Carney et al., 2017).

Table 15.18 Mannitol for the Acute Management of Intracranial Pressure Post ABI

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
Jagannatha et al. (2016) India RCT PEDro=5 N=38	<p>Population: TBI; <i>Hypertonic Saline (HTS, n=18)</i>: Mean Age=27 yr; Gender: Male=16, Female=2; Mean Time Post Injury=6.1 hr; Median GCS=4. <i>Mannitol (MAN, n=20)</i>: Mean Age=31 yr; Gender: Male=18, Female=2; Mean Time Post Injury=6.7 hr; Median GCS=5.</p> <p>Intervention: Participants were randomized to receive HTS (3%) or MAN (20%). Outcomes were assessed daily for 6 days.</p> <p>Outcome Measures: Intracranial Pressure (ICP), Mean Arterial Pressure (MAP), Heart Rate (HR), Blood Glucose, Fluid Balance, Serum Osmolality, Serum Sodium.</p>	<ol style="list-style-type: none"> 1. There was no significant difference between groups in reduction in ICP (p=0.135). 2. Blood Glucose significantly decreased over 6 d in the HTS group (p=0.003). 3. There was no significant difference in Blood Glucose over 6 d in the MAN group (p=0.36). 4. There was no significant difference in HR, MAP, Fluid Balance, Serum Osmolality, or Serum Na+ (all p>0.05) for both MAN and HTS groups over 6 days.
Jagannatha et al. 2018 India Post-Hoc Analysis N= 38	<p>Intervention: A post-hoc analysis of the study conducted by Jagannatha et al. (2016), focusing on comparing urinary sodium and urine osmolarity in the HTS and Mannitol groups.</p> <p>Outcome Measures: Urinary Sodium, Urinary Osmolarity.</p>	<ol style="list-style-type: none"> 1. Urinary sodium excretion was significantly higher in the HTS group compared to the Mannitol group (p=0.02)

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
		2. Urinary Osmolarity was not different between groups (=0.63)
Cottenceau et al. (2011) Israel RCT PEDro=6 N=47	Population: TBI; <i>Hypertonic Saline (HTS, n=22)</i> : Mean Age=42.7 yr; Median GCS=5. <i>Mannitol (MAN, n=25)</i> : Mean Age=36.1 yr; Median GCS=7. Intervention: Participants were randomized to receive HTS (7.5%, 2 mL/kg) or MAN (20%, 4 mL/kg). Outcomes were assessed at baseline, 30 min, 120 min, and 6 mo. Outcome Measures: Intracranial Pressure (ICP), Mean Arterial Pressure (MAP), Cerebral Perfusion Pressure (CPP), Global Cerebral Blood Flow Oxygen (CBF), Arterial Jugular Difference for Oxygen Content (AVDO ₂), Global Cerebral Metabolic Rate of Oxygen (CMRO ₂).	1. The HTS group had significantly greater CBF when compared to the MAN group (p=0.0087) over time. 1. There was no significant difference between groups over time in ICP, MAP, CPP, AVDO ₂ , or CMRO ₂ (all p>0.05).
Battison et al. (2005) UK RCT Crossover PEDro=5 N=9	Population: TBI=6, SAH=3. Intervention: Participants received intravenous infusions of 20% mannitol (200 mL), a solution of 7.5% hypertonic saline (100mL) and 6% dextran-70 (HSD) over 5 min in a randomized order. Outcomes were assessed before and after treatment. Outcome Measure: Intracranial Pressure (ICP).	1. Both mannitol and HSD were effective in reducing ICP. 2. HSD caused a significantly greater decrease in median ICP than mannitol (13 mmHg versus 7.5 mmHg, p=0.044). 2. HSD had a longer duration of effect than mannitol (p=0.044).
Harutjunyan et al. (2005) Germany RCT PEDro=5 N=40	Population: TBI; <i>Hypertonic Saline group (HTS; n=17)</i> : Mean Age=47 yr; Gender: Male=9, Female=8; Mean GCS=6. <i>Mannitol group (MAN; n=15)</i> : Mean Age=47 yr; Gender: Male=8, Female=7; Mean GCS=5.8. Intervention: Patients at risk of increased ICP were randomized to receive either 7.2% hypertonic saline or 15% mannitol. Treatment was stopped when ICP was <15 mmHg. Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Heart Rate (HR), Mean Arterial Pressure (MAP).	1. There was no significant difference over time or between groups for HR (all p>0.05). 2. There was no significant difference in MAP between groups (p>0.05). 3. There was a significant reduction in ICP over time for both the HTS and MAN groups (all p<0.0001), however, there was no significant difference between groups (p>0.05). 3. There was a significant increase in CCP over time for both the HTS and MAN groups (all p<0.0001); with the HTS group significantly higher than the MAN group (p<0.05).
Violet et al. (2003) France RCT PEDro=7 N=20	Population: TBI; <i>Hypertonic Saline (HTS, n=10)</i> : Mean Age=35 yr; Gender: Male=5, Female=5; Mean GCS=4.7. <i>Mannitol (MAN, n=10)</i> : Mean Age=31 yr; Gender: Male=4, Female=6; Mean GCS=6.0. Intervention: Participants were randomized to receive intravenous infusions of 7.5% HTS or 20% MAN. Infused volume was the same for both medications: 2 ml/kg of body weight in 20min. Outcomes were assessed over a mean of 7 days. Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Glasgow Outcome Scale (GOS), Mortality.	1. HTS had significantly fewer mean episodes of ICP>25 mmHg per day (6.9 versus 14.6, p<0.01) and shorter mean daily duration of these episodes (67 min versus 131 min, p<0.01) than MAN. 2. There was no significant difference between HTS and MAN in mean episodes of CPP<70 mmHg (4.0 versus 3.1, p>0.05) or mean daily duration of these episodes (58 min versus 62 min, p>0.05).

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
		<ol style="list-style-type: none"> 3. Failure of treatment was significantly greater in MAN than HTS (70% versus 10%, $p=0.01$). 4. There was no significant difference between HTS and MAN in poor GOS (60% versus 50%, $p>0.05$) or mortality (40% versus 50%, $p>0.05$).
<p>Mangat et al. (2015) USA Case Control N=1238</p>	<p>Population: TBI; <i>Hypertonic Saline (HTS, n=45)</i>: Mean Age=38.37 yr; Mean GCS=5.46. <i>Mannitol (MAN, n=477)</i>: Mean Age=36.13 yr; Mean GCS=4.75. <i>Hypertonic Saline & Mannitol (HTS+MAN; n=137)</i>: Mean Age=31.42 yr; Mean GCS=4.82. <i>Control (n=589)</i>: Mean Age=42.63 yr; Mean GCS=4.96. Intervention: Patients who received HTS, MAN, or neither (control) were retrospectively analyzed. Outcome Measures: Intracranial Pressure (ICP) Length of Stay (LOS), Mortality.</p>	<ol style="list-style-type: none"> 1. There was no significant difference in total number of ICP recording days between the HTS and MAN groups ($p=0.09$). 2. The cumulative and daily ICP burdens were significantly lower in patients who received HTS compared to patients who received MAN ($p=0.003$ and $p=0.001$, respectively). 3. LOS was significantly lower in the HTS compared to MAN with a 1:1 match ($p=0.004$); however, this became insignificant with a 1:2 match ($p=0.06$). 4. There was no significant difference between HTS and MAN in mortality rate ($p=0.53$).
<p>Tang et al. (2015) Taiwan Pre-Post N=21</p>	<p>Population: TBI=8, Stroke=10, Tumor=3; Mean Age=52.05 yr; Gender: Male=12, Female=9; Mean GCS=10.6. Intervention: Participants received 1 g/kg of 20% mannitol. Outcome Measures: Intracranial Pressure (ICP), Pressure Reactivity Index (PRx), Cerebral Perfusion Pressure (CPP), Cerebrovascular Pressure Reactivity (CVPR).</p>	<ol style="list-style-type: none"> 1. At baseline, ICP was significantly correlated with PRx ($p=0.0044$). 2. There was a significant decrease in ICP after mannitol ($p=0.036$). 3. Low baseline CPP was the only significant association with the improvement of CVPR after mannitol ($p=0.039$).
<p>Colton et al. (2014b) USA Case Series N=117</p>	<p>Population: TBI; Mean Age=40.0 yr; Gender: Male=93, Female=24; Median GCS=6. Intervention: Participants were included in retrospective analysis after having received one of the following ICP therapies: hypertonic saline (HTS), mannitol, propofol, fentanyl, and barbiturates. Outcome Measure: Intracranial Pressure (ICP).</p>	<ol style="list-style-type: none"> 1. Treatment with HTS resulted in the largest ICP decrease of the treatments examined. 2. Propofol and fentanyl escalations resulted in smaller but significant ICP reductions. 3. Mannitol resulted in statistically insignificant reductions in the first hr but rebounded by the second hr.
<p>Diringer et al. (2012) USA Pre-Post N=6</p>	<p>Population: TBI; Mean Age=30.2 yr; Gender: Male=5, Female=1; Median GCS=6. Intervention: Participants received 1 g/kg of 20% mannitol. Outcome Measures: Intracranial Pressure (ICP), Cerebral Blood Volume (CBV), Blood Pressure (BP), Cerebral Blood Flow (CBF), Cerebral Metabolic Rate for</p>	<ol style="list-style-type: none"> 1. There was a significant reduction in ICP 1hr after mannitol (21.5 mmHg to 13.7 mmHg, $p<0.003$). 2. There was no significant change in CBV, BP, CBF, CMRO₂ or oxygen content 1hr after mannitol (all $p>0.05$).

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
	Oxygen (CMRO ₂), Oxygen Content.	
Sakellariadis et al. (2011) Greece Case Control N=29	Population: TBI; Mean Age=36 yr; Mean GCS=5.4. Intervention: Participants who received hypertonic saline (HTS) or mannitol were retrospectively analyzed. Outcome Measures: Intracranial Pressure (ICP), Duration of effectiveness.	<ol style="list-style-type: none"> 1. There was no significant difference between HTS and mannitol in reducing ICP. 2. There was no significant difference between HTS and mannitol in duration of effectiveness.
Kerwin et al. (2009) USA Cohort N=22	Population: TBI; Mean Age=35.7 yr; Gender: Male=16, Female=6; Mean GCS=6.9. Intervention: Patients received intravenous infusions of 23.4% hypertonic saline (HTS) or mannitol (15-75 g, at the discretion of the neurosurgeon). Outcome Measure: Intracranial Pressure (ICP).	<ol style="list-style-type: none"> 1. Mean ICP reduction was significantly greater by HTS than mannitol (9.3mmHg versus 6.4 mmHg, p=0.0028). 2. Patients with initial ICP>30 mmHg had a significantly greater mean ICP reduction by HTS than mannitol (12.6 mmHg versus 8 mmHg, p=0.0105). 3. More patients responded to HTS than mannitol (93% versus 74%, p=0.002). 4. HTS was more likely to yield an ICP reduction of >10 mmHg, while mannitol was more likely to yield a reduction of <5 mmHg. 5. There was no significant difference between HTS and mannitol in amount of time ICP>20 mmHg (9.7 hr versus 7.4 hr, p=0.236) or duration of response (4.1 hr versus 3.8hr, p=0.854).
Oddo et al. (2009) USA Cohort N=12	Population: TBI; Mean Age=36 yr; Gender: Male=9, Female=3; Mean GCS=3; Mean Time Post Injury=8 hr. Intervention: Participants received intravenous infusions of 7.5% hypertonic saline (HTS) or 25% mannitol. Outcome Measures: Intracranial Pressure (ICP), Mean Arterial Pressure (MAP), Cerebral Perfusion Pressure (CPP), Brain Tissue Oxygen Tension (P _{bt} O ₂), Central Venous Pressure (CVP), Cardiac Output (CO).	<ol style="list-style-type: none"> 1. Mean ICP was more significantly reduced (p<0.001) by HTS than mannitol after 60min (15 mmHg versus 23 mmHg) and 120min (15 mmHg versus 24 mmHg). 2. Mean CPP was more significantly increased by HTS than mannitol after 120min (76 mmHg versus 65 mmHg, p=0.02). 3. Mean CO was more significantly increased by HTS than mannitol after 30 min (7.5 L/min versus 5.3 L/min, p=0.003), 60 min (7.8 L/min versus 6.6 L/min, p=0.007), and 120min (7.5 L/min versus 6.1 L/min, p=0.002). 4. Mean P_{bt}O₂ was significantly increased by HTS (p<0.01) and decreased by mannitol (p>0.05) over time, with significant differences at 60min (37 mmHg versus 28 mmHg, p<0.05) and 120 min (41 mmHg versus 27.5 mmHg, p<0.01). 5. There were no significant differences in MAP or CVP between groups.

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
Ware et al. (2005) USA Case Control N=13	Population: TBI; Mean Age=42.0 yr; Gender: Male=10, Female=3; Time Post Injury<12 hr; Mean GCS=7.7. Intervention: Participants received intravenous infusions of 23.4% hypertonic saline (HTS) and mannitol. Outcome Measure: Intracranial Pressure (ICP).	<ol style="list-style-type: none"> Both HTS and mannitol significantly reduced ICP ($p<0.001$) and there was no significant difference between them ($p=0.174$). Mean duration of ICP reduction by HTS was significantly longer than mannitol (96 min versus 59 min, $p=0.016$).
Hartl et al. (1997) Germany Pre-Post N=11	Population: TBI; GCS<9. Intervention: Patients received 30 intravenous administrations of 20% mannitol (125 mL) infused over 30 min. Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP).	<ol style="list-style-type: none"> When initial ICP was <20 mmHg, neither ICP nor CPP change significantly during or after mannitol infusion. When initial ICP was >20 mmHg, there was a significant decrease in mean ICP (maximal decrease from 23 mmHg to 16 mmHg at 60min, $p<0.05$) and a significant increase in mean CPP (maximal increase from 68 mmHg to 80 mmHg at 120 min, $p<0.05$) in response to mannitol.

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002)

Discussion

Overall, findings of single group interventions suggest that mannitol is effective in significantly reducing ICP (Diringer et al., 2012; Scalfani et al., 2012; Tang et al., 2015), and improving CPP (Hartl et al., 1997; Tang et al., 2015) following TBI. In addition, Tang et al. reported an increase in cerebrovascular pressure reactivity, a measure of cerebrovascular autoregulation, in patients with a low baseline CPP.

The Brain Trauma Foundation recommends that mannitol only be used if a patient has signs of elevated ICP or deteriorating neurological status; this is primarily due to the significant side effects associated with mannitol treatment. While side effects were not reported, one study indicated that mannitol was only effective in diminishing ICP and improving CPP when the initial ICP was hypertensive (>20mmHg(Hartl et al., 1997)).

Several studies have compared HTS to mannitol in terms of efficacy in lowering elevated ICP and improving long-term outcomes. While one case-control study found no significant difference between the treatments in the level or duration of ICP reduction (Sakellaridis et al., 2011), another found that HTS had a longer lasting effect (Ware et al., 2005). Two cohort studies reported significantly greater reductions in ICP from HTS than mannitol (Kerwin et al., 2009; Oddo et al., 2009), with one noting that these ICP reductions were associated with greater increases in CPP (Oddo et al., 2009). The benefits of HTS were also reported in 2 retrospective studies where HTS was compared to mannitol (Mangat et al., 2015), and mannitol, propofol, fentanyl and barbiturates (Colton et al., 2014a). Both studies described improvements in either acute (Colton et al., 2014a) or sustained (Mangat et al., 2015) ICP management, with the latter also reporting a decrease in length of hospitalization compared to mannitol.

In an RCT, Vialet et al. (2003) found that patients receiving HTS had fewer episodes of ICP hypertension and fewer clinical failures than those receiving mannitol, although clinical outcomes at three months did not differ between groups. Another small RCT demonstrated that HTS yielded a significantly greater decrease in ICP over a longer period of time when compared to mannitol (Battison et al., 2005). However, three other RCTs were identified that found no benefit of HTS over mannitol in controlling elevated ICP, despite improvements in CPP (Harutjunyan et al., 2005), Cerebral Blood Flow (Cottenceau et al., 2011), and blood glucose control (Jagannatha et al., 2016). A secondary analysis of the Jagannatha et al. (2006) study attempted to explain the lack of efficacy of HTS over mannitol and found that urinary sodium concentrations were greater in patients receiving HTS (Jagannatha et al., 2018). The authors suggested that unless sodium excretion could be reduced, the efficacy of HTS would continue to be equivalent to that of mannitol in reducing ICP.

The comparison of HTS and mannitol was not just limited to the treatment's ICP-lowering potential, but also the morbidity and mortality associated with each. Hypertonic Saline was associated with a decrease in hospital length of stay (Mangat et al., 2015); however, no differences were observed in mortality or GOS/GOSE scores when compared to mannitol (Baker et al., 2009; Cooper et al., 2004; Mangat et al., 2015; Vialet et al., 2003).

Conclusions

There is level 4 evidence that mannitol may be effective in controlling elevated intracranial pressure post ABI.

There is level 4 evidence that mannitol may be effective in increasing cerebral perfusion pressure post ABI.

There is level 4 evidence that mannitol may only improve intracranial pressure and cerebral perfusion pressure post ABI in hypertensive patients (Intracranial pressure > 20 mmHg).

There is level 1a evidence that hypertonic saline is similar to mannitol in terms of mortality or Glasgow outcome scale (extended) scores in patients post TBI.

There is conflicting (level 1b) evidence as to whether hypertonic solution lowers elevated intracranial pressure more effectively than mannitol post ABI.

There is conflicting (level 2 and level 3) evidence that hypertonic saline lowers intracranial pressure for longer compared to mannitol post ABI. The level 2 evidence suggest that it does.

There is level 2 evidence that hypertonic saline is superior to mannitol at improving cerebral perfusion pressure, cerebral blood flow, and blood-glucose control in patients post ABI.

There is level 2 evidence that urinary sodium excretion is higher in hypertonic saline patients compared to those receiving mannitol post ABI.

There is level 4 evidence that hypertonic saline is superior to barbiturates, propofol, and fentanyl at lowering intracranial pressure post ABI.

Mannitol may effectively improve intracranial pressure and cerebral perfusion pressure post ABI; however, this benefit may only be seen in hypertensive (intracranial pressure >20 mmHg) patients.

It is unclear whether hypertonic saline is more effective than mannitol at lowering intracranial pressure or reducing hospital length of stay.

Hypertonic saline can improve cerebral perfusion pressure, cerebral blood flow, and brain tissue oxygenation more effectively than mannitol. However, hypertonic solution is not different than mannitol in terms of morbidity and mortality associated with treatment.

Hypertonic saline is superior to barbiturates, propofol, and fentanyl at lowering intracranial pressure post TBI.

15.1.4.2.1 Comparative or Combination Mannitol Interventions

Rapid administration of mannitol is among the first-line treatments recommended for the management of increased ICP. This section reviews varying dosages or combination therapies involving mannitol.

Table 15.19 Mannitol for the Multimodal Acute Management of Intracranial Pressure Post ABI

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
Ichai et al. (2009) France RCT PEDro=6 N=34	<p>Population: TBI; <i>Mannitol (MAN, n=17)</i>: Mean Age=33.8 yr; Gender: Male=11, Female=6; Time Post Injury<8 hr; Median GCS=6. <i>Sodium Lactate (SL, n=17)</i>: Mean Age=37.6 yr; Gender: Male=13, Female=4; Time Post Injury<8 hr; Median GCS=4.</p> <p>Intervention: Patients were randomized to receive intravenous infusion of 20% MAN (1.5 mL/kg) and/or SL over 15 min.</p> <p>Outcome Measure: Intracranial Pressure (ICP).</p>	<ol style="list-style-type: none"> Both treatments were effective in reducing ICP from baseline ($p<0.0001$). SL showed significantly lower ICP levels compared to MAN ($p=0.016$). The effect of SL alone on ICP was more pronounced ($p=0.0061$) and more prolonged ($p=0.0049$) than MAN alone. The percentage of episodes requiring rescue treatment was higher with mannitol than lactate (29.6% versus 9.6%, $p=0.053$).
Francony et al. (2008) France RCT PEDro=6 N=20	<p>Population: TBI=17, ABI=3. <i>Mannitol (MAN, n=10)</i>: Mean Age=43 yr; Gender: Male=7, Female=3; Mean GCS=8; Mean Time Post Injury=6 days. <i>Hypertonic Saline (HTS, n=10)</i>: Mean Age=37 yr; Gender: Male=9, Female=1; Mean GCS=7; Mean Time Post Injury=5d.</p> <p>Intervention: Patients were randomized to receive a single intravenous infusion of 20% MAN (231 mL) or of 7.45% HTS (100 mL) administered over 20 min.</p> <p>Outcome Measures: Intracranial Pressure (ICP), Mean Arterial Pressure (MAP), Cerebral Perfusion Pressure (CPP), Urine Output (UO), Serum Sodium/Chloride.</p>	<ol style="list-style-type: none"> ICP was reduced in both groups of patients following treatment. In MAN, ICP was significantly reduced by 45% of baseline values (-14mmHg,) at 60 min ($p=0.01$) and by 32% of baseline values (-10 mmHg) at 120 min ($p=0.01$). In HTS, ICP was significantly reduced by 35% of baseline values (-10mmHg) at 60 min ($p=0.01$) and by 23% of baseline values (-6 mmHg) at 120min ($p=0.01$). MAP was unchanged and comparable between groups ($F=1.2$, $p=0.32$).

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
		5. CPP was significantly elevated only in the MAN ($p<0.05$). 6. MAN showed significantly greater increase in UO ($p<0.05$). 7. HTS showed significantly greater increase in serum sodium and chloride after 120 min ($p<0.01$).
Cruz et al. (2004) Brazil RCT PEDro=5 N=44	Population: TBI; <i>High-Dose Mannitol (HDM, n=23)</i> : Mean Age=34 yr; Mean GCS=3. <i>Conventional-Dose Mannitol (CDM, n=21)</i> : Mean Age=31 yr; Mean GCS=3. Intervention: Patients were randomized to receive rapid intravenous infusion of HDM (up to 1.4 g/kg) or CDM (up to 0.7 g/kg). Both groups received normal saline infusions immediately after the mannitol infusions. Outcome Measures: Intracranial Pressure (ICP), Glasgow Outcome Scale (GOS), Mortality, Additional Therapy Required.	1. At 6 mo, mortality rates were 39.1% and 66.7% for the HDM and CDM groups, respectively. 2. Clinical outcome on the GOS was significantly better for the HDM group, with a greater number of patients in this group showing a favourable outcome ($GOS\geq 4$) compared with the CDM group (43.5% versus 9.5%, $p<0.02$). 3. No significant difference was found between the HDM and CDM groups in percentage of patients requiring decompressive surgery for refractory ICP elevations (43.5% versus 47.6%).
Cruz et al. (2002) Brazil RCT PEDro=5 N=141	Population: TBI; <i>High-Dose Mannitol (HDM, n=72)</i> : Mean Age=29 yr; Mean GCS=5.3. <i>Conventional-Dose Mannitol (CDM, n=69)</i> : Mean Age=31 yr; Mean GCS=5.5. Intervention: Patients were randomized to receive rapid intravenous infusion of HDM (up to 1.4 g/kg) or CDM (up to 0.7 g/kg). Outcome Measures: Intracranial Pressure (ICP), Glasgow Outcome Scale (GOS), Additional Therapy Required.	1. At 6mo, mortality rates were 19.4% and 36.2% for the HDM and CDM groups, respectively. 2. Clinical outcome on the GOS was significantly better for the HDM group, with a greater number of patients in this group showing favourable outcome ($GOS\geq 4$) compared with the CDM group (61.1% versus 33.3%, $p<0.005$). 3. A greater proportion of patients in the CDM group required decompressive surgery for refractory ICP elevations than the HDM group (24.6% versus 9.7%, $p<0.03$).
Cruz et al. (2001) Brazil RCT PEDro=4 N=178	Population: TBI; <i>High-Dose Mannitol (HDM, n=91)</i> : Mean Age=30 yr; Mean GCS=6. <i>Conventional-Dose Mannitol (CDM, n=87)</i> : Mean Age=28 yr; Mean GCS=6.2. Intervention: Patients were randomized to receive intravenous infusion of HDM (Conventional dose + 0.6 to 0.7 g/kg in the absence of pupillary widening or 1.2 to 1.4 g/kg with pupillary widening) or CDM (0.6-0.7 g/kg). Outcome Measures: Intracranial Pressure (ICP), Glasgow Outcome Scale (GOS), Additional Therapy Required.	1. At 6 mo, mortality rates were 14.3% and 25.3% for the HDM and CDM groups, respectively. 2. Clinical outcome on the GOS was significantly better for the HDM group, with a greater number of patients in this group showing favourable outcome ($GOS\geq 4$) compared with the CDM group (69.2% versus 46%, $p<0.01$). 3. No significant difference between HDM and CDM groups in percentage of patients requiring barbiturate therapy for refractory ICP elevations (46.1% versus 54%).

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
Smith et al. (1986) USA RCT PEDro=4 N=77	<p>Population: TBI; Mean Age=27 yr; Gender: Male=60, Female=17; Time Post Injury ≤6 hr; GCS ≤8.</p> <p>Intervention: Patients were randomized to receive intravenous infusion of mannitol based on careful monitoring (Group 1; n=37) or irrespective of monitoring (Group 2; n=40). For Group 1, an initial bolus of 20% mannitol (250 mL, 0.75 gm/kg) was administered at ICP>25mmHg; pentobarbital coma was induced if ICP>25 mmHg while mannitol was administered. For Group 2, initial bolus of 20% mannitol (250 mL, 0.75 gm/kg) was given, followed by 0.25g m/kg boluses administered every 2 hr.</p> <p>Outcome Measures: Mortality, Glasgow Outcome Scale (GOS), Intracranial Pressure (ICP).</p>	<ol style="list-style-type: none"> 1. There was no significant difference in mortality between Groups 1 and 2 (35% versus 42.5%, p=0.26). 2. There were no significant differences in GOS between groups. 3. The proportion of patients achieving favourable outcome (GOS≥4) in Group 1 was 54% and in Group 2 was 47.5%. 4. Mean highest ICPs for survivors in Groups 1 and 2 were 35.2mmHg and 29.7mmHg, respectively, and for non-survivors were 46.2 mmHg and 40.7 mmHg, respectively. 5. Mean highest ICP in all non-survivors was significantly higher (by approx. 11 mmHg) than that in all survivors (p=0.0002).
Scalfani et al. (2012) USA Pre-Post N=8	<p>Population: TBI; Mean Age=37.4 yr; Gender: Male=7, Female=1; Median Time Post Injury=3 days; Median GCS=7.</p> <p>Intervention: Participants received 20% mannitol (n=6) or 23.4% saline (n=2) infused over 15 min.</p> <p>Outcome Measures: Intracranial Pressure (ICP), Mean Arterial Pressure (MAP), Cerebral Perfusion Pressure (CPP).</p>	<ol style="list-style-type: none"> 1. Results from patients who received saline and mannitol were not different and were combined for all analyses 2. Treatment resulted in a significant reduction in ICP (22.4 mmHg to 15.7 mmHg, p<0.05). 3. Treatment resulted in a significant elevation in CPP (75.7 mmHg to 81.9 mmHg, p<0.05). 4. Treatment resulted in a stable MAP (103.3 mmHg versus 102.6 mmHg, p>0.05).
Sorani et al. (2008) USA Case Control N=28	<p>Population: TBI; Mean Age=39.3 yr; Gender: Male=24, Female=4; Median GCS=8.</p> <p>Intervention: Patients treated with 100 g, 50 g, or both doses of mannitol were included in retrospective analysis.</p> <p>Outcome Measure: Intracranial Pressure (ICP).</p>	<ol style="list-style-type: none"> 1. Initial mean ICP was slightly higher in the 100 g group compared to the 50g group (23.9 mmHg versus 20.9 mmHg, p=0.14). 2. By 100 min post treatment, mean ICP was significantly lower in the 100 g group compared to the 50 g group (14.2 mmHg versus 18.6 mmHg, p=0.001). 3. Over time, mean ICP decrease in the 50 g group was 3.6 mmHg, which was nearly two-fold lower than that of the 100 g group (8.8 mmHg). 4. ICP response to mannitol was dose-dependent: every 7 g achieved an additional reduction of ~1.0 mmHg in ICP.

Discussion

Overall, a large proportion of studies reported that mannitol is effective in significantly reducing ICP (Cruz et al., 2001, 2002; Cruz et al., 2004; Francony et al., 2008; Ichai et al., 2009; Scalfani et al., 2012; Sorani et al., 2008). Consequently, some studies went on to further contrast the therapeutic difference between high and low doses of mannitol in treating patients with ABI. Cruz and colleagues conducted three separate trials to investigate the effects of high dose mannitol on clinical outcomes in patients with ABI at six months post injury (Cruz et al., 2001, 2002; Cruz et al., 2004). All three trials reported that high dose mannitol (1.4 g/kg) was superior to conventional mannitol (0.7 g/kg) in lowering elevated ICP and improving clinical outcomes. Further supporting the benefits of high-dose over low-dose mannitol, Sorani et al. (2008) found that for every 0.1 g/kg increase in mannitol dosage there was a 1.0 mmHg drop in ICP.

Most reports have recommended administering mannitol only when elevated ICP is proven or strongly suspected. However, a RCT by Smith et al. (1986) reported that patients who received mannitol only after the onset of intracranial hypertension (>25 mmHg) were not significantly different from those who received mannitol irrespective of ICP measurements in terms of mortality rates or neurological outcomes. Thus, it is unclear whether the use of mannitol prophylactically against potential elevations in ICP is appropriate.

Three studies analyzed compared mannitol to either HTS or Ringer's (sodium) lactate as therapy for ABI. Francony et al. (2008) found that equimolar doses of mannitol and HTS were comparable in reducing ICP in stable patients with intact autoregulation post ABI. Mannitol was shown to improve brain circulation through possible improvements in blood rheology; however, treatment also significantly increased urine output. The authors suggested that both treatments may be effective, but patient pre-treatment factors should be considered before selection. A second study reported that while mannitol significantly decreased ICP, increased CPP, and stabilized mean arterial pressure, saline treatment yielded the same results with no inter-group differences reported (Scalfani et al., 2012). The results from these studies suggest mannitol and HTS may have similar abilities to improve ICP and CPP, and given the favored safety profile of saline, HTS may become the preferred osmolar treatment for ABI. In another trial, Ichai et al. (2009) reported that an equimolar dose of Ringer's (sodium lactate) had a significantly greater effect on lowering elevated ICP that lasted longer than treatment with mannitol. Sodium lactate was also successful in reducing elevated ICP more frequently. Based on these results, further research into the effectiveness of sodium lactate in reducing ICP is warranted.

Conclusions

There is level 1a evidence that mannitol effectively reduces elevated intracranial pressure in patients post TBI.

There is level 1b evidence that mannitol is no more effective than hypertonic saline in improving intracranial pressure or cerebral perfusion pressure in individuals with an ABI.

There is level 1b evidence that mannitol is less effective than Ringer's (sodium) lactate in controlling elevated intracranial pressure post ABI.

There is level 2 evidence that early versus late administration of mannitol is the same at lowering elevated intracranial pressure in individuals with an ABI.

There is level 2 evidence that higher doses of mannitol (1.4 g/kg) are more effective than lower doses (0.7 g/kg) at reducing intracranial pressure in patients post TBI.

Mannitol effectively decreases intracranial pressure post ABI but can increase urine output and plasma sodium and chloride; furthermore, high doses may yield improved intracranial pressure control, lower mortality rates and better clinical outcomes compared to lower doses.

Prophylactic mannitol administration may not be associated with different morbidity or mortality outcomes compared to its standard use post TBI.

Mannitol may be equally effective as hypertonic saline at reducing intracranial pressure and cerebral perfusion pressure, and less effective than Ringer’s (sodium) lactate at reducing intracranial pressure.

15.1.4.3 Urea

Urea is a nitrogenous waste product of protein metabolism that is excreted by the kidneys. An osmotically active agent, urea gained popularity in the 1950’s as a compound that could rapidly reduce ICP. Although an effective agent, intravenous urea use was associated with complications such as rebound hypertension (due to its filtration into the brain), local skin necrosis and sloughing, platelet dysfunction, and renal dysfunction (Rocque, 2012). In the decades that followed urea was replaced as the mainstay in treatment for compounds with equal efficacy but superior safety profiles, such as mannitol and HTS. Today urea is rarely used to treat ICP in ABI, save for very specific cases where the mainstay therapies are not appropriate.

Table 15.20 Urea for the Acute Management of Intracranial Pressure Post ABI

Author Year Country Research Design PEDro Sample Size	Methods	Outcome
Annoni et al. (2017) Belgium Case Series N=40	Population: ABI; Median Age=53 yr, Gender: Male=21, Female=19; Median GCS Score=9 Intervention: Records of patients who had ABI, received enteral urea because of hyponatremia, and had elevated ICP were reviewed. Outcome Measures: Intracranial Pressure (ICP), Sodium (mEq/L).	1. After the first urea dose (15 g), median ICP decreased from 14 mmHg to 11 mmHg (p<0.001). 2. Sodium levels increased significantly over the study period from 133 mEq/L to 141 mEq/L (p<0.05). 3. Body temperature, blood pressure and PaCO ₂ all remained steady during the 12hr study period.

Discussion

Annoni *et al.* (2017) studied the effect of enteral urea administration on patients with ABI who presented with elevated ICP and syndrome of inappropriate antidiuretic hormone secretion (SIADH). The researchers

concluded that urea administration effectively lowered ICP and was able to increase serum sodium in the process. In addition to the primary outcomes, no notable side-effects or complications were reported. Although a small trial, these findings suggest that enterally-administered urea has a safer profile than the previously common intravenous route.

Conclusions

There is level 4 evidence that enteral urea may lower elevated intracranial pressure in patients with ABI and syndrome of inappropriate antidiuretic hormone secretion.

Enteral urea may lower elevated intracranial pressure in patients with ABI and syndrome of inappropriate antidiuretic hormone secretion.

15.1.5 Blood Product Interventions

Pre-hospital resuscitation of hypotensive patients with ABI focuses on maintaining appropriate blood pressure, and by extension adequate cerebral perfusion, to reduce the degree of secondary brain injury in patients with ABI (Hernandez et al., 2017; Werner & Engelhard, 2007). While isotonic fluid is commonly used for resuscitation, evidence exists supporting the use of packed red blood cells (RBC) in severely injured patients with ABI (Hernandez et al., 2017; Riskin et al., 2009). However, studies have come out proposing that plasma, or blood products with a high plasma to RBC ratio, are superior to RBCs alone at improving mortality in severely injured patients with ABI (Bhangu et al., 2013; del Junco et al., 2013). Complimentary to those findings, large animal trials with TBI models have found improvements in post-injury neurological outcomes after administration of plasma (Halaweish et al., 2016; Shakeri et al., 2013) (Shakeri et al., 2013).

Despite evidence supporting the use of blood products, and specifically plasma, in the resuscitation of patients with severe TBI, the Brain Trauma Foundation recommends solely the use of isotonic fluid in the management of hypotensive patients (Bratton et al., 2007).

Table 15.21 Miscellaneous Outcomes -Blood Products for Acute Management Post ABI

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Holzmacher et al. 2018 USA Cohort N=66	Population: SDH=23, EDH=3, IVH/SAH=30, IPH=46. <i>Transfusion group (n=23):</i> Mean Age=76 yr; Gender: Male=8, Female=15. <i>Non-transfusion Group (n=43):</i> Mean Age=78 yr; Gender: Male=23, Female=20. Intervention: Eligible patients on anti-platelet therapy who received a platelet transfusion,	<ol style="list-style-type: none"> 1. Patients receiving a transfusion had significantly lower platelet signalling inhibition [% Inh(AA), p=0.01]. 2. Mean Marshall CT scores were not significantly differently between groups. 3. Transfused patients were more likely to undergo craniectomy/craniotomy (p=0.01), and had a

	were compared to those who did not. Outcomes were assessed before and after treatment. Outcome Measures: Platelet dysfunction (TEG-PM Assay), Marshall CT Score, Mortality, Need for Intervention, Hospital Length of Stay (LOS).	longer hospital LOS ($p=0.01$) compared to non-transfused patients. 4. Mortality was four times higher in the transfused group, however this was not significant ($p=0.28$).
Hernandez et al. 2017 USA Case Control N=76	Population: TBI; <i>pRBC group (n=40)</i> : Median Age=47.5 yr; Gender: Male=23, Female=17; Median GCS=4. <i>Plasma group (n=36)</i> : Median Age=65 yr; Gender: Male=24, Female=12; Median GCS=8. Intervention: All patients with multiple injuries who received remote damage control blood transfusions at a Level 1 trauma center between 2002 and 2013 were retrospectively identified. Outcomes of patients who received thawed plasma transfusions were compared with those who received pRBCs alone. Outcome Measures: Glasgow Outcome Score Extended (GOSE), Disability Rating Scale (DRS).	1. Patients who received plasma (Median GOSE=7) demonstrated significantly higher neurological function at discharge compared with the pRBC only group (Median GOSE=5.5) ($p<0.001$). This improvement persisted at follow-up ($p<0.001$). 2. At discharge, DRS scores were also significantly higher in the plasma group (Median DRS=2) compared to the pRBC only group (Median DRS=9) ($p<0.001$). This improvement persisted at follow-up ($p<0.001$).

Discussion

One study was reviewed investigating the effects of different blood products on neurological and disability outcomes. In the study by Hernandez et al. (2017), patients with TBI and multiple injuries who received either thawed plasma, or pRBCs were retrospectively analyzed. The study concluded that the thawed plasma group demonstrated significantly higher neurological function and DRS scores at both discharge and follow-up compared to the pRBC group. While further research is required, these results show promise in the benefits of plasma products in patients with multiple injuries post TBI.

Holzmacher et al. (2018) investigated the effect of platelet transfusion in the unique subset of patients with TBI who are concurrently on anti-platelet medication. While it was hypothesized that the transfusion of platelets would decrease the risk of further bleeding and complications, patients receiving the transfusion were more likely to undergo a craniotomy/craniectomy and had a longer hospital stay. In spite of said results, CT severity (Mean Marshall CT) scores and mortality rates were the same for both transfused and non-transfused patients. In conclusion, while platelet transfusion improves platelet dysfunction in this subset of patients, there appears to be no beneficial effect in injury outcome and survival.

Conclusions

There is level 2 evidence that platelet transfusion in patients concurrently on anti-platelet therapy improves platelet dysfunction but has no effect on morbidity or mortality post ABI.

There is level 3 evidence that thawed plasma may be superior to packed red blood cells at improving neurological function and disability at both discharge and follow up in patients with multiple injuries post TBI.

Thawed plasma may be superior to packed red blood cells at improving neurological function and disability in patients with multiple injuries post TBI.

Platelet transfusion in patients receiving anti-platelet therapy likely improves platelet dysfunction, but not mortality post ABI. Patients may also be at higher risk of requirement for intervention, and a longer hospital stay.

15.1.6 Surgical Interventions

15.1.6.1 Cerebrospinal Fluid Drainage

In an attempt to control ICP, ventricular CSF drainage is a frequently used neurosurgical technique. Catheters are generally inserted in to the anterior horn of a lateral ventricle and attached to an external strain gauged transducer allowing for concurrent pressure monitoring and fluid drainage (Bracke et al., 1978; March, 2005). Generally, a few milliliters of fluid are drained from the ventricle at a time, resulting in an immediate decrease in ICP (Kerr et al., 2000). However, ventricular space is often compressed due to associated brain swelling, which limits the potential for drainage as a stand-alone therapy for ICP (James, 1979). Criticisms of external ventricular drainage generally surround the intrusiveness of the procedure and the complication of potential infections (Hoefnagel et al., 2008; Zabramski et al., 2003).

When ventricular drainage is not possible, lumbar drainage has been proposed as an alternative method for reducing elevated ICP. Standard practice has been to avoid lumbar drainage for fear of transtentorial or tonsillar herniation. However, technological improvements have renewed interest in its potential for reducing ICP in patients refractory to other treatments (Tuettenberg et al., 2009).

The AANS guidelines made a Level III recommendation for the use of CSF drainage to lower ICP in patients with GCS<6 during the first 12 hours post injury (Carney et al., 2017). As well, the authors noted that an external ventricular system at the midbrain may be more effective with continuous drainage than with intermittent use. According to the earlier EBIC, CSF drainage is an acceptable treatment for ICP reduction post ABI (Maas et al., 1997).

Table 15.22 Cerebrospinal Fluid Drainage for the Acute Management of Intracranial Pressure Post ABI

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Kerr et al. (2001) USA RCT PEDro=7 N=58	Population: TBI; Mean Age=31.6 yr; Gender: Male=45, Female=13; Mean GCS=5.7. Intervention: Participants were randomized to receive one of three ventricular CSF drainage protocols: 1 ml, 2 ml, or 3 ml. Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP).	<ol style="list-style-type: none"> 1. Significant dose-time interactions were seen in all three drainage protocols in relation to ICP decreases (p=0.0001). 2. There was a significant difference in CPP proportional to the amount of CSF drained (p=0.04). 3. A 3ml withdrawal of CSF resulted in a 10.1% decrease in ICP and a 2.2% increase in CPP that were sustained for 10 min.

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Manet et al. (2017) Canada Case Series N=33	Population: TBI=22, TBI=11; Median Age=51; Median GCS=8. Intervention: Retrospective analysis of patients who did not respond to initial ICP treatments and received an external lumbar device (ELD). Outcome Measures: Modified Rankin Scale (mRS), Intracranial Pressure (ICP), CSF output.	<ol style="list-style-type: none"> 1. Median time of ELD insertion was 5day after brain insult, and the drain was removed after a median duration of 7 days. 2. ICP decreased significantly from 25 mmHg before to 7 mmHg after ELD placement (p<0.001). 3. Median CSF flow was 119 mL/day. 4. Ten patients had favourable neurological outcome, while 19 had poor outcome based on the mRS.
Lescot et al. (2012) France Pre-Post N=20	Population: TBI; Median Age=49yr; Gender: Male=14, Female=6; Median GCS=8. Intervention: Participants received ventricular CSF drainage. Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP).	<ol style="list-style-type: none"> 1. Mean ICP significantly decreased at 12hr and 24hr when compared to pre-treatment (p<0.05). 2. Mean CPP significantly increased at 12hr when compared to pre-treatment (p<0.05).
Murad et al. (2012) USA Pre-Post N=15	Population: TBI; Mean Age=36.9 yr; Gender: Male=12, Female=3; Mean GCS=6.8. Intervention: Participants received lumbar CSF drainage. Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Mean Arterial Pressure (MAP), Additional Treatments.	<ol style="list-style-type: none"> 1. ICP significantly decreased from a mean of 28.2mmHg to 10.1mmHg after treatment (p<0.001). 2. CPP increased from a mean of 76.7mmHg to 81.2mmHg after treatment, but the difference was not significant (p>0.05). 3. MAP decreased from 96.8mmHg to 91.4mmHg after treatment, but the difference was not significant (p>0.05). 4. Requirements for additional treatments significantly decreased from 80% to 7% (p<0.05).
Llompert-Pou et al. (2011) Spain Case Series N=30	Population: TBI; Mean Age=34.9 yr; Gender: Male=25, Female=5; Mean GCS=8. Intervention: Participants who underwent lumbar CSF drainage were retrospectively analyzed. Outcome Measures: Intracranial Pressure (ICP), Glasgow Outcome Scale (GOS), Mortality.	<ol style="list-style-type: none"> 1. ICP significantly decreased following treatment (p<0.0001). 2. Positive outcome (GOS≥4) was found in 30% after ICU discharge and 62.2% in the long term. 3. Poor outcome (GOS<4) was found in 26.6% after ICU discharge and 17.2% in the long term. 4. Mortality rate was 13.3% after ICU discharge and 20.7% in the long term.
Tuettenberg et al. (2009) Germany Pre-Post N=100	Population: TBI=45, SAH=55; Mean Age=43.7yr; Mean GCS=7. Intervention: Participants received lumbar CSF drainage. Outcome Measures: Intracranial Pressure (ICP), Glasgow Coma Scale (GOS), Cerebral Perfusion Pressure (CPP).	<ol style="list-style-type: none"> 1. ICP was significantly reduced (32.7 mmHg to 13.4 mmHg, p<0.05) and CPP was significantly increased (70.6 mmHg to 86.2 mmHg, p<0.05) after treatment. 2. Favorable outcomes (GOS=4-5) were found in 36 participants, 12 were severely disabled (GOS=3), 7 remained in a persistent vegetative state (GOS=2), and 45 died (GOS=1).

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Timofeev et al. (2008b) UK Pre-Post N=24	Population: TBI. Intervention: Participants received ventricular CSF drainage. Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Cerebral Oxygenation ($P_{bt}O_2$).	<ol style="list-style-type: none"> 1. ICP significantly decreased in all participants after treatment, with reduction maintained up to 24hr in 13 participants. 2. When ICP reduction remained stable, significant improvements in CPP and $P_{bt}O_2$ were also seen.
Murad et al. (2008) USA Case Series N=8	Population: TBI; Mean Age=36 yr. Intervention: Participants who underwent lumbar CSF drainage were retrospectively analyzed. Outcome Measures: Intracranial Pressure (ICP), Complications.	<ol style="list-style-type: none"> 1. ICP levels were significantly reduced (27 to 9 mmHg, $p<0.05$) after drainage. 2. In the 24-hr post drainage, reductions were seen in the need for other medications. 3. No complications were noted.
Nwachuku et al. (2014) USA Case Control N=62	Population: TBI; <i>Treatment Group 1 (TG1, n=31):</i> Mean Age=35.1 yr; Gender: Male=21, Female=10; Mean GCS=5.5. <i>Treatment Group 2 (TG2, n=31):</i> Mean Age=34.3 yr; Gender: Male=21, Female=10; Mean GCS=5.5. Intervention: Participants who underwent continuous/open (TG1) or intermittent/ closed (TG2) ventricular CSF drainage were compared. Outcome Measures: Glasgow Outcome Scale (GOS), Intracranial Pressure (ICP) Length of Stay (LOS), Additional Treatments.	<ol style="list-style-type: none"> 1. There was no significant difference between TG1 and TG2 in rate of good outcome ($GOS\geq 4$; 8% versus 13%, $p=0.35$) or survival (24% versus 22%, $p=0.56$) at 6 mo. 2. Overall ICP and $ICP\geq 20$ mmHg were significantly lower in TG1 than in TG2 ($p<0.0001$, $p=0.0002$). 3. There was no significant difference between groups in ICU LOS (19.8 days versus 20.1 days, $p=0.92$). 4. There was no significant difference between groups in rate of cranial surgery (15% versus 11%, $p=0.36$) or hypothermia treatment (1% versus 3%, $p=0.32$).
Kerr et al. (2000) USA Case Series N=31	Population: TBI; Mean Age=29.9 yr; Gender: Male=25, Female=6; GCS Range ≤ 8 . Intervention: Participants who underwent ventricular CSF drainage of 6 ml were retrospectively analyzed. Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP).	<ol style="list-style-type: none"> 1. ICP significantly decreased immediately after treatment and was maintained for up to 10 min ($p=0.0001$). 2. CPP significantly increased immediately after treatment, but it was not maintained ($p=0.0001$).
Fortune et al. (1995) USA Case Series N=22	Population: TBI; GCS Range < 8 . Intervention: Patients who underwent ventricular CSF drainage were retrospectively analyzed. Outcome Measures: Intracranial Pressure (ICP), Jugular Venous Oxygen Saturation ($S_{jv}O_2$).	<ol style="list-style-type: none"> 1. ICP decreased in 90% of the observations by a mean of 8.6 mmHg. 2. In patients where ICP decreased, $S_{jv}O_2$ only increased by a mean of 0.39%. 3. ICP steadily increased once treatment was stopped.

Discussion

Ventricular drainage of CSF has shown to be an effective intervention for lowering elevated ICP post ABI in small-scale studies (Fortune et al., 1995; Kerr et al., 2000; Timofeev et al., 2008b). While the retrospective studies noted steady increases in ICP after treatment cessation (Fortune et al., 1995; Kerr et al., 2000), the prospective studies found that ICP reductions were maintained for up to 24 hours in

select participants (Lescot et al., 2012; Timofeev et al., 2008b). Two of the studies reported significant improvements in CPP associated with ICP reductions (Kerr et al., 2000; Lescot et al., 2012), and only one reported short-term improvements in cerebral blood flow (Fortune et al., 1995). Lumbar drainage of CSF has shown similar effectiveness in lowering elevated ICP post ABI. The results of two small retrospective studies showed significant reductions in ICP after lumbar drainage (Llompert-Pou et al., 2011; Murad et al., 2008), which were supported by two prospective studies (Murad et al., 2012; Tuettenberg et al., 2009).

The rate of favourable long-term outcomes in these studies ranged from 36% (Tuettenberg et al., 2009) to 62% (Llompert-Pou et al., 2011), and one study reported a 70% decrease in therapeutic intensity levels following treatment. Following the increasing body of evidence for the benefit of lumbar drainage, Manet et al. (2017) studied the efficacy of an External Lumbar Device (ELD) in patients refractory to standard ICP treatment. The ELD allowed for continuous CSF extraction, draining an average of 199mL/d, which resulted in a 3.6-fold reduction in ICP. Based on these findings, lumbar drainage appears to be a viable alternative when ventricular drainage is not possible. However, how much CSF to drain and in which manner to produce optimal results is not clear from these studies.

A case-control study examining drainage frequency showed that continuous treatment demonstrated significantly greater reductions in ICP than intermittent treatment (Nwachuku et al., 2014). However, both treatments yielded comparable long-term outcomes and required similar therapeutic intensity levels. In a prospective trial evaluating drainage intensity, Kerr et al. (2001) randomized patients to have different amounts of CSF drained. The authors found that all patients experienced significant decreases in ICP and increases in CPP in the short term, regardless of the fluid amount drained. As such, ventricular CSF drainage, regardless of amount, is a feasible treatment when elevated ICP remains refractory to other interventions.

Conclusions

There is level 1b evidence that ventricular cerebrospinal fluid drainage, regardless of amount drained, effectively lowers elevated intracranial pressure, and increases cerebral perfusion pressure post ABI.

There is level 3 evidence that continuous cerebrospinal fluid drainage is superior to intermittent cerebrospinal fluid drainage at lowering intracranial pressure, but the same at improving long-term outcomes and therapeutic intensity post ABI.

There is level 4 evidence that ventricular cerebrospinal fluid drainage lowers elevated intracranial pressure post ABI.

There is conflicting (level 4) evidence that ventricular cerebrospinal fluid drainage lowers elevated intracranial pressure for prolonged periods (24 hours) post ABI.

There is level 4 evidence that ventricular cerebrospinal fluid drainage increases cerebral perfusion pressure and cerebral blood flow post ABI.

There is level 4 evidence that lumbar cerebrospinal fluid drainage lowers elevated intracranial pressure post ABI.

There is level 4 evidence that continuous cerebrospinal fluid extractions through an external lumbar device lowers intracranial pressure in patient's refractory to standard intracranial pressure treatment.

Ventricular cerebrospinal fluid drainage, regardless of amount drained, likely improves intracranial and cerebral perfusion pressure post ABI.

Continuous cerebrospinal fluid drainage may be more effective than intermittent drainage at acutely lowering elevated intracranial pressure post ABI, with no differences existing in long-term outcomes.

Cerebrospinal fluid drainage may effectively lower elevated intracranial pressure post ABI, using either a ventricular or lumbar device. It is unclear how long this improvement is sustained for. In addition, ventricular devices may potentially increase cerebral perfusion pressure and cerebral blood flow.

External lumbar devices may effectively lower intracranial pressure in patients' refractory to first line treatments.

15.1.6.2 Decompressive Craniectomy

Surgical decompression involves the removal of skull sections in patients with ABI to reduce the rising ICP caused by secondary injury (i.e., delayed brain damage). Sahuquillo and Arikan (2006) identified two types of surgical decompression: prophylactic/primary decompression and therapeutic/secondary Decompressive Craniectomy (DC). The former involves performing the surgical procedure as a preventive measure against expected increases in ICP while the latter is performed to control high ICP "refractory to maximal medical therapy" (Sahuquillo & Arikan, 2006).

However, debate regarding if and when to perform these surgeries continues. Factors such as age and initial GCS score have been proposed as potential prognostic factors (Guerra et al., 1999). The majority of decompressive techniques are precipitated by evacuation of a mass lesion (Compagnone et al., 2005). On the other hand, therapeutic DC is typically performed after other therapeutic measures to control ICP have been exhausted (Morgalla et al., 2008). Once decompression is decided upon, resection of a larger bone fragment is generally recommended to allow for greater dural expansion with less risk of herniation (Compagnone et al., 2005; Csókay et al., 2001). Two meta-analyses evaluating the effectiveness of DC in ICP were analysed. The earlier study found that postoperative ICP was significantly lower than preoperative values and remained stable for up to 48 hours (Bor-Seng-Shu et al., 2012), while the later study reported that DC resulted in reduced ICP and shorter hospital stay when compared to standard care (Wang et al., 2015). However, both studies were limited by a small sample size, lack of high-quality studies, significant heterogeneity between studies, and absence of a bias assessment. In a 2006 Cochrane review, the authors found no evidence to recommend routine use of DC to reduce unfavorable outcomes in adults with uncontrolled ICP (Sahuquillo & Arikan, 2006). A systematic review reported improved GOS scores and reduced mortality rates associated with DC, particularly in younger individuals with less severe (GCS>5) and more acute (<5hr) injuries (Barthelemy et al., 2016). However, the authors refrained from providing clinical recommendations given a lack of prospective data and significant results.

The AANS reported that there was insufficient evidence to support Level I recommendations regarding DC, although Level II recommendations were provided (Carney et al., 2017). A bifrontal DC was not recommended for improving long-term outcomes in individuals with severe TBI and prolonged, elevated

ICP. The authors noted, however, that bifrontal DC demonstrated significant reductions in ICP and ICU stay. As well, a larger frontotempoparietal DC was recommended over a smaller procedure for reduced mortality and improved neurological outcomes. The earlier EBIC suggested that DC should only be considered in “exceptional situations” (Maas et al., 1997).

Table 15.23 Decompressive Craniectomy for the Acute Management of Intracranial Pressure Post ABI

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Hutchinson et al. (2016b) UK RCT PEDro=7 N=408	<p>Population: TBI; <i>Treatment Group (TG, n=202):</i> Mean Age=32.3 yr; Gender: Male=165, Female=37. <i>Control Group (CG, n=196):</i> Mean Age=34.8 yr; Gender: Male=156, Female=43.</p> <p>Intervention: Participants were randomly assigned to receive decompressive craniectomy (TG) or standard care (CG). Outcomes were assessed at discharge, 6 mo, and 12 mo.</p> <p>Outcome Measures: Intracranial Pressure (ICP), Glasgow Outcome Scale Extended (GOSE), Mortality, Additional Treatments.</p>	<ol style="list-style-type: none"> Median ICP was significantly higher in the CG than the TG after treatment (17.1 mmHg versus 14.5 mmHg, $p<0.001$). Median ICP>25 mmHg duration was significantly higher in the CG than the TG after treatment (17.0hr versus 5.0 hr, $p<0.001$). Mortality was significantly higher ($p<0.001$) in the CG than the TG at ICU discharge (48.5% versus 22.7%), 6 mo (48.9% versus 26.9%), and 12 mo (52.0% versus 30.4%). At 6 mo and 12 mo, there were significant differences between groups in distribution on GOSE ($p<0.001$), with a greater proportion of the TG on the lower end ($GOSE\leq 4$) and a greater proportion of the CG on the higher end ($GOSE>4$). There was no significant difference between groups in additional treatments before/after trial.
Wang et al. (2014) China RCT PEDro=5 N=128	<p>Population: TBI; <i>Treatment Group 1 (TG1, n=64):</i> Mean Age=41.8 yr; Gender: Male=50, Female=14; Mean GCS=5.4. <i>Treatment Group 2 (TG2, n=64):</i> Mean Age=44.2 yr; Gender: Male=58, Female=6; Mean GCS=4.8.</p> <p>Intervention: Participants were randomized to receive decompressive craniectomy (TG1) or controlled decompression (TG2). Outcomes were assessed after treatment and at 6 mo.</p> <p>Outcome Measures: Intracranial Pressure (ICP), Glasgow Outcome Scale (GOS).</p>	<ol style="list-style-type: none"> There was no significant difference between TG1 and TG2 in postoperative ICP (45.6 mmHg versus 45.0 mmHg, $p=0.741$). There was no significant difference between groups in GOS classification at 6 mo ($p=0.417$).
Cooper et al. (2011) Australia RCT PEDro=6 N=155	<p>Population: TBI; <i>Treatment Group (TG, n=73):</i> Median Age=23.7 yr; Gender: Male=59, Female=14; Median Time Post Injury=35.2 hr; Median GCS=5. <i>Control Group (CG, n=82):</i> Median Age=24.6 yr; Gender: Male=61, Female=21; Median Time Post Injury=34.8 hr; Median GCS=6.</p> <p>Intervention: Participants were randomized to receive decompressive craniectomy (TG) or standard care (CG) for ICP. Outcomes were measured at 6 mo and physiological measures were monitored 12 hr</p>	<ol style="list-style-type: none"> Mean ICP was similar in both groups before treatment (20 mmHg), but was significantly lower in the TG than the CG after treatment (14.4 mmHg versus 19.1mmHg, $p<0.001$). Mean time ICP>20 mmHG was significantly longer in the CG than the TG (30.0 hr versus 9.2 hr, $p<0.001$).

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
	<p>before and 36hr after randomization. Outcome Measures: Glasgow Outcome Scale Extended (GOSE), Intracranial Pressure (ICP), Length of Stay (LOS), Mortality.</p>	<ol style="list-style-type: none"> 3. Mean LOS in ICU was significantly longer in the CG than the TG (18 days versus 13 days, $p<0.001$). 4. GOSE was significantly higher in the CG than the TG (4 versus 3; $OR=18.4$, $p=0.03$). 5. Poor outcome ($GOSE\leq 4$) was significantly greater in the TG than the CG (70% versus 51%; $OR=2.21$ $p=0.02$). 6. After adjustment for age and GCS, the results were similar for GOSE ($OR=1.66$, $p=0.08$) and poor outcome ($OR=2.31$, $p=0.03$), although the former was no longer significant. 7. There were no significant differences in mortality between the TG and CG (19% versus 18%).
<p>Qiu et al. (2009) China RCT PEDro=7 N=74</p>	<p>Population: TBI; <i>Treatment Group (TG, n=37)</i>: Mean Age=39.9 yr; Gender: Male=27, Female=10; $GCS\leq 8$. <i>Control Group (CG, n=37)</i>: Mean Age=40.2 yr; Gender: Male=24, Female=13; $GCS\leq 8$. Intervention: Participants were randomized to receive unilateral decompressive craniectomy (TG) or unilateral routine temporoparietal craniectomy (CG). Outcome Measures: Intracranial Pressure (ICP), Mortality Rate, and Glasgow Outcome Score (GOS).</p>	<ol style="list-style-type: none"> 1. ICP levels were significantly lower in the TG at 24, 48, 72 and 96 hr post operation in comparison to the CG. 2. Good outcome ($GOS=4-5$) at 1 yr was 56.8% in the TG and 32.4% in the CG ($p=0.035$). 3. Mortality rates at 1 mo were 27% in the TG and 57% in the CG ($p=0.01$).
<p>Jiang et al. (2005) China RCT PEDro=5 N=486</p>	<p>Population: TBI; <i>Treatment Group 1 (TG1, n=245)</i>: Mean Age=43.5 yr; Gender: Male=178, Female=67; Mean Time Post Injury=6.21 hr; Mean $GCS=5.21$. <i>Treatment Group 2 (TG2, n=241)</i>: Mean Age=45.4 yr; Gender: Male=169, Female=72; Mean Time Post Injury=6.45 hr; Mean $GCS=5.3$. Intervention: Participants were randomly assigned to either standard trauma craniectomy (TG1) with a unilateral frontotemporoparietal bone flap (12x15 cm) or limited craniectomy (TG2) with a routine temporoparietal bone flap (6x8 cm). Outcome Measures: Glasgow Outcome Score (GOS), Intracranial Pressure (ICP), Complications.</p>	<ol style="list-style-type: none"> 1. At 6 mo, more patients in the TG1 showed favourable outcome ($GOS=4-5$) compared with TG2 ($p<0.05$). 2. The incidence of some secondary complications was lower in TG1 than in TG2 ($p<0.05$). 8. ICP fell more rapidly and to a lower level in TG1 than in TG2 ($p<0.05$).
<p>Reid et al. (2018a) USA Cohort N=58</p>	<p>Population: TBI=58. Gender: Male=38, Female=20; Mean Time Post Injury=24hr; Mean $GCS=7.5$. Intervention: Patient data was retrospectively analyzed. Post-Craniectomy CT scans were analyzed for calculation of bone-flap surface area. Intracranial pressure (ICP) and GCS were recorded and monitored before surgery, post-operatively (6, 24, and 72hr) and at 1 year follow up. Outcome Measures: Intracranial Pressure (ICP), Glasgow Coma Scale (GCS).</p>	<ol style="list-style-type: none"> 1. Mean ICP was significantly lower after DC (16.7mmHg) compared to before (24.5 mmHg; $p=0.006$). 2. No change was found between pre-operative and post-operative mean GCS score ($p=0.959$). 3. Linear regression analysis showed that the DC surface area was not an independent predictor of postoperative ICP or GCS score.

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Gridlinger et al. (2016) USA Case Series N=31	Population: TBI; Mean Age=39 yr; Gender: Male=26, Female=5; Mean GCS=6. Intervention: Participants who received decompressive craniectomy were retrospectively analyzed. Outcome Measures: Intracranial Pressure (ICP), Glasgow Outcome Scale Extended (GOSE).	<ol style="list-style-type: none"> 1. Mean ICP was reduced from 30.7 mmHg at baseline to 12.1 mmHg after treatment. 2. At 6mo, 55% showed good outcome (GOSE=7-8), 19% showed moderate impairment (GOSE=5-6), 19% showed poor outcome (GOSE=2-4), and 7% died (GOSE=1).
Nambiar et al. (2015) Australia Case Series N=57	Population: TBI; Median Age=30 yr; Gender: Male=42, Female=15; Median GCS=4. Intervention: Participants who received decompressive craniectomy were retrospectively analyzed. Outcome Measures: Glasgow Outcome Scale Extended (GOSE), Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Mortality.	<ol style="list-style-type: none"> 1. ICP and CPP showed a mean decrease of 7.7mmHg and 3.5 mmHg after treatment, respectively. 2. Mortality was significantly correlated with ICP (p=0.03). 3. Poor outcome (GOSE≤4) was seen in 68% and good outcome (GOSE>4) was seen in 26% at 6 mo. 4. GOSE at 6 mo was significantly correlated with age (p=0.007).
Goksu et al. (2012) Turkey Case Series N=28	Population: TBI; Mean Age=28 yr; Gender: Male=17, Female=11; Mean GCS=5. Intervention: Participants who received decompressive craniectomy were retrospectively analyzed. Outcome Measures: Intracranial Pressure (ICP), Glasgow Outcome Scale (GOS), Mortality.	<ol style="list-style-type: none"> 1. There was a significant decrease in ICP after treatment (p<0.05). 2. Mortality at discharge was 61%. 3. Favourable outcome (GOS=4-5) was seen in 18% at 1 yr. 4. GCS was significantly correlated with survival (p<0.05).
Al-Jishi et al. (2011) Canada Case-Control N=70	Population: TBI; <i>Treatment Group 1 (TG1, n=44):</i> Mean Age=46.3 yr; Gender: Male=38, Female=6; Mean GCS=7.7. <i>Treatment Group 2 (TG2, n=26):</i> Mean Age=29.3 yr; Gender: Male=22, Female=4; Mean GCS=7.3. Intervention: Participants were compared based on timing and rationale for Decompressive craniectomy (DC): ≤24 hr for mass lesion (primary, TG1) or >24 hr for refractory ICP (secondary, TG2). Outcomes were assessed before and after treatment, and at a mean 11 mo follow-up. Outcome Measures: Glasgow Outcome Scale (GOS), Intracranial Pressure (ICP), Mortality.	<ol style="list-style-type: none"> 1. ICP significantly decreased after DC in TG1 (p=0.046) and TG2 (p<0.001). 2. Mean GOS was significantly higher in TG2 than TG1 after DC (3.69 versus 2.89, p=0.0286). 3. Good outcome (GOS≥4) was significantly higher in TG2 than TG1 (73.1% versus 45.5%, p=0.014). 4. Mortality was significantly higher in TG1 than in TG2 (40.9% versus 15.4%, p=0.026). 5. In TG1, age ≥40yr was a significant predictor of poor outcome (OR=10.56, p=0.001) and mortality (OR=5.82, p=0.018). 6. In TG2, there were no significant predictors of poor outcome or mortality.
De Bonis et al. (2011) Italy Post-Test N=44	Population: Mean Age=76.6 yr; Gender: Male=26, Female=18; Mean GCS=6.7. Intervention: Participants who received decompressive craniectomy (DC) for intracranial pressure (ICP) were recruited and analyzed. Outcomes were assessed at discharge from ICU and hospital and 1 yr follow-up.	<ol style="list-style-type: none"> 1. Mortality at ICU discharge was 48%, 57% at hospital discharge, and 77% at 1 yr. 2. ICP was controlled (<20 mmHg) in 89% of participants. The 11% with sustained ICP≥20 mmHg died in ICU. 3. Poor outcome (GOS<4) was found in 82% of subjects at hospital discharge and 1 yr.

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
	Outcome Measures: Glasgow Outcome Scale (GOS), Simplified Acute Physiology Score (SAPS II), Intracranial Pressure (ICP), Mortality.	<ol style="list-style-type: none"> 4. Mean GCS was significantly lower in participants who died than those who lived (5.9 versus 8.6, $p=0.02$). 5. Mean SAPS II was significantly higher in participants who died than those who lived (57.3 versus 45.2, $p=0.002$), and in those who died in ICU rather than after ICU discharge (60.3 versus 52.4, $p=0.04$). 6. Only GCS was an independent predictive factor for outcome (OR=7.764, $p=0.012$). 7. In those with GCS=3-5 ($n=22$), none had a good outcome. In those with GCS=6-8 ($n=10$), 20% had a good outcome. In those with GCS≥ 9 ($n=12$), 50% had a good outcome.
Giroto et al. (2011) Croatia Case Control N=95	Population: TBI; Age Range=15-65 yr; GCS Range ≤ 8 . Intervention: Participants who received decompressive craniectomy ($n=39$) or craniotomy ($n=34$) were compared to those who did not receive any surgical procedures ($n=22$). Outcome Measures: Intracranial Pressure (ICP), Mortality.	<ol style="list-style-type: none"> 1. Percentage of participants with ICP<25 mmHg was significantly higher in those who received surgery than those who did not ($p=0.001$). 2. Mortality rate at 1 yr was 18% for those who received surgery <24 hr post injury, 54% for those who received surgery ≥ 24 hr post injury, and 35% for those who received no surgery.
Bao et al. (2010) China Case Series N=37	Population: TBI; Mean Age=38 yr; Gender: Male=25, Female=12; Time Post Injury ≤ 7 days; GCS Range ≤ 8 . Intervention: Participants who received decompressive craniectomy were retrospectively analyzed. Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Glasgow Outcome Score (GOS).	<ol style="list-style-type: none"> 1. Mean ICP was reduced from 37.7 mmHg pre surgery to 27.4 mmHg ($p<0.05$) after bone removal and 11.2 mmHg ($p<0.05$) after dura mater opening and enlargement. 2. Mean ICP was 16.3 mmHg at 1-day post surgery, 17.4 mmHg at 3 days, and 15.5 4.6 mmHg at 7 days. 3. Mean CPP was increased from 57.6mmHg pre surgery to 63.3 mmHg ($p<0.05$) after bone removal and 77.8mmHg ($p<0.05$) after dura mater opening and enlargement. 4. At 6mo, 54.1% of patients made moderate (GOS=4, 32.5%) or good (GOS=5, 21.6%) recovery.
Eberle et al. (2010) USA Case Series N=43	Population: TBI; Mean Age=35.7 yr; Gender: Male=34, Female=9; Mean GCS=8.6. Intervention: Participants who received decompressive craniectomy were retrospectively analyzed. Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Glasgow Outcome Scale (GOS).	<ol style="list-style-type: none"> 1. Mean ICP significantly decreased after treatment (41 mmHg to 16 mmHg, $p<0.05$), but was significantly lower among survivors ($p=0.001$). 2. Mean CPP significantly decreased after treatment (49.4 mmHg to 64.8 mmHg, $p<0.05$), and was significantly higher among survivors ($p=0.005$).

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
		<ol style="list-style-type: none"> 3. Favourable outcome (GOS=4-5) was seen in 42% of participants and unfavourable outcome (GOS=1-3) was seen in 58%. 4. There was no significant correlation between admission time and GOS (p=0.470).
Soustiel et al. (2010) Israel Pre-Post N=36	<p>Population: TBI; Mean Age=35.1 yr; Mean GCS=5.8. Intervention: Participants received decompressive craniectomy. Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Cerebral Blood Flow (CBF).</p>	<ol style="list-style-type: none"> 1. Mean ICP decreased from 20.4 mmHg to 4.1 mmHg after treatment (p=0.0098). 2. CPP increased from 66.8 mmHg to 74.6mmHg after treatment (p>0.05). 3. CBF increased from 34.8 mmHg to 38.4 mmHg after treatment (p=0.0073).
Aarabi et al. (2009) USA Case Control N=54	<p>Population: TBI; Mean Age=35 yr; Gender: Male=45, Female=9; Mean GCS=6.6. Intervention: Participants underwent decompressive craniectomy (DC) for mass lesion evacuation or DC with ICP monitoring (DC+ICP). Outcome Measures: Intracranial Pressure (ICP), Glasgow Outcome Scale (GOS), Mortality.</p>	<ol style="list-style-type: none"> 1. No difference was noted between groups for survival or outcome. 2. Twelve patients died in group A and 10 in group B, while 11 had good recovery in group A and 8 in group B. 3. Good outcome (GOS=4-5) was 41% in DC and 30% in DC+ICP. 4. Poor outcome (GOS=2-3) was 11% in DC and 30% in DC+ICP. 5. Mortality was 44% in DC and 37% in DC+ICP. 6. Of the survivors, good outcome was 79% in DC and 47% in DC+ICP (OR=0.2).
Daboussi et al. (2009) France Pre-Post N=26	<p>Population: TBI; Mean Age=35.3 yr; Gender: Male=23, Female=3; Mean Time Post Injury=66.8 hr; Mean GCS=8.9. Intervention: Participants received decompressive craniectomy. Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Neurological Outcomes, Mortality.</p>	<ol style="list-style-type: none"> 1. Mean ICP was reduced from 37 mmHg to 20 mmHg (p=0.0003) and mean CPP was increased from 61 mmHg to 79 mmHg (p<0.05) immediately post surgery and remained significant at 48 hr. 2. Mortality was 27% and among those that survived 53% had favourable neurologic outcomes.
Kim et al. (2009) South Korea Case Series N=28	<p>Population: TBI; Mean Age=52.3 yr; Gender: Male=21, Female=7; Mean Time Post Injury=9.6 hr; Severity: Severe=20, Moderate=8. Intervention: Participants who received decompressive craniectomy were retrospectively analyzed. Outcome Measures: Intracranial Pressure (ICP), Glasgow Outcome Scale (GOS).</p>	<ol style="list-style-type: none"> 1. Mean ICP significantly decreased after treatment (37.9 mmHg to 19.4 mmHg, p<0.05). 2. Favourable outcome (GOS=4-5) was seen in 57% of patients and unfavourable outcome (GOS=1-3) was seen in 43%. 3. Decrease in ICP was significantly correlated with GOS scores (t=-2.87, p=0.01).
Ho et al. (2008) Singapore Case Series N=16	<p>Population: TBI; Mean Age=38 yr; Gender: Male=13, Female=3, Median GCS=5. Intervention: Participants who received decompressive craniectomy were retrospectively analyzed. Outcome Measures: Glasgow Outcome Score (GOS),</p>	<ol style="list-style-type: none"> 1. Five participants had a favourable outcome at 6 mo and 1 made a good recovery. 2. Significant reductions in ICP and pressure reactivity were seen in those with favourable and unfavourable outcomes.

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
	Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Pressure Reactivity, Cerebral Oxygenation.	<ol style="list-style-type: none"> 3. Significant increases in CPP were seen in the poor outcome group (p=0.001). 4. Those with favourable outcomes saw significant improvements in cerebral oxygenation and a reduction in cerebral ischemia.
Howard et al. (2008) USA Case Series N=40	<p>Population: TBI; <i>Group 1 (G1, n=12):</i> Mean Age=28.2 yr; Mean GCS=6.1. <i>Group 2 (G2, n=28):</i> Mean Age=33.6 yr; Mean GCS=3.6.</p> <p>Intervention: Participants who received decompressive craniectomy (DC) were divided into those who had favorable (G1) and unfavorable (G2) outcomes.</p> <p>Outcome Measures: Intracranial Pressure (ICP), Glasgow Outcome Score Extended (GOSE), Mortality.</p>	<ol style="list-style-type: none"> 1. DC effectively lowered ICP (p=0.005). 2. Twenty-two patients died in hospital. Of the survivors, 12 of 18 had good outcomes on the GOSE. 3. Initial GCS score was associated with outcomes while age and ISS score did not.
Timofeev et al. (2008a) UK Case Series N=27	<p>Population: TBI; Median Age=35 yr; Gender: Male=22, Female=5; Severity: Severe=20, Moderate=7.</p> <p>Intervention: Participants who received decompressive craniectomy were retrospectively analyzed.</p> <p>Outcome Measures: Intracranial Pressure (ICP), Glasgow Outcome Score (GOS), Pressure Reactivity.</p>	<ol style="list-style-type: none"> 1. Mean ICP levels were reduced from 21.2 mmHg pre operation to 15.7 mmHg post operation (p=0.01). 2. ICP exceeded 25 mmHg 28.6% of the time pre operation and only 2.2% of the time post operation (p<0.01). 3. Pressure reactivity post operation was significantly associated with favourable outcome (GOS=4-5) at 6 mos post operation (p=0.02) but pre-operation pressure reactivity was not (p=0.462).
Olivecrona et al. (2007) Sweden Case Series N=93	<p>Population: TBI; Mean Age=37.6 yr; Gender: Male=71, Female=22; Mean GCS=6.1</p> <p>Intervention: Participants who received decompressive craniectomy were retrospectively analyzed.</p> <p>Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP).</p>	<ol style="list-style-type: none"> 1. Craniectomy patients showed a decrease in mean ICP from 36.4 mmHg to 12.6 mmHg after surgery. 2. There was an increase in ICP to 20mmHg 8-12hr after surgery, leveling off at 25 mmHg within 72 hr.
Aarabi et al. (2006) USA Case Series N=50	<p>Population: TBI; Mean Age=25.3 yr; Gender: Male=33, Female=17; Time Post Injury<11 days; Severity: Severe=38, Moderate/Mild=12.</p> <p>Intervention: Participants who received decompressive craniectomy were retrospectively analyzed.</p> <p>Outcome Measures: Intracranial Pressure (ICP), Glasgow Outcome Score (GOS).</p>	<ol style="list-style-type: none"> 1. ICP was reduced to <20 mmHg in 85% of patients. 2. Good outcome was experience in 40% of patients on discharge and 34% after 3 mo. Outcomes were independent of timing of surgery and patient age.
Heppner et al. (2006) USA Pre-Post N=6	<p>Population: TBI; Mean Age=27 yr; Gender: Male=5, Female=1; Mean Time Post Injury=11 hr; Mean GCS=4.3.</p> <p>Intervention: Participants received decompressive craniectomy.</p> <p>Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP).</p>	<ol style="list-style-type: none"> 1. Mean ICP significantly decreased after treatment (35 mmHg to 12 mmHg, p<0.05) and remained significantly reduced up to 2 days. 2. Mean CPP significantly increased after treatment (55 mmHg to 78 mmHg,

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
		p<0.05) and remained significantly increased up to 2 days.
Skoglund et al. (2006) Sweden Case Series N=19	Population: TBI; Mean Age=22 yr; Gender: Male=13, Female=6; Mean Time Post Injury=4.5 days; Mean GCS=7.05. Intervention: Participants who received decompressive craniectomy were retrospectively analyzed. Outcome Measures: Intracranial Pressure (ICP), Glasgow Outcome Score (GOS), Mortality.	<ol style="list-style-type: none"> 1. ICP was reduced from 29.2±3.5 to 11.1±6.0 mmHg after surgery and 13.9±9.7 mmHg after 24 hr (p<0.01). 2. Sixty-eight percent of patients had favorable outcomes at least 1 yr post surgery. 3. There was a significant correlation between the size of craniectomy and decrease in ICP (p<0.05).
Ucar et al. (2005) Turkey Case Series N=100	Population: TBI; Mean Age=29.9 yr; Gender: Male=68, Female=32; Mean Time Post Injury=17.1 hr; GCS≤8. Intervention: Participants who received decompressive craniectomy were retrospectively analyzed. Outcome Measures: Intracranial Pressure (ICP), Glasgow Outcome Score (GOS).	<ol style="list-style-type: none"> 1. There was a significant decrease in ICP after decompression from 29.8 mmHg to 23.9 mmHg (p<0.001). 2. Age (p=0.046) and GCS (p<0.05) were significantly related to favourable outcome (GOS=4-5).
Stiefel et al. (2004) USA Pre-Post N=7	Population: TBI=5, SAH=2; Mean Age=30.6 yr; Gender: Male=5, Female=2; Mean GCS=3. Intervention: Participants received decompressive hemicraniectomy. Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP).	<ol style="list-style-type: none"> 1. Mean ICP significantly decreased after treatment (26 mmHg to 19 mmHg, p<0.05) 2. Mean CPP significantly increased after treatment (71 mmHg to 84 mmHg, p<0.05).
Schneider et al. (2002) Germany Case Series N=62	Population: TBI; Mean Age=36.6 yr; Gender: Male=48, Female=14; Mean GCS=6. Intervention: Participants who received decompressive craniectomy were retrospectively analyzed. Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Glasgow Outcome Scale (GOS).	<ol style="list-style-type: none"> 1. Mean ICP significantly decreased 40.5 mmHg to 9.8 mmHg after treatment (p<0.05) but increased to 21.6 mmHg after 12hr. 2. Mean CPP significantly increased from 65.3mmHg to 78.2 mmHg after treatment (p<0.05), but decreased to 73.6 mmHg after 12 hr. 3. At 6mo, 23% of patients died (GOS=1), 48% had unfavourable outcome (GOS=2-3), and 29% had favourable outcome (GOS=4-5).
Whitfield et al. (2001) UK Pre-Post N=26	Population: TBI; Mean Age=23 yr; Gender: Male=21, Female=5; Severity: Mild=3, Moderate=5, Severe=18. Intervention: Participants received bifrontal decompressive craniectomy. Outcome Measures: Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP).	<ol style="list-style-type: none"> 1. Mean ICP significantly decreased after treatment (37.5 mmHg to 18.1 mmHg, p=0.003). 2. There was no significant change in mean CPP after treatment (62.1 mmHg to 69.4 mmHg, p=0.18).
Munch et al. (2000) Germany Case Series	Population: TBI; Mean Age=43.4 yr; Gender: Male=41, Female=8; Mean GCS=8. Intervention: Participants who received decompressive craniectomy were retrospectively	<ol style="list-style-type: none"> 1. Midline shift showed a significant mean decrease after treatment (-3.2 mm, p=0.0004).

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
N=49	analyzed. Outcome Measures: Midline Shift, Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Glasgow Outcome Scale (GOS).	<ol style="list-style-type: none"> There were no significant differences in ICP or CPP after treatment. At discharge, 72% of patients had poor outcome (GOS=1-3) and 28% had good outcome (GOS=4-5). At 6 mo, 59% had poor outcome and 41% had good outcome. GOS was significantly correlated with younger age and earlier treatment.
Polin et al. (1997) USA Case Control N=70	Population: TBI; <i>Treatment Group (TG, n=35):</i> Mean Age=18.7 yr; Mean GCS=5.62. <i>Control Group (CG, n=35):</i> Mean Age=19.1 yr; Mean GCS=5.68. Intervention: Participants who received bifrontal decompressive craniectomy (TG) were compared to those who did not receive it (CG). Outcome Measures: Intracranial Pressure (ICP), Glasgow Outcome Scale (GOS).	<ol style="list-style-type: none"> ICP after treatment was significantly lower in the TG than in the CG (p=0.0003). Favourable outcomes (GOS=4-5) were significantly higher in the TG than in the CG (p=0.014). Those in the TG who did not exhibit ICP>40Torr and underwent surgery <48 hr after injury revealed a 60% favorable outcome rate and had an advantage over the CG (p=0.0001).

Table 15.24 Miscellaneous Outcomes - Decompressive Craniectomy for Acute Management Post ABI

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Khan et al. (2016) Pakistan RCT PEDro=4 N=59	Population: ABI; Gender: Male=53, Female=6; GCS:3-5=23, 6-8=28, 9-11=8. Intervention: Expansile Duraplasty and dural-slits were compared for patients who underwent decompressive craniectomy for acute subdural haematoma. Outcome Measures: Glasgow Outcome Scale (GOS), mortality.	<ol style="list-style-type: none"> Neither mortality nor postoperative GOS scores differed significantly between groups. Surgery duration was significantly shorter for the Expansile Duraplasty group (p=0.000).
Moein et al. (2012) RCT PEDro=6 N=20	Population: ABI; <i>Treatment Group (TG, n=10):</i> Mean Age=34.6 yr; Mean GCS=5.6. <i>Control Group (CG, n=10):</i> Mean Age=31.8 yr; Mean GCS=5.6. Intervention: Participants were randomized to receive decompressive craniectomy with standard treatment (TG) or standard treatment alone (CG). Outcomes were assessed at 6 mo. Outcome Measures: Glasgow Coma Scale (GCS), Glasgow Outcome Scale (GOS).	<ol style="list-style-type: none"> GCS improved after treatment in the TG when compared to the CG, but the difference was not significant (p=0.087). Favourable outcome (GOS=4-5) was found in 60% of the TG and 20% of the CG, but the difference was not significant (p=0.85). Mortality (GOS=1) was found in 10% of the TG and 30% of the CG, but the difference was not significant (p=0.28). Age group was not significantly correlated with GOS (p=0.57).

<p>Grassner et al. (2018) Germany & Austria Case Series N=9</p>	<p>Population: TBI=6, Intracerebral hemorrhage=2. Extraaxial tumours=2. Mean Age=48yr; Gender: Male=6, Female=3; Mean GCS=7. Intervention: Patients in need of a DC, where initial skin closure was not possible due to brain swelling or significantly raised ICP were retrospectively analyzed. Outcome Measures: Synthetic Skin Substitution, Mortality, Complications.</p>	<ol style="list-style-type: none"> 1. Epiguard (synthetic skin substitute) was used during a primary DC in 5 cases. The remainder were applied in secondary DC, or revision surgeries. 2. Mortality rates in the TBI population were 50%. 3. Four patients developed a wound infection. 4. Average time to skin closure was 21 days.
<p>Kelly et al. (2018) USA Case Control N=1,470</p>	<p>Population: TBI=1,470. <i>Craniotomy Group (n=1,470):</i> Median Age=43yr; Gender: Male=1102, Female: 368; Median GCS=11. <i>Control Group (n=1,470):</i> Mean Age=42yr; Gender: Male= 1,097, Female= 373; Median GCS= 11. Intervention: Individuals who had received either a Craniotomy (CO) or a Craniectomy (CE) after sustaining a TBI were retrospectively analyzed using the National Institute on Disability, Independent living, and Rehabilitation Research TBI model systems (TBIMS). Outcomes were measured during treatment, rehabilitation, and up to 2yr post intervention. Outcome Measures: Hospital LOS, Rehospitalization, Mortality, Functional Independence Measure (FIM), Glasgow Outcome Scale-Extended (GOSE) score, Satisfaction with Life Scale.</p>	<ol style="list-style-type: none"> 1. On average, CE patients had significantly longer hospital LOS compared to CO patients (22 versus 18d, p=0.01). 2. Rehospitalization rates were significantly higher in the CE group at 1 and 2yr post intervention compared to the CO group (P<0.01). 3. Mortality was significantly higher in the CE group at 6mo (p=0.09), but not 1 or 2yr compared to the CO group. 4. The FIM total, motor, and cognitive score was significantly higher in the CO group compared to the CE group at rehab discharge, 1 and 2 years post treatment (p=0.02). 5. Significantly more patients in the CE group had GOSE scores ≤4 at 1 and 2 years post treatment compared to the CO group (p=0.02). 6. Satisfaction with Life Scale score was not different for either group at 1 or 2 years post-treatment.
<p>Nasi et al. (2018) Italy Pre-Post test N= 190</p>	<p>Population: TBI=190; Mean Age=50yr; Gender: Male=149, Female=41; Mean Time Post Injury to Intervention= 24.5hr; GCS: 3-5= 129, 6-8= 59, 8+=2. Intervention: Patients receiving a decompressive craniectomy (primary or secondary) following a severe TBI were retrospectively analyzed. Outcomes were assessed before and after the intervention. Outcome Measures: Glasgow Outcome Scale (GOS), Mortality, Complications.</p>	<ol style="list-style-type: none"> 1. Primary DC was performed on 109 patients, whereas secondary DC was performed on 81. 2. Overall mortality was 46.8%, with 31.6% of all patients dying within 30d. 3. Age over 65, lower GCS at admission, absence of bilateral pupil reactivity, and SDH and brain contusion were associated with higher risk of 30d mortality. 4. At 6mo after DC, 51.5% of patients who were alive had a poor outcome (GOS severe disability, persistent vegetative state) 5. The overall rate of complication was 46.8%. The most common complication was the development of Hydrocephalus (19.5% of all patients).
<p>Jehan et al. (2017) USA</p>	<p>Population: TBI; DC (n=33): Mean Age=47.9 yr; Gender: Male=23, Female=10; Mean Time Post Injury=3.8 hr; Median GCS=9. CO (n=66): Mean Age=49.2 yr; Gender: Male=46, Female=20; Mean Time Post Injury=3.5 hr;</p>	<ol style="list-style-type: none"> 1. There were no significant differences between groups for mortality, LOS, GOS or GCS.

<p>Case Control N=99</p>	<p>Median GCS=11. Intervention: Patients with TBI underwent decompressive craniectomy (DC) in conjunction with evacuation of intracranial hemorrhage (ICH) to control intracranial pressure (ICP). Controls were treated by craniotomy (CO) in conjunction with ICH evacuation. Outcome Measures: Mortality, Glasgow Coma Scale (GCS), Glasgow Outcome Scale (GOS), Complications, Length of Stay (LOS).</p>	<p>2. The DC group had significantly more returns to the OR ($p=0.04$), events of hydrocephalus requiring shunt ($p=0.03$) and median days on ventilator ($p=0.02$) than the CO group.</p>
<p>Shibahashi et al. (2017) Japan Case Series N=1391</p>	<p>Population: TBI; with Emergency Trepanation (n=305): Median Age=62 yr; Gender: Male=207, Female=98; Median GCS=4. without Emergency Trepanation (n=1086): Median Age=65 yr; Gender: Male=717, Female=369; Median GCS=6. Intervention: Patients with thick subdural hemorrhages who had undergone craniotomy were retrospectively identified. Those who underwent trepanation in an emergency room were compared with those who did not. Outcome Measure: Survival at Discharge.</p>	<p>1. Survival at discharge was significantly lower for those who underwent emergency trepanation (37.7%) compared with those who did not (59.3%), even after adjusting for possible cofounders (adjusted odds ratio=0.55; $p<0.001$).</p>
<p>Tapper et al. (2017) Australia Case Series N=822</p>	<p>Population: TBI; No operation (n=363): Median Age=57 yr; GCS:3-8=133, 9-12=83, 13-15=147. Craniotomy (n=401): Median Age=61 yr; GCS:3-8=183, 9-12=100, 13-15=118. Craniectomy (n=58): Median Age=45 yr; GCS:3-8=42, 9-12=13, 13-15=3. Intervention: Patients admitted to a neurosurgical ICU during 2009-2012 were divided into 3 groups (decompressive craniectomy, craniotomy, and conservative). Outcome Measures: Glasgow Outcome Scale (GOS), Mortality.</p>	<p>1. Patients in the decompressive craniectomy group (60%) were more likely to have an unfavourable outcome when compared to the craniotomy (53%) and conservative group (41%) ($p<0.001$). 2. Decompressive craniectomy was not associated with increased mortality at 6mo compared to conservatively treated patients. However, it was associated with increased 6mo mortality compared to patients in the craniotomy group ($p=0.029$).</p>
<p>Rush et al. (2016) USA & Canada Case Series N=1940</p>	<p>Population: TBI; Craniotomy (n=1763): Mean Age=68.9 yr; Gender: Male=1150, Female=613. Craniectomy (n=177): Mean Age=49.5 yr; Gender: Male=127, Female=50. Intervention: Patients data was gathered retrospectively to compare craniectomy and craniotomy for the management of acute subdural hemorrhage (ASDH). Outcome Measures: Mortality, Length of Hospital Stay (LOS).</p>	<p>1. Compared to craniotomy (22%), craniectomy (32%) was associated with increased hospital mortality ($p=0.044$). 2. LOS is significantly higher in craniectomy patients (14.3 days) compared to craniotomy (10.9 days) ($p<0.0001$).</p>
<p>Quintard et al. (2015) France Case Control N=25</p>	<p>Population: TBI; Treatment Group (TG, n=13): Mean Age=32 yr; Gender: Male=11, Female=2; Mean GCS=8. Control Group (CG, n=12): Mean Age=30 yr; Gender: Male=10, Female=2; Mean GCS=8. Intervention: Participants who received decompressive craniectomy (TG) were compared to those who received standard care (CG). Outcome Measure: Glasgow Outcome Scale (GOS).</p>	<p>1. At baseline, the CG had significantly lower ICP than the TG. 2. No significant differences were found between groups on GOS ($p>0.05$).</p>
<p>Gong et al. (2014) China</p>	<p>Population: TBI; Mean Age=46 yr; Gender: Male=47, Female=25; Mean GCS=5. Intervention: Participants who received decompressive</p>	<p>1. Mortality at was 23% at 1 mo and 29% at 6mo.</p>

Case Series N=72	craniectomy were retrospectively analyzed. Outcome Measure: Glasgow Outcome Scale (GOS), Mortality.	<ol style="list-style-type: none"> 2. Favourable outcome (GOS=4-5) at 6 mo was seen in 39%. 3. GOS was significantly associated with GCS on admission.
Nirula et al. (2014) USA Case Control N=420	Population: TBI; Mean Age=40yr; Gender: Male=330, Female=90; Mean GCS=7. Intervention: Participants received standard care (SC) and early decompressive craniectomy (DC, n=210) or SC alone (n=210). Outcome Measure: Mortality.	<ol style="list-style-type: none"> 1. There was no survival benefit SC+DC when compared to SC (RR=1.07, p=0.77).
Galal et al. (2013) Egypt Case Series N=37	Population: ABI; Age Range=14-65 yr; Gender: Male=30, Female=7; GCS<8. Intervention: Participants who received decompressive craniectomy were retrospectively analyzed. Outcome Measure: Glasgow Outcome Scale (GOS).	<ol style="list-style-type: none"> 1. At discharge, 70% of participants had favourable outcomes (GOS=4-5). 2. At discharge, 14% of participants had died (GOS=1).
Huang et al. (2013) China Case Series N=201	Population: TBI; Mean Age=45.78 yr; Gender: Male=144, Female=57; Mean GCS=6.95. Intervention: Participants who received decompressive craniectomy were retrospectively analyzed. Outcome Measure: Mortality.	<ol style="list-style-type: none"> 1. Overall, mortality was 26.4% at 30 days. 2. In univariate analysis, significant predictors of 30 days mortality included age (OR=1.020, p=0.014) and GCS (OR=0.5444, p<0.001). 3. In multivariate analysis, significant predictors of 30 days mortality included age (OR=1.035, p=0.018) and GCS (OR=0.0769, p=0.041).
Limpastan et al. (2013) Thailand Case Series N=159	Population: TBI; Mean Age=37 yr; Gender: Male=130, Female=29; Mean GCS=6. Intervention: Participants who received decompressive craniectomy were retrospectively analyzed. Outcome Measure: Glasgow Outcome Scale (GOS), Mortality.	<ol style="list-style-type: none"> 1. Mortality at discharge was 45%. 2. Favourable outcome (GOS=4-5) was seen in 13% at discharge and 24% at 6 mo. 3. GOS was significantly associated with age and GCS.
Yuan et al. (2013) China Case Series N=164	Population: TBI; Mean Age=47.60 yr; Gender: Male=123, Female=41; GCS: 3-5=51, 6-8=52, 9-12=61. Intervention: Participants were included in retrospective analysis following decompressive craniectomy with (n=93) or without (n=71) mass evacuation. Outcome Measure: Glasgow Outcome Scale (GOS), Mortality.	<ol style="list-style-type: none"> 1. At 60 days, good outcome (GOS>4) was found in 42%, poor outcome in 36% (GOS=2-3), and death (GOS=1) in 22% of patients. 2. Predictors of death at 60 days included age>50 yr (OR=2.36, p=0.047) and mass evacuation (OR=0.31, p=0.014). 3. Predictor of good outcome at 60 days was GCS=9-12 (OR=2.43, p=0.002).
Agrawal et al. (2012) India Case Series N=273	Population: TBI; Mean Age=34 yr; Gender: Male=229, Female=44; Mean GCS=6. Intervention: Participants who received decompressive craniectomy were retrospectively analyzed. Outcome Measure: Glasgow Outcome Scale (GOS), Mortality.	<ol style="list-style-type: none"> 1. In-hospital mortality rate (GOS=1) was 54%. 2. At discharge, 22% of participants showed favourable outcome (GOS=4-5).
Li et al. (2012) UK Case-Control N=91	Population: ABI; Treatment Group 1 (TG1, n=36): Median Age=59 yr; Gender: Male=18, Female=18; Median GCS=9.5. Treatment Group 2 (TG2, n=49): Median Age=49 yr; Gender: Male=33, Female=16; Median GCS=5. Intervention: Participants were compared on treatment received for elevated intracranial pressure	<ol style="list-style-type: none"> 1. Initially, TG2 were significantly older (p=0.015), more severely injured (p=0.001), and had a higher rate of extracranial injury (33% versus 3%, p=0.001) than TG1.

	(ICP): craniotomy (TG1) versus decompressive craniectomy (TG2). Outcomes were assessed at 6 mo. Outcome Measures: Glasgow Outcome Scale (GOS), Mortality.	<ol style="list-style-type: none"> At 6mo, there was no significant difference between TG1 and TG2 for mortality (32% versus 38%, $p=0.65$). At 6mo, there was no significant difference between TG1 and TG2 for poor outcome (GOS<4; 55% versus 58%, $p=0.83$).
Chen et al. (2011) Taiwan Case-Control N=102	<p>Population: ABI; Treatment Group 1 (TG1, n=42): Mean Age=47.4 yr; Gender: Male=21, Female=21; Mean Time Post Injury=6.7 hr; Mean GCS=6.3. Treatment Group 2 (TG2, n=60): Mean Age=41.2 yr; Gender: Male=41, Female=19; Mean Time Post Injury=5.8 hr; Mean GCS=5.9.</p> <p>Intervention: Participants were compared based on treatment for ICP: craniotomy (TG1) or decompressive craniectomy (TG2). Outcomes were assessed at 1 yr.</p> <p>Outcome Measures: Glasgow Outcome Scale (GOS), Complications.</p>	<ol style="list-style-type: none"> Mortality (GOS=1) was significantly higher in TG2 than TG1 (23.3% versus 7.1%, $p=0.04$). There was no significant difference between groups in GOS scores ($p=0.21$), functional survival (GOS>4; $p=0.78$), non-functional survival (GOS=2-3; $p=0.57$), or poor outcome (GOS<4; $p=0.78$). There were no significant differences between groups in clinical features of injury (e.g. severity, timing, CT scan). There were no significant differences between groups in postoperative complications.
Chibbaro et al. (2011) France Post-Test N=147	<p>Population: TBI; Median Age=39 yr; Gender: Male=111, Female=36; Median GCS=6.</p> <p>Intervention: Participants received decompressive craniectomy (DC) within 28 hr and cranioplasty within 12 wk. Outcomes were assessed at a mean follow-up of 26 mo.</p> <p>Outcome Measure: Glasgow Outcome Scale (GOS).</p>	<ol style="list-style-type: none"> Outcome was good (GOS>4) in 67% of participants and poor (GOS=2-3) in 19%; 14% died (GOS=1). Significant predictors of positive outcome were age <50 yr ($p<0.0001$) and DC <9 hr post injury ($p<0.03$).
Ho et al. (2011) Australia Post-Test N=104	<p>Population: TBI; Mean Age=33yr; Gender: Male=86, Female=18; Mean GCS=7.</p> <p>Intervention: Participants who received decompressive craniectomy and had moderate to severe neurological disability at 6mo were recruited and analyzed. Outcomes were assessed at 6, 12, and 18 mo.</p> <p>Outcome Measure: Glasgow Outcome Scale (GOS).</p>	<ol style="list-style-type: none"> At 6mo, 43% had good outcomes (GOS>4) and 57% had poor outcomes (GOS<4). At 12mo, 54% had good outcomes, 43% had poor outcomes, and 1% died; 2% were lost to follow-up. At 18mo, 55% had good outcomes, 37% had poor outcomes, and 2% died; 8% were lost to follow-up. GCS score was a predictor of improvement from poor to good outcome over 6-18 mo (OR=1.44, $p=0.18$) and of good outcome at 18 mo (OR=1.47, $p=0.001$).
Wen et al. (2011) China Cohort N=44	<p>Population: TBI; Treatment Group (TG1, n=25): Mean Age=46.7 yr; Gender: Male=17, Female=8; Mean GCS=6.0. Treatment Group 2 (TG2, n=19): Mean Age=50.2 yr; Gender: Male=15, Female=4; Mean GCS=6.6.</p> <p>Intervention: Participants who received decompressive craniectomy (DC) were recruited and compared based on timing of DC: early (<24 hr, TG1) or late (>24 hr, TG2). Outcomes were assessed at 1 mo and 6 mo.</p> <p>Outcome Measures: Glasgow Outcome Scale (GOS), Mortality.</p>	<ol style="list-style-type: none"> There was no significant difference between TG1 and TG2 in good outcome (GOS>4) at 1 mo (28% versus 37%, $p=0.533$) or 6 mo (52% versus 63%, $p=0.459$). There was no significant difference between TG1 and TG2 in mortality at 1 mo (16% versus 15.8%, $p=0.985$) or 6 mo (20% versus 21%, $p=0.932$).

<p>Otani et al. (2010) Japan Case Control N=80</p>	<p>Population: TBI; Mean Age=37.3 yr; Gender: Male=60, Female=20; Severity: Severe=40, Moderate=16, Mild=24. Intervention: Participants underwent either Hematoma Evacuation (HE) or HE with Decompressive Craniectomy (HE+DC). Outcome Measure: Glasgow Outcome Scale (GOS).</p>	<ol style="list-style-type: none"> 1. Significant differences in patient characteristics were noted between groups. 2. Favorable outcome on GOS was noted in 78.2% of patients in the HE group, while only in 55.8% of the HE+DC group.
<p>Rubiano et al. (2009) Colombia Case Control N=36</p>	<p>Population: TBI; Mean Age=20yr; Gender: Male=21, Female=15; Mean GCS=4.5. Intervention: Participants received early frontotempoparietal Decompressive Craniectomy (DC, n=16) or Standard Care (SC, n=10). Outcome Measures: Glasgow Outcome Scale (GOS), Mortality.</p>	<ol style="list-style-type: none"> 1. Mortality was significantly higher in the DC group than in the SC group (25% versus 65%, p<0.05). 2. Mean GOS was significantly higher in the DC group than in the SC group (3.1 versus 1.6, p=0.0002).
<p>Williams et al. (2009) USA Case Series N=171</p>	<p>Population: TBI; Median Age=35yr; Gender: Male=137, Female=34; Median GCS=8. Intervention: Participants who received decompressive craniectomy were retrospectively analyzed. Outcome Measures: Glasgow Outcome Score Extended (GOSE), Mortality.</p>	<ol style="list-style-type: none"> 1. Thirty-two percent of patients died in hospital. 2. Of the survivors, 82% achieved good outcomes (GOSE=5-8). 3. Patients who experienced good outcomes were younger (26yr versus 43yr, p=0.0028), had higher pre-surgery GCS (7 versus 5, p<0.001), and experienced a greater reduction in ICP post surgery (23mmHg versus 10 mmHg, p<0.0001).
<p>Flint et al. (2008) USA Pre-Post N=40</p>	<p>Population: TBI; Mean Age=43 yr; Gender: Male=30, Female=10; Median GCS=7.5. Intervention: Participants received decompressive craniectomy. Outcome Measures: Glasgow Outcome Score (GOS), Mortality, Contusions.</p>	<ol style="list-style-type: none"> 1. New or expanded hemorrhagic contusions of ≥5cc were observed in 58% of participants. 2. Mean volume of increase hemorrhage in these participants was 37.1cc. 3. Contusions expanded >20 cc post treatment were strongly associated with mortality and poor outcome on the GOS at 6 mo, even after controlling for age and GCS.
<p>Huang et al. (2008) Taiwan Case Control N=54</p>	<p>Population: TBI; Mean Age=43.37 yr; Median Time Post Injury=48.65 min; Mean GCS=7.98. Intervention: Participants who received standard craniotomy (n=16) or Decompressive Craniectomy (DC, n=38) for hemorrhagic contusions were retrospectively analyzed. Outcome Measures: Glasgow Outcome Score-Extended (GOSE), Length of Stay (LOS), Reoperation Rate, Mortality.</p>	<ol style="list-style-type: none"> 1. Reoperation rates (7.9% versus 37.5%, p<0.05) were significantly lower after DC than craniotomy. 2. GOSE scores at 6 mo were significantly higher in DC than craniotomy (5.55 versus 3.56, p<0.01) 3. LOS and mortality were not significantly different between groups.
<p>Li et al. (2008) China Case Control N=135</p>	<p>Population: TBI; Mean Age=46.3 yr; Gender: Male=91, Female=44; GCS≤8 Intervention: Participants received routine (10x15cm, n=128) or large (n=135) Decompressive Craniectomy (DC). Outcome Measures: Glasgow Outcome Score (GOS), Complications, Recurrent Surgery.</p>	<ol style="list-style-type: none"> 1. Satisfactory outcomes (GOS=3-5) were obtained from 71.1% of the large DC group, compared to 58.6% of routine DC group (p<0.05). 2. Large DC was more effective in treating very severe TBI than routine DC (p<0.01).

		3. Large DC was associated with a lesser need for recurrent surgery and fewer complications than routine DC.
Meier et al. (2008) Germany Case Series N=131	Population: TBI; Mean Age=36 yr; Gender: Male=99, Female=32; Mean Time Post Injury=49 mo; GCS≤8. Intervention: Participants who received decompressive craniectomy were retrospectively analyzed. Outcome Measure: Glasgow Outcome Scale (GOS).	1. GOS was correlated with age and GCS.
Morgalla et al. (2008) Germany Case Series N=33	Population: TBI; Mean Age=36.3 yr; Gender: Male=20, Female=13; Mean Time Post Injury=3 yr. Intervention: Participants who received decompressive craniectomy were retrospectively analyzed. Outcome Measure: Barthel Index (BI), Mortality.	1. Twenty percent died and 20% remained in a vegetative state. 2. Thirteen of the surviving patients made a full recovery (BI=90-100).
Chibbaro et al. (2008) USA Case Series N=80	Population: TBI; Mean Age=35 yr; Gender: Male=58, Female=22; Mean GCS=5. Intervention: Participants who received decompressive craniectomy were retrospectively analyzed. Outcome Measure: Glasgow Outcome Score (GOS).	1. Seventy-five percent of patients had a favourable outcome. 2. Younger age and earlier operations were associated with better outcomes. 3. Preoperative GCS had no effect on outcome.
Yang et al. (2008) China Case Series N=108	Population: TBI; Mean Age=44.3 yr; Gender: Male=74, Female=34; Severity: Severe=94, Moderate/Mild=14. Intervention: Participants who received decompressive craniectomy were retrospectively analyzed. Outcome Measures: Glasgow Outcome Score (GOS), Mortality, Complications.	1. Twenty-five patients died within 1 mo. 2. Lower GCS was associated with poorer outcomes on GOS. 3. Complications secondary to surgery occurred in 50%, 28% of whom developed >1 complication. 4. Older patients and more severe injuries were associated with more complications.

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

The effectiveness of DC following ABI has been examined in numerous retrospective studies. The majority of these studies reported significant decreases in ICP immediately following the procedure (Aarabi et al., 2006; Bao et al., 2010; Daboussi et al., 2009; De Bonis et al., 2011; Eberle et al., 2010; Goksu et al., 2012; Grindlinger et al., 2016; Ho et al., 2008; Howard et al., 2008; Nambiar et al., 2015; Olivecrona et al., 2007; Polin et al., 1997; Schneider et al., 2002; Skoglund et al., 2006; Soustiel et al., 2010; Stiefel et al., 2004; Timofeev et al., 2008a; Tuettenberg et al., 2009; Ucar et al., 2005; Whitfield et al., 2001; Williams et al., 2009), while only one did not (Munch et al., 2000). Given that the overwhelming number of studies credit DC with a decrease in ICP, this last study stands as an outlier and its results should be interpreted in the context of the existing data.

In addition to the effects on ICP, several studies reported a change in the CPP of patients after a DC. Of those studies the majority reported an increase in CPP (Bao et al., 2010; Daboussi et al., 2009; Heppner et al., 2006; Ho et al., 2008; Schneider et al., 2002; Soustiel et al., 2010; Stiefel et al., 2004), while a few reported no change (Munch et al., 2000; Olivecrona et al., 2007; Whitfield et al., 2001), or a decrease (Eberle et al., 2010; Nambiar et al., 2015) after receiving a DC post ABI. Given the heterogeneity of results, further research is necessary to elucidate the effect of DC on CPP.

Considering the invasiveness of DC and its potential complications, evaluating its long-term outcomes is of particular importance. Few studies have reported an association between decreased ICP and improved long-term outcomes (Chibbaro et al., 2008; Galal, 2013; Kim et al., 2009; Nambiar et al., 2015; Skoglund et al., 2006; Williams et al., 2009). Several factors were found to correlate with positive long-term outcomes, including younger age (Chibbaro et al., 2011; Chibbaro et al., 2008; Huang et al., 2013; Limpastan et al., 2013; Meier et al., 2008; Nambiar et al., 2015; Ucar et al., 2005; Williams et al., 2009; Yang et al., 2008; Yuan et al., 2013), higher GCS score (De Bonis et al., 2011; Goksu et al., 2012; Gong J, 2014; Ho et al., 2011; Howard et al., 2008; Huang et al., 2013; Limpastan et al., 2013; Meier et al., 2008; Ucar et al., 2005; Williams et al., 2009; Yang et al., 2008; Yuan et al., 2013), earlier DC (Chibbaro et al., 2011; Chibbaro et al., 2008; Girotto et al., 2011; Polin et al., 1997), and larger DC (Li et al., 2008; Skoglund et al., 2006). Furthermore, certain studies found that DC was associated with improved GOS scores and reduced mortality (Bao et al., 2010; Grindlinger et al., 2016; Kim et al., 2009; Skoglund et al., 2006) while others reported poor outcomes in the majority of their patients (Aarabi et al., 2006; De Bonis et al., 2011; Eberle et al., 2010; Goksu et al., 2012; Munch et al., 2000; Nambiar et al., 2015; Schneider et al., 2002). When interpreting these results, it is important to consider that DC is used to control high ICP refractory to standard treatment, and the poor outcomes reported could be a result of the fragile state that patients were in before the procedure. At this moment however, given the conflicting results, it is unclear if DCs impact long term outcomes and mortality positively or negatively.

A few studies have delved further and compared patients who received DC to those treated with standard therapy finding that DC more effectively lowers ICP, and the time spent with cranial hypertension (ICP>20 mmHg; (Cooper et al., 2011; Hutchinson et al., 2016a). Furthermore, one study noted a decrease in hospital LOS (Hutchinson et al., 2016b) while both studies associated DC with an increase in poor outcomes (GOSE<4) compared to standard care. It is worth noting however that in Cooper et al., after controlling for age and initial GCS scores, there was no longer a significant difference in poor outcomes between treatments (Cooper et al., 2011). There was less agreement, however, as to which treatment was superior at improving mortality, with one study reporting a decrease in mortality up to a year after DC (Hutchinson et al., 2016a) and the other finding no difference in mortality between treatments (Cooper et al., 2011). There were a number of concerns regarding the methodological quality of the Cooper et al. trial, including time to randomization, length of accrual, initial group differences, timing of DC, and DC technique (Cooper et al., 2011). As well, the ICP threshold was deemed too low (>20 mmHg for >15 min) such that standard medical management was not fully exhausted. As a result, conclusions from this study should be drawn with caution.

Decompressive craniectomies are performed after standard treatment has been exhausted and ICP control has not yet been achieved. However, craniotomies, or the prophylactic removal of skull sections, have been compared to DCs to explore their viability in treating ABIs. Girotto et al. (2011) compared patients receiving either a DC or craniotomy to those receiving standard therapy alone, and found that patients who underwent surgery spent significantly less time in cranial hypertension (ICP>25 mmHg). Furthermore, a second study went on to directly compare DC (>24 h, refractory to first line treatments) to a craniotomy (<24 h) and concluded that treatments were not different in their ability to decrease ICP post ABI (Al-Jishi et al., 2011). While the procedures similarly lowered ICP, they differed in their morbidity and mortality outcomes. Decompressive craniectomies were associated with better GOS scores and good outcomes; however, conflicting results exist regarding their benefit on patient mortality. Given the available data and considering the intrusiveness and potential complications of removing bone fragments from the skull, it is suggested that DCs remain a last line intervention to ICP refractory to first line treatment.

Researchers have published the results of clinical trials evaluating long-term outcomes following DC. A retrospective study analyzed patients who has undergone a DC, and found that only the patient's initial GCS score was associated with favourable outcomes post DC (Howard et al., 2008). When compared to controlled decompression, one trial found that DC was just as effective in reducing elevated ICP and improving GOS score (Wang et al., 2014). Additionally, the impact of bone flap size was investigated in three other trials (Jiang et al., 2005; Qiu et al., 2009). Participants received either standard trauma craniectomy with a unilateral frontotemporoparietal bone flap (12x15cm) or limited craniectomy with a routine temporoparietal bone flap (6x8cm) (Jiang et al., 2005; Qiu et al., 2009). Both studies reported that significantly more patients in the 12x15cm group showed favourable outcomes on the GOS than those in the 6x8cm group at six months (Jiang et al., 2005) and one year (Qiu et al., 2009). As well, ICP fell more rapidly and to a lower level following standard craniectomy than limited craniectomy (Jiang et al., 2005; Qiu et al., 2009). In contrast to the size-dependent benefits noted in the previous 2 studies, a retrospective review concluded through linear regression analysis that the surface area of the DC was not an independent predictor of post-operative ICP or GCS score (Reid et al., 2018b). Taking into consideration the study methodology and sample size, more emphasis should be placed on the results of the RCTs with regards to the benefits of bone-flap size in DCs.

Considering the invasiveness of a DC and its potential complications, evaluating the long-term outcomes associated with the procedure is of particular importance. Several factors were found to correlate with positive long-term outcomes, including younger age (Chibbaro et al., 2011; Chibbaro et al., 2008; Huang et al., 2013; Limpastan et al., 2013; Meier et al., 2008; Nambiar et al., 2015; Ucar et al., 2005; Williams et al., 2009; Yang et al., 2008; Yuan et al., 2013), higher GCS score (De Bonis et al., 2011; Goksu et al., 2012; Gong J, 2014; Ho et al., 2011; Howard et al., 2008; Huang et al., 2013; Limpastan et al., 2013; Meier et al., 2008; Ucar et al., 2005; Williams et al., 2009; Yang et al., 2008; Yuan et al., 2013), earlier DC (Chibbaro et al., 2011; Chibbaro et al., 2008; Giroto et al., 2011; Polin et al., 1997), and larger DC (Li et al., 2008; Skoglund et al., 2006). However, a number of studies reported high mortality rates (Agrawal et al., 2012), low recovery rates (Morgalla et al., 2008), and expansion of new/ existing hemorrhagic contusions (Flint et al., 2008) after treatment with DC.

Some retrospective studies found that DC was associated improved GOS scores and reduced mortality when compared to standard care (Polin et al., 1997; Rubiano et al., 2009), while others did not (Giroto et al., 2011; Nirula et al., 2014; Quintard et al., 2015). The results are similarly mixed when DC is compared to other procedures. An earlier study found that DC yielded more favourable long-term outcomes than craniotomy (Huang et al., 2008), but later studies found that there were no significant differences between the procedures (Chen et al., 2011; Li et al., 2012). Conversely, other studies exist reporting that a DC is associated with greater mortality (Rush et al., 2016; Tapper et al., 2017), longer hospital LOS (Rush et al., 2016), and a greater chance of developing unfavourable outcomes such as rehospitalization compared to craniotomies (Tapper et al., 2017). Further, a study by Kelly et al. (2018), a retrospective study of over 1,400 patients across the USA, reported superior Functional Independence Measure (FIM) total, motor, and cognitive scores in the craniotomy group up to 2 years following the intervention. Given the direction the evidence is trending towards and the increasing sample sizes from which to draw conclusions off of, a prospective study is warranted to investigate the potentially superior outcomes associated with craniotomies in comparison to the more standard DC procedure.

Decompressive craniectomy was further discussed in terms of its efficacy as an intervention for the development of ICH post ABI. A group led by Otani (2010) concluded that in comparison to a hematoma

evacuation alone, DC + hematoma evacuation resulted in a lower rate of favourable outcomes (78.2% versus 55.8%). Conflicting results exist comparing a DC to a craniotomy for the treatment of ICH. While one group noted that patients who underwent a DC showed an increase in mortality and hospital LOS compared to those receiving a craniotomy (Rush et al., 2016), another found that DC combined with ICH evacuation was no different from a craniotomy combined with ICH evacuation in the same parameters (Jehan et al., 2017). Notably, while the latter study did not report a difference in mortality, GOS score, GCS score, or hospital LOS, the DC group did have an increased return to the OR, number of events of hydrocephalus requiring a shunt, and number of days on a ventilator compared to the craniotomy group. Finally, Shibahashi et al. (2017) found that in thick subdural ICH's, trepanation was associated with higher mortality compared to those who did not undergo trepanation.

Concluding the discussion on DC, two groups evaluated variations of standard DC procedures for morbidity, mortality and feasibility outcomes. Khan et al. (Khan et al., 2016) conducted an RCT comparing DCs with expansile duraplasty to DCs with dural-slits. The study reported no differences existed between the techniques with respect to mortality or GOS scores; however, the expansile duraplasty surgery was significantly shorter than the dural-slit procedure. The other group, Grassner et al. (2018), investigated the use of synthetic skin substitution in patients where skin closure was not possible due to brain herniation. The authors observed very high mortality rates in the TBI population (50%), as well as high rates of infections. While the findings may be partially attributed to the vulnerable state of these patients, the risk of infection is undoubtedly increased due to the need to repeatedly reapply the material over a 21-day period. Further research is warranted to encourage routine use of synthetic skin substitutes; however, in situations where skin closure is not possible then its use is likely justified.

Conclusions

There is level 1a evidence that a decompressive craniectomy is more effective than standard care at reducing elevated intracranial pressure, while producing poorer outcomes (Glasgow outcome scale extended scores < 4) post ABI.

There is conflicting (level 1b) evidence that a decompressive craniectomy is superior at improving mortality compared to standard care in patients post ABI.

There is level 1b evidence that a decompressive craniectomy with a unilateral frontotemporoparietal bone flap (12x15 cm) may be superior to a limited decompressive craniectomy with a temporoparietal bone flap (6x8 cm) in lowering intracranial pressure and improving Glasgow Outcome Scale scores post ABI.

There is level 2 evidence that a decompressive craniectomy is just as effective as a controlled decompression at reducing intracranial pressure and improving Glasgow outcome scale scores in patients post ABI.

There is level 2 evidence that the surface area of the bone flap removed in a decompressive craniectomy does not affect intracranial pressure or Glasgow coma scale scores post TBI.

There is level 3 evidence that decompressive craniectomy and craniotomy interventions are similar at decreasing intracranial pressure post ABI.

There is conflicting (level 3) evidence as to whether decompressive craniectomies have better mortality outcomes compared than a craniotomy post ABI.

There is level 4 evidence that patient's initial GCS score is correlated with favourable outcomes post decompressive craniectomy.

There is conflicting (level 3 and level 4) evidence as to the effect of a decompressive craniectomy on mortality and long-term outcomes. There is level 3 evidence that an earlier intervention is associated with positive long-term outcomes.

There is conflicting (level 4) evidence whether or not a decompressive craniectomy effectively reduces elevated intracranial pressure post ABI compared to no treatment.

There is conflicting (level 4) evidence regarding whether or not a decompressive craniectomy effectively improves cerebral perfusion pressure post ABI.

There is level 4 evidence that younger age, higher Glasgow coma scale score and larger decompressive craniectomy are associated with improved long-term outcomes in patients receiving decompressive craniectomies post ABI.

There is level 2 evidence that a decompressive craniectomy with expansile duraplasty is not different than a decompressive craniectomy with dural-slits with respect to mortality or Glasgow Outcome Scale scores in patients post acute subdural hematoma.

There is level 3 evidence that a larger decompressive craniectomy may be associated with positive long-term outcomes compared to routine care in patients post ABI.

There is conflicting (level 3) evidence as to whether decompressive craniectomy is superior to craniotomy at improving mortality, long-term outcomes, and hospital length of stay in patients post ABI.

There is level 3 evidence that an intracranial hemorrhage evacuation with a decompressive craniectomy may increase the need for additional treatment but is not different in terms of mortality and neurological outcomes than an intracranial hemorrhage evacuation with a craniotomy post ABI.

There is level 3 evidence that a hematoma evacuation may be superior to a hematoma evacuation combined with decompressive craniectomy at producing favourable outcomes in patients post ABI.

There is conflicting (level 3) evidence as to whether a decompressive craniectomy is associated with higher Glasgow Outcome Scale scores and lower mortality than standard care post ABI.

There is level 4 evidence that a decompressive craniectomy may be associated with increased mortality, low recovery rates, and expansion of hemorrhagic contusions in patients post ABI.

There is level 4 evidence that younger age, higher initial Glasgow Coma Scale score, and earlier decompressive craniectomy may be associated with positive long-term outcomes in patients post ABI.

There is level 4 evidence that trephination in patients with thick subdural intracranial hemorrhages may increase mortality post ABI.

These is level 4 evidence that the use of synthetic skin substitution in patients where skin closure is not possible post decompressive craniectomy is associated with high rates of infections and mortality post TBI.

Conflicting results exist as to whether a decompressive craniectomy can lower elevated intracranial pressure post ABI; however, the vast majority of the data support its efficacy as an effective intervention.

The effect of a decompressive craniectomy on cerebral perfusion pressure is unclear.

It is unclear whether a decompressive craniectomy is associated with improved long-term outcomes and mortality; however young age, early decompressive craniectomy, large decompressive craniectomy, and higher Glasgow Coma Score scores may all be predictors for favourable outcomes.

Decompressive craniectomy is more effective than standard treatment at reducing intracranial pressure; however, it is unclear which treatment best improves morbidity and mortality post ABI. Initial Glasgow Outcome Scale score, but not intracranial pressure monitoring post decompressive craniectomy, might be a predictor for improved outcomes in patients post ABI.

Decompressive craniectomy may be similar to controlled decompression in reducing elevated intracranial pressure and improving Glasgow Outcome Scale scores.

It is unclear whether bone flap size affects intracranial pressure or morbidity outcomes in patients receiving a decompressive craniectomy post TBI. The strongest evidence supports the use of a larger (12x15cm) bone flap for better intracranial pressure control and morbidity outcomes.

Decompressive craniectomies and craniotomies may be similar at reducing intracranial pressure post ABI, but a decompressive craniectomy could be superior at improving good outcomes. It is unclear which procedure improves mortality the most.

Decompressive craniectomies may worsen mortality, recovery and complications in patients post ABI; however young age, early decompressive craniectomy, large decompressive craniectomy, and higher Glasgow Coma Scale scores may all be predictors for favourable outcomes.

It is unclear whether a decompressive craniectomy is superior to a craniotomy at improving mortality and long-term outcomes post ABI. However, large studies have trended towards showing improved morbidity and mortality following a craniotomy.

An intracranial hemorrhage evacuation with a decompressive craniectomy may be inferior to an intracranial hemorrhage evacuation, or the same as an intracranial hemorrhage evacuation with a craniotomy at improving mortality and long-term outcomes in patients post ABI.

Trephination after a thick subdural intracranial hemorrhage might increase patient mortality.

It is unclear whether a decompressive craniectomy is superior to standard care at improving Glasgow Outcome Scale scores and mortality in patients post ABI.

The type of decompressive craniectomy (with dural slits or expansile duraplasty) post acute subdural hematoma may not affect mortality and neurological outcomes.

Synthetic skin substitutions might be associated with increased rates of infections and mortality post TBI; however, its use may be warranted in patients where skin closure is not possible.

15.2 Prompting Emergence from Coma

Consciousness is composed of two distinct dimensions: arousal (i.e., wakefulness or vigilance) and awareness (i.e., knowledge of self and environment) (Zeman, 2006). Disorders of Consciousness (DOC) are a spectrum of medical conditions that inhibit elements of consciousness (Schiff & Plum, 2000), and include the following:

- **Coma:** a state of complete unconsciousness, lacking both arousal and awareness (Posner & Plum, 2007).
- **Vegetative state:** a state of arousal without awareness, considered “persistent” when lasting longer than one month (Jennett, 2002).
- **Minimally conscious state:** a state of arousal with limited but discernable awareness (Giacino et al., 2002).

DOC present clinical challenges in both the diagnosis and treatment of patients following brain injury, and thus significantly impact outcomes in acute care (Nakase-Richardson et al., 2012).

Guideline Recommendations

The Royal College of Physicians (RCP) in the UK developed a set of guidelines for the diagnosis and management of DOC, in order to update and replace a previous report from 2003 (*Prolonged disorders of consciousness: National clinical guidelines, 2013*). We have added these recommendations into our evaluation of each intervention, but our conclusions are based on our methodology. The RCP provided descriptive guidelines but did not incorporate levels of evidence.

15.2.1 Non-Pharmacological Interventions

15.2.1.1 Sensory Stimulation

It has been reported that one in eight patients with severe closed head injury suffer from being in a prolonged coma and vegetative state following their injury (Levin et al., 1991). It has also been estimated that 50% of survivors from severe brain injuries who are in a vegetative state regain consciousness within one year of their injury, with up to 40% subsequently improving to a higher level on the Glasgow Outcome Scale (Multi-Society Task Force on PVS, 1994). The theory that sensory stimulation could enhance the speed and degree of recovery from coma has gained traction as a viable treatment post ABI. Early studies employed a single stimuli to a single sense (unimodal stimulation), whereas other studies have focused on stimulation to all the senses using various stimuli (multimodal stimulation). These studies have

evaluated stimulation of several modalities: visual, auditory, tactile, olfactory, gustatory, kinesthetic, proprioceptive, and vestibular.

We identified two systematic reviews evaluating the effectiveness of sensory stimulation in improving consciousness of individuals in a coma or vegetative state following ABI. In a Cochrane review, Lombardi et al. (2002) identified three clinical trials with a total of 68 patients. The studies were found to be of poor quality and there was considerable diversity between them in terms of experimental design and conduct. Due to the lack of consistent outcome measures in these studies, a quantitative meta-analysis could not be conducted. The authors concluded that there was no reliable evidence supporting the efficacy of intensive multisensory stimulation programs. They recommended that larger multicenter RCTs be conducted with rigorous methodology and specific outcomes for impairment and disability. However, in a review, Padilla and Domina (2016) found strong evidence for multisensory stimulation improving arousal and enhancing clinical outcomes. The authors recommended early, frequent, and sustained stimulation that is tailored to patient tolerance and preferences.

The RCP reported a lack of high-quality research regarding sensory stimulation programs for patients with DOC (*Prolonged disorders of consciousness: National clinical guidelines, 2013*). However, the authors noted that such programs may provide the best opportunities to observe recovery in patients. It was recommended that stimulation focus on pleasurable and familiar sensations that are presented discretely, in order to detect individual effects and minimize overstimulation.

Table 15.25 Sensory Stimulation for Recovery of Consciousness Post ABI

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Moattari et al. (2016) Iran RCT PEDro=8 N=60	<p>Population: TBI; Mean Age=37 yr; Gender: Male=50, Female=10; Mean GCS=6.</p> <p>Intervention: Participants in a coma were randomized to receive standard care (control, n=20) or a sensory stimulation program (treatment) from a qualified nurse (n=20) or a family member (n=20). The program involved awakening (5 min), auditory (10 min), visual (10 min), tactile (5 min), and olfactory (10 sec) stimulation 2x/ day for 7 days. Outcomes were assessed daily over 7 days.</p> <p>Outcome Measures: Glasgow Coma Scale (GCS), Rancho Los Amigos Scale (RLAS), Western Neurosensory Stimulation Profile (WNSSP).</p>	<ol style="list-style-type: none"> 1. Mean GCS scores were significantly higher in the family group than in the nurse and control groups at 6 days (8.85 versus 7.15 versus 6.60, p=0.035) and 7 days (9.20 versus 7.15 versus 6.70, p=0.001). 2. Mean RLAS scores were significantly higher in the family group than in the nurse and control groups at 5 days (2.60 versus 2.15 versus 2.10, p=0.006), 6 days (2.95 versus 2.15 versus 2.15, p=0.001), and 7 days (3.10 versus 2.15 versus 2.15, p=0.001). 3. Mean WNSSP scores were significantly higher in the family group than in the nurse and control groups at 4 days (17.55 versus 11.05 versus 11.15, p=0.03), 5 days (28.15 versus 15.45 versus 14.75, p=0.003), 6 days (44.75 versus 17.65 versus 14.45, p=0.001), and 7 days (50.35 versus 18.4 versus 14.55, p=0.001). 4. The family group showed significant improvements on GCS (p=0.001), RLAS (p<0.01), and WNSSP (p=0.001) in

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
		<p>separate comparisons to the nurse group and controls.</p> <p>5. The nurse group showed significant improvements on WNSSP ($p=0.002$), but not GCS ($p=0.98$) or RLAS ($p=0.38$) when compared to controls.</p>
<p>Tavangar et al. (2015) Iran RCT PEDro=7 N=40</p>	<p>Population: ABI; Mean Age=36 yr; Mean GCS=6. Intervention: Participants in a coma were randomized to receive standard care (control, $n=20$) or auditory stimulation (treatment, $n=20$). Stimulation involved listening to 5-15 min voice recordings of a family member 2 x/day for 10 days. Outcome Measure: Glasgow Coma Scale (GCS).</p>	<p>1. Mean GCS significantly improved in both groups after 10 days ($p=0.0001$). 1. Mean GCS at 10 days was significantly higher in the treatment group than in controls (10.25 versus 7.75, $p=0.0001$).</p>
<p>Gorji et al. (2014b) Iran RCT PEDro=5 N=13</p>	<p>Population: TBI; GCS Range\leq8. Intervention: Patients were randomly assigned to receive standard care (control) or listen to a 10-min voice recording of a "loved one" 2x/ day for 2 wk (treatment). Outcome Measure: Coma Duration.</p>	<p>1. Coma duration (time to GCS=15) was significantly shorter in the treatment group compared to controls ($p<0.0001$).</p>
<p>Megha et al. (2013) India RCT PEDro=6 N=30</p>	<p>Population: TBI; <i>Treatment Group 1 (TG1, $n=10$):</i> Mean Age=35 yr; Mean Time Post Injury=7.8 days; Mean GCS=3.4. <i>Treatment Group 2 (TG2, $n=10$):</i> Mean Age=40.9 yr; Mean Time Post Injury=7.8 days; Mean GCS=3.5. <i>Control Group (CG, $n=10$):</i> Mean Age=43.2 yr; Mean Time Post Injury=7.5 days; Mean GCS=3.4. Intervention: Participants in a coma were randomly assigned to receive conventional physiotherapy (CG) or multimodal stimulation for 2 wk. Stimulation was delivered in 20 min sessions 5x/ days (TG1) or 50 min sessions 2x/ days (TG2). Outcomes were assessed before and after treatment. Outcome Measures: Glasgow Coma Scale (GCS), Western Neuro Sensory Stimulation Profile (WNSSP).</p>	<p>1. GCS significantly improved in TG1 ($z=2.821$, $p=0.005$), TG2 ($z=2.848$, $p=0.004$), and CG ($z=2.724$, $p=0.006$) after treatment. 2. WNSSP significantly improved in TG1 ($z=2.809$, $p=0.005$), TG2 ($z=2.807$, $p=0.005$), and CG ($z=2.812$, $p=0.005$) after treatment. 3. After treatment, there were significant overall differences between groups in GCS ($\chi^2=9.516$, $p=0.009$) and WNSSP ($\chi^2=17.136$, $p<0.001$). 4. GCS after treatment was significantly higher in TG1 ($U=14$, $p=0.005$) than in CG. GCS was higher in TG2 than CG ($U=19$, $p=0.019$) and in TG1 than TG2 ($U=42.5$, $p=0.579$), but these differences were not significant. 5. WNSSP after treatment was significantly higher in TG1 than TG2 ($U=14.5$, $p=0.005$) and CG ($U=6$, $p<0.001$), and in TG2 than CG ($U=11$, $p=0.002$).</p>
<p>Abbasi et al. (2009) Iran RCT PEDro=7 N=50</p>	<p>Population: ABI; <i>Treatment Group ($n=25$):</i> Mean Age=30.4 yr; Gender: Male=22, Female=3; Mean GCS=7.0. <i>Control Group ($n=25$):</i> Mean Age=30.4 yr; Gender: Male=21, Female=4; Mean GCS=6.9. Intervention: Participants were randomized to receive either a regular family visiting program (treatment) or routine care (control). Family visits</p>	<p>1. The treatment group showed significant increases in GCS scores on each day during the study period ($p<0.05$). 2. After 6 days, GCS scores in the treatment group were significantly higher than in the control group (8.8 versus 6.8, $p=0.0001$).</p>

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
	<p>were 15 min for 6 days and were structured to include affective, auditory, and tactile stimulation. Outcomes were assessed at baseline and 30min after each visit.</p> <p>Outcome Measure: Glasgow Coma Scale (GCS).</p>	
<p>Johnson et al. (1993) UK RCT PEDro=3 N=14</p>	<p>Population: ABI; <i>Treatment Group (TG, n=7):</i> Mean Age=27.7 yr; Time Post Injury<48 hr; Mean GCS=4.8. <i>Control Group (CG, n=7):</i> Mean Age=31.4 yr; Time Post Injury<48 hr; Mean GCS=4.8.</p> <p>Intervention: Participants were randomized to receive sensory stimulation (TG) or no stimulation (CG). Treatment involved stimulation of the five senses (olfactory, visual, auditory, gustatory, and tactile) for 20 min/ day during ICU stay.</p> <p>Outcome Measures: Physiological parameters (heart rate, skin conductance), Biochemical parameters (Methoxy-4-Hydroxyphenylglycol (MHPG), Acetylcholinesterase (ACHE), Catecholamine, Serotonin).</p>	<ol style="list-style-type: none"> MHPG levels were significantly higher in the TG than CG post treatment (F=8.54, p<0.006). No significant group differences post treatment were seen in heart rate (F=0.70, p<0.499) or skin conductance (F=2.51, p<0.092), nor for levels of catecholamine, serotonin, or ACHE.
<p>Park et al. (2016) Korea & USA Pre-Post N=9</p>	<p>Population: TBI; Mean Age=29.7 yr; Gender: Male=9, Female=0; Mean GCS=5.88; Mean SSAM=3.44.</p> <p>Intervention: Comatose patients underwent both direct, and non-direct auditory stimulation in random order (15 min each, 1 hr between treatments).</p> <p>Outcome Measures: Glasgow Coma Scale (GCS), Sensory Stimulation Assessment Measure (SSAM).</p>	<ol style="list-style-type: none"> GCS and SSAM scores were significantly increased above baseline after exposure to direct and non-direct auditory stimulation (both p=0.008). Compared to non-direct auditory stimulation, SSAM scores improved significantly more after direct stimulation (p=0.021).
<p>Di Stefano et al. (2012) Italy Case Series N=12</p>	<p>Population: TBI; Mean Age=30.75 yr; Gender: Male=7, Female=5; Mean Time Post Injury=5.75 mo.</p> <p>Intervention: Participants in a vegetative state (VERSUS, n=6) or minimally conscious state (MCS, n=6) received sensory stimulation based on biographically meaningful objects. The order of phases was: Hygienic Care (H1), Cognitive Stimulation (CS1), Enriched Stimulation (ES), Cognitive Stimulation (CS2), and Hygienic Care (H2).</p> <p>Outcome Measures: Wessex Head Injury Matrix (WHIM) – Number of Behaviours (NB) and Best Behaviours (BB).</p>	<ol style="list-style-type: none"> NB was statistically greater in the ES phase (p<0.01). There was no significant difference in NB between H1 and H2 (p>0.05) or CS1 and CS2 (p>0.05). There was no significant difference in NB between VERSUS patients and MCS patients (p>0.05). The BB was observed in the ES phase for all 12 patients.
<p>Urbenjaphol et al. (2009) Thailand PCT N=40</p>	<p>Population: TBI; Mean Age=34 yr; Gender: Male=28, Female=12; Mean Time Post Injury=7 days; Mean GCS=5.</p> <p>Intervention: Participants received standard care (control, n=20) or a multimodal sensory stimulation program (treatment, n=20). The program involved tactile, gustatory, olfactory, auditory, and visual stimulation. Each modality was stimulated for 30m in/day at 2 hr intervals over 14 days.</p>	<ol style="list-style-type: none"> Mean GCS scores were significantly higher in the treatment group than in controls at 14 days (10.45 versus 5.9, p<0.05). Mean SMART scores were significantly higher in the treatment group than in controls at 14 days (14.76 versus 8.72, p<0.05).

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
	Outcome Measures: Glasgow Coma Scale (GCS), Sensory Modality Assessment & Rehabilitation Technique (SMART).	
Davis & Gimenez (2003) USA PCT N=12	Population: TBI; <i>Treatment Group (n=9):</i> Mean Age=30 yr; Mean Time Post Injury=9 days; Mean GCS=5.5. <i>Control Group (n=3):</i> Mean Age=30 yr; Mean Time Post Injury=6 days; Mean GCS=6. Intervention: Participants received either a structured auditory sensory stimulation program (treatment) or no stimulation (control). Stimulation included: orientation and commands, bells, blocks and claps, music, familiar voices, and television or radio. Participants received stimulation 5-8x/d for 5-15min each up to 7d days. Outcome Measures: Glasgow Coma Scale (GCS), Disability Rating Scale (DRS), Ranchos Los Amigos Scale (RLAS), Sensory Stimulation Assessment Measure (SSAM).	<ol style="list-style-type: none"> 1. Mean change in GCS score was not significantly different between groups (p=0.278). However, GCS were lower in the treatment group and increased over time, while they were higher in the control group and decreased over time. 2. Mean change in DRS score was significantly greater in the treatment group than the control group (2.7 versus 0.3, p=0.0005). 3. Mean change in SSAM score was significantly greater in the treatment group than the control group (11 versus 0.3, p=0.015). 4. Mean change in RLAS score was 1.2 in the treatment group, while there was no change in the control group.
Gruner & Terhaag (2000) Germany Pre-Post N=16	Population: ABI; Mean Age=43.6 yr; Mean Time Post Injury=28 days; Mean GCS=6.5. Intervention: Participants received multimodal early onset stimulation (MEOS) for 1 hr, 2x/day for 10 days (1-30 days). MEOS involved acoustic, tactile, olfactory, gustatory, and kinesthetic stimulation. Outcome Measures: Physiological parameters (cardiovascular and respiratory).	<ol style="list-style-type: none"> 1. Changes in heart and respiratory frequencies were noted; the most significant changes were found following tactile and acoustic stimulation. 2. No statistical comparisons were reported.
Wilson et al. (1996) UK Pre-Post N=24	Population: TBI; Mean Age=29 yr; Mean Time Post Injury=16 mo. Intervention: Participants received multimodal and unimodal stimulation. Familiar personal items were also used with both stimulations. Stimulation was administered 2x/ day in 3 wk blocks until they were no longer in a vegetative state or were discharged. Outcome Measure: Behaviour.	<ol style="list-style-type: none"> 1. Frequency with which eyes were observed opened increased significantly following multimodal (p<0.001) and multimodal familiar (p<0.05) stimulation; no significant changes were seen following unimodal stimulation. 2. Significant increases in the frequency of spontaneous movements with eyes opened following multimodal (p<0.005), unimodal (p<0.05) and multimodal familiar stimulation (p<0.05). 3. There was a significant decrease in the frequency of eyes shut with no body movement following both multimodal (p<0.005) and multimodal familiar stimulation (p<0.05). 4. There was a significant reduction in reflexive movements with eyes shut following multimodal stimulation (p<0.025).

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Hall et al. (1992) Canada PCT N=6	<p>Population: TBI; Mean Age=37.5yr; Gender: Male=5, Female=1; Mean Time Post Injury=15.8d; Mean GCS=4.8.</p> <p>Intervention: Participants were alternated every week between either specific directed stimulation (SDS), or non-directed stimulation (NDS), each for 30 min/day, for the duration of the treatment period. SDS involved multisensory input based on level of response, while NDS did not.</p> <p>Outcome Measures: Glasgow Coma Scale (GCS), Rancho Los Amigos Scale (RLAS), Western Neuro Sensory Stimulation Profile (WNSSP), Sensory Stimulation Assessment Measure (SSAM).</p>	<ol style="list-style-type: none"> 1. General improvement on the GCS and RLAS was seen over the course of the treatment for both conditions. 2. General improvement on the WNSSP was seen over the course of the treatment for both conditions, with improvement from 20% to 80%. 3. Subjects obtained higher SSAM scores for eye movements during the SDS condition than during the NDS condition.
Wood et al. (1992) USA PCT N=8	<p>Population: ABI; Mean Age=23.3 yr; Mean Time Post Injury=56.5 days; Mean GCS=9.5.</p> <p>Intervention: Participants received intensive regulated sensory stimulation (treatment, n=4) or standard unregulated stimulation (control, n=4). Treatment involved sensory stimulation with low ambient noises, regular rest intervals free from stimulation, and appropriate inter-stimulus intervals during therapy.</p> <p>Outcome Measures: Glasgow Coma Scale (GCS), Rancho Los Amigos Scale (RLAS), Length of Stay (LOS).</p>	<ol style="list-style-type: none"> 1. Mean LOS was shorter in the treatment group than the control group (88.7 days versus 125.7 days). 2. The treatment group made greater progress on GCS and RLAS scores than the control group. 3. All patients in the treatment group progressed into an acute rehab setting compared with only one of the control patients. 4. No statistical comparisons were reported.
Kater (1989) USA PCT N=30	<p>Population: ABI; Mean Age=28yr; Gender: Male=18, Female=12; Time Post Injury<6 mo.</p> <p>Intervention: Participants received controlled structured sensory stimulation (treatment, n=15) or standard care (control, n=15). Treatment involved visual, auditory, olfactory, gustatory, tactile, and kinesthetic stimulation for 45min, 2x/d, 6d/wk for 1-3 mo.</p> <p>Outcome Measure: Rancho Los Amigos Scale (RLAS).</p>	<ol style="list-style-type: none"> 1. Patients in the treatment group had a significantly improved mean RLAS score compared with controls (6.33 versus 4.40, p<0.05); RLAS was inversely correlated with initial GCS. 2. Subjects with moderate and deep coma (GCS=3-10) benefitted more from treatment, while subjects with light coma severity (GCS=11-14) showed little difference from the controls. 3. Subjects from enriched environments showed significant improvement compared with subjects from non-enriched environments (t=2.20, p<0.05).
Mitchell et al. (1990) UK PCT N=24	<p>Population: ABI; Mean Age=23yr; Gender: Male=20, Female=4; Mean Time Post Injury=8d; Mean GCS=5.</p> <p>Intervention: Participants received a multisensory stimulation program (treatment, n=12) or standard care (control, n=12). The program involved vigorous stimulation of auditory, tactile, olfactory, gustatory, visual, kinesthetic, proprioceptive, and vestibular modalities in a cyclical manner for 1hr, 1-2x/d over 4 days.</p> <p>Outcome Measures: Glasgow Coma Scale (GCS),</p>	<ol style="list-style-type: none"> 1. Mean GCS increased more rapidly in the treatment group. 2. Mean coma duration for the treatment group was significantly shorter than for controls (22d versus 27d, p<0.05).

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
	Coma Duration.	
Pierce et al. (1990) USA Case Control N=31	Population: ABI; Mean Age=24 yr; Gender: Male=21, Female=10; GCS Range<6. Intervention: Participants received vigorous multisensory stimulation (auditory, vestibular, visual and cutaneous) provided by close family for up to 8 hr/day and 7 days/wk, continuing until conventional rehabilitation. The control group was composed of a historical group of consecutive patients in prolonged coma (n=135). Outcomes were assessed 10-12 mo post injury. Outcome Measures: Coma Duration, Glasgow Outcome Scale (GOS).	<ol style="list-style-type: none"> 1. The number patients who emerged from the coma did not differ significantly between groups. 2. No significant improvements were noted between groups in GOS scores ($p>0.25$). 3. No significant differences were found in reasonable recovery rate between treatment and control groups (42% versus 31%, $p>0.025$).

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

One of the major challenges for evaluating the efficacy of sensory stimulation in promoting recovery of consciousness is that outcome assessment measures are often qualitative and difficult to assess. Several studies have reported improvements in parameters such as coma duration (Gorji et al., 2014b; Mitchell et al., 1990; Pierce et al., 1990) and behaviour (Wilson et al., 1996). Clinical assessment tools for measuring level of consciousness are preferred, including the GCS, Coma Recovery Scale, Coma/Near Coma Scale, and DOC Scale. These measures can be used in conjunction with the RLAS or Wessex Head Injury Matrix for the assessment of cognitive functioning. As well, tools such as WNSSP, Sensory Stimulation Assessment Measure, and Sensory Modality Assessment & Rehabilitation Technique were developed in order to better quantify the efficacy of sensory stimulation programs (Ansell & Keenan, 1989; Gill-Thwaites, 1997; Rader & Ellis, 1994).

Two prospective trials using multisensory stimulation programs described marked improvements in terms of coma duration, recovery rate, or long-term outcomes when compared to standard care. One study reported that patients receiving treatment had significantly shorter coma duration than those who received standard care (Mitchell et al., 1990). The other study noted that treated patients showed significantly greater improvement on the RLAS (Kater, 1989). It also found that patients with moderate or severe coma ($GCS \leq 10$) showed greater benefit from the multisensory treatment. Further trials have examined intensive and frequent multisensory stimulation delivered over a period of one to two weeks. These studies reported significant improvements on the GCS (Abbasi et al., 2009; Megha et al., 2013; Moattari et al., 2016; Urbenjaphol et al., 2009), RLAS (Urbenjaphol et al., 2009), WNSSP (Megha et al., 2013; Moattari et al., 2016), and Sensory Modality Assessment & Rehabilitation Technique (Moattari et al., 2016; Urbenjaphol et al., 2009) when compared to standard care.

The type of stimulation and form of delivery may have an impact on its effectiveness. In an early trial, it was demonstrated that specific, directed, and regulated stimulation yielded greater improvements on the GCS, RLAS (Wood et al., 1992) and SSAM when compared to indiscriminate stimulation. In the same year, Hall et al. (1992) found that while both specific directed stimulation (SDS; multisensory input), and non-

directed stimulation (no multisensory input) increased GCS, RLAS and WNSSP, only the SDS was able to increase SSAM scores. Further lending support to the engagement of multiple senses, a study found that multimodal stimulation was superior than unimodal stimulation at increasing behaviours corresponding with arousal (Wilson et al., 1996). For example, in the multimodal stimulation group but not the unimodal group increases were noted in the “frequency with which eyes were open”, and the “frequency of eyes shut with no body movement” was decreased. Park et al. (2016) discovered that both direct and indirect stimulation improved GCS and SSAM scores. Notably, direct stimulation increased SSAM scores more than the indirect stimulation intervention. In a trial, Megha et al. (2013) found that stimulation delivered five times a day generated greater improvements on GCS and WNSSP than when delivered twice a day. Further, Moattari et al. (2016) showed that stimulation was most effective at improving GCS, RLAS and WNSSP when delivered by a family member compared to a nurse.

Studies evaluating auditory stimulation over standard care have also shown favourable results. Patients who listened to recordings of familiar voices or music had a shorter coma duration (Gorji et al., 2014a) and showed improvements on GCS (Tavangar et al., 2015) compared to those receiving standard care. Similarly, patients were found to have a greater response to the sound of their name than a musical sound (Cheng et al., 2013). Patient responsiveness to both sounds was associated with higher Coma Recovery Scale scores.

A single study was reviewed that investigated the effects of a structured auditory sensory stimulation program (5-8x/d for 5-15min each up to 7d days) on patients post ABI (Davis & Gimenez, 2003). The researchers reported no significant difference between groups in GCS scores; however, they did note that both DRS scores and SSAM scores had a significantly greater change in the treatment group compared to the control group.

Focus has shifted from stimulation of a single sense to multi-sensory stimulation as a means of arousing patients from a coma post ABI. Of the the studies analyzed, two groups quantified the response to the multimodal stimulation by measuring either physiological (Gruner & Terhaag, 2000; Johnson et al., 1993), or biochemical (Johnson et al., 1993) parameters, one group examined motor responses (Di Stefano et al., 2012), and the last morbidity outcomes (Pierce et al., 1990). After multimodal stimulation Johnson et al. only reported a change in the plasma concentration of MHPG, a metabolite of norepinephrine and an indicator of sympathetic nervous system arousal, but found no differences in heart rate, skin conductance, or concentration of molecules associated with sympathetic nervous system activation (serotonin, catecholamines, AChase).

Interestingly, Gruner & Terhaag (2000) did note that multimodal stimulation caused a change in heart and respiratory rate frequencies; however, no statistical tests were performed. The difference in results could be attributed to the lack of appropriate statistical tests in Gruner & Terhaag, as the observed change could be non-significant. In addition, the protocols employed by the two studies were different; while both interventions stimulated the 5 senses (olfactory, visual, auditory, gustatory, and tactile) the treatment in Johnson et al. involved stimulation for 20 min/day during ICU stay, compared to 1 hr, 2 x/day for 10 days (1-30 days) in Gruner & Terhaag.

One study investigated the use of multimodal stimulation on patient motor response using biographically meaningful objects from a patient’s life (Di Stefano et al., 2012). The group found increases in number and quality of behaviours during the Enriched Stimulation phase of the protocol; however, these improvements were not sustained at any other time in the study. The last study that looked at multi-

sensory stimulation discussed the efficacy of the intervention (multimodal stimulation by close family for up to 8 hrs/day and 7 days/wk) in the context of morbidity outcomes (Pierce et al., 1990). The study found no difference in emergence from coma, GOS scores, or recovery rate in patients receiving treatment when compared to those who did not (Pierce et al., 1990). By combining the results of these two studies, it would appear that the use of familiar people or items during the ABI recovery process might have transient motor improvements, but no long-term benefits to justify its use.

Based on the reviewed studies, it is difficult to support any uni- or multimodal stimulation protocols as effective interventions in the arousal of patients from a coma post ABI.

Conclusions

There is level 1a evidence that multisensory stimulation may be more effective than standard care at improving consciousness and cognitive function post ABI.

There is level 1b evidence that familiar auditory stimulation may be more effective than standard care at improving consciousness post ABI.

There is level 1b evidence that multisensory stimulation delivered five times per day may be more effective at improving consciousness and cognitive function post ABI than stimulation delivered twice a day.

There is level 1b evidence that multisensory stimulation delivered by a family member may be more effective at improving consciousness and cognitive function post ABI when compared to stimulation delivered by a nurse.

There is level 2 evidence that specific, directed, and regulated sensory stimulation may be more effective at improving consciousness and cognitive function post ABI than indiscriminate stimulation.

There is level 2 evidence that multimodal stimulation may be superior to standard care at reducing coma duration post ABI.

There is level 4 evidence that multimodal stimulation is superior to unimodal stimulation at increasing behaviours corresponding with arousal post ABI.

There is level 2 evidence that structured auditory sensory stimulation improves Sensory Stimulation Assessment Measure and Disability Rating Scale, but not Glasgow Outcome Scale scores compared to controls in individuals in a coma post ABI.

There is conflicting (level 2 and level 4) evidence that multi-sensory stimulation may reduce heart rate in patients in a coma post ABI. The level 2 evidence suggests there is no increase in heart rate of physical signs of patient arousal, but only biochemical ones.

There is level 3 evidence that multi-sensory stimulation has no effect on emergence from coma, Glasgow Outcome Scale scores, or recovery post ABI compared to controls.

There is level 4 evidence that the use of biographically meaningful objects for sensory stimulation post ABI transiently improves motor behaviours.

Multimodal stimulation is more effective than standard care at improving consciousness and cognitive function post ABI, however its improvement in physical arousal behaviours are not as clear.

Sensory stimulation may be most effective when it is early, frequent, and sustained as well as specific, directed, and regulated.

Sensory stimulation may be most effective when stimuli are familiar or delivered by a familiar individual.

Auditory sensory stimulation may improve functional outcomes; however, the evidence is unclear.

Multi-sensory stimulation may cause physiological or biochemical sympathetic arousal; however, it is unlikely it improves more concrete parameters such as heart rate, motor ability, or recovery post ABI.

15.2.1.2 Music Therapy

Musical sounds stimulate the auditory pathway and activate an emotional response in the brain (Sun & Chen, 2015). If the music is familiar to the patient, then the stimuli can become meaningful for them. Anecdotally, it has been noted that music encourages arousal from coma post ABI. We identified one study which used music therapy as a specific treatment for this purpose, this is presented in Table 15.26.

The RCP made no specific recommendations regarding the use of music therapy for the recovery of consciousness post ABI.

Table 15.26 Music Therapy for Recovery of Consciousness Post ABI

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Sun & Chen (2015) China PCT N=40	Population: TBI; <i>Treatment Group (TG, n=20):</i> Mean Age=39.35 yr; Gender: Male=15, Female=5; Mean Time Post Injury=6.55 days; Mean GCS=5.55. <i>Control Group (CG, n=20):</i> Mean Age=40.05 yr; Gender: Male=15, Female=5; Mean Time Post Injury=6.70 days; Mean GCS=5.65. Intervention: Participants in a coma were assigned to receive musical stimuli (TG) or silence (CG). Music was delivered during 15-30 min sessions in the morning, afternoon, and evening for 4 wk. Outcomes were assessed before and after treatment.	<ol style="list-style-type: none"> 1. Mean GCS improved significantly ($p<0.05$) in both the TG (5.55 to 11.30) and CG (5.65 to 9.45) 1 mo after treatment. 2. GCS improvement was significantly greater in the TG than in the CG ($p<0.05$). 3. Mean QEEG improved significantly ($p<0.05$) in both the TG (9.38 to 6.30) and CG (9.54 to 7.99) 1 mo after treatment. 4. QEEG improvement was significantly greater in the TG than in the CG ($p<0.05$).

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
	Outcome Measures: Glasgow Coma Scale (GCS), Quantitative Electroencephalogram (QEEG).	5. GCS and QEEG were inversely correlated both before ($r=-0.482$, $p=0.002$) and after ($r=-0.493$, $p=0.005$) treatment.

Discussion

In a prospective trial conducted by Sun and Chen (2015), participants were exposed to either musical stimuli or silence. While the authors reported that GCS scores and brain electrical activity improved in both groups, the increases were significantly greater in those that received musical stimuli. The promising results of this study suggest that music therapy may improve outcomes and warrants future research. In addition, the study proposes the use of the QEEG as a means of objectively quantifying brain activity and has the potential to be an effective tool in monitoring recovery from coma in patients post ABI.

Conclusions

There is level 2 evidence that musical therapy is superior to silence at improving consciousness and brain activity in individuals in a coma 1 month post ABI.

Music therapy may improve consciousness in individuals in a coma post ABI.

15.2.1.3 Electrical Stimulation

Electrical stimulation is a common therapeutic approach used in the rehabilitation of a variety of neurological diseases. Some reports have proposed that electrical stimulation may be beneficial in patients with severe ABI. It is believed that electrical stimulation applied peripherally may stimulate the reticular activating centre and cortical areas responsible for consciousness and arousal (Peri et al., 2001). Furthermore, stimulation of the median nerve has been shown to cause significant increments in blood flow and improved electroencephalogram activity (Cooper et al., 1999).

The RCP reported that the research regarding neurostimulation, including electrical stimulation, only showed modest results in recovery of consciousness (*Prolonged disorders of consciousness: National clinical guidelines*, 2013). The authors cautioned against the use of invasive techniques, such as those that involve electrode implantation, due to significant ethical concerns. As such, it was recommended that neurostimulation only be used as part of an approved and registered clinical trial.

Table 15.27 Electrical Stimulation for Recovery of Consciousness Post ABI

<p>Author Year Country Research Design PEDro Sample Size</p>	<p>Methods</p>	<p>Outcomes</p>
<p>Peri et al. (2001) USA RCT PEDro=6 N=10</p>	<p>Population: TBI; Mean Age=40 yr; Gender: Male=8, Female=2; Mean Time Post Injury=6 2hr; Mean GCS=5. Intervention: Participants were randomized to receive right median nerve stimulation (RMNS, n=6), with 300 msec intermittent pulses at 40 Hz (20 sec on and 40 sec off), or sham stimulation (n=4) for 8 hr/day up to 14 days. Outcomes were assessed at 3mo. Outcome Measures: Glasgow Coma Scale (GCS), Glasgow Outcome Scale (GOS), Functional Independence/Assessment Measure (FIM/FAM), Coma Duration.</p>	<ol style="list-style-type: none"> 1. Mean coma duration was shorter in the RMNS group than the sham group, but this difference was not significant (9.5 days versus 11.5 days, p=0.31). 2. There was no significant difference between RMNS and sham groups in GOS (3 versus 3) or FIM/FAM scores (114.4 versus 64.5).
<p>Cooper et al. (1999) USA RCT PEDro=4 N=6</p>	<p>Population: TBI; Mean Age=28 yr; Time Post Injury<1 wk; Mean GCS=7. Intervention: Patients were randomized to receive right median nerve stimulation (RMNS, n=3), with asymmetric biphasic pulses (20 mA, 300 μs, 40 Hz, 20 sec/min) or sham stimulation (control, n=3) for 8-12 hr/day for 2 wk. Outcomes were assessed at 1 wk, 2 wk, and 1 mo. Outcome Measures: Glasgow Coma Scale (GCS), Glasgow Outcome Scale (GOS), Length of Stay (LOS).</p>	<ol style="list-style-type: none"> 1. At 1 wk, the RMNS group improved by an average of 4.0 on the GCS compared with 0.7 in controls. 2. By 2 wk, the RMNS group improved by an average of 6.4 on the GCS compared with 1.3 in controls. 3. The RMNS group LOS in the ICU was an average of 7.7 days compared with 17.0 days for controls. 4. Mean GOS for the RMNS group was 3 compared with 2 for controls. 5. No statistical comparisons were reported.
<p>Lei et al. (2015) China Cohort N=437</p>	<p>Population: TBI; <i>Treatment Group (TG, n=221):</i> Mean Age=41.31 yr; Gender: Male=154, Female=67; Mean GCS=6.27. <i>Control Group (CG, n=216):</i> Mean Age=43.21 yr; Gender: Male=145, Female=71; Mean GCS=6.31. Intervention: Participants in a Minimally Conscious State (MCS) or vegetative state (VERSUS) were assigned to receive right median electrical stimulation (RMNS, TG) or standard care (CG). RMNS was delivered for 8 hr/day over 2 wk (15-20 mA, 40 Hz, 20 sec/min). Outcomes were assessed before and after each treatment session, with follow-up at 6mo. Outcome Measures: Glasgow Coma Scale (GCS), Functional Independence Measure (FIM).</p>	<ol style="list-style-type: none"> 1. Over 2 wk, GCS increased in both groups. The increase was more rapid in the TG than the CG, but the difference was not significant (p=0.1472). 2. At end of 2 wk, mean GCS was higher in the TG than the CG, but the difference was not significant (8.43 versus 7.47, p=0.0532). 3. At 6 mo, significantly more of the TG regained consciousness than the CG (60% versus 46%, p=0.0073). 4. At 6mo, significantly more of the CG remained in VERSUS than the TG (32% versus 18%, p=0.0012), but there was no significant difference in those remaining in MCS (22% versus 23%, p=0.8929). 5. At 6 mo, mean FIM score was significantly in the TG than the CG (91.45 versus 76.23, p<0.0001).
<p>Liu et al. (2003) Taiwan Pre-Post N=6</p>	<p>Population: TBI=2, Hypoxia=2, Stroke=1, Aneurysm=1. Intervention: Patients received right median nerve stimulation (RMNS): asymmetric biphasic pulses (20 mA, 300 μs, 35 Hz, 20 sec on and 50 sec off).</p>	<ol style="list-style-type: none"> 1. Significant increases in CPP were seen bilaterally in all patients following RMNS (p<0.05). 2. Four patients regained consciousness within 35 days of initial RMNS.

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
	Stimulation was performed for 10 hr/ day (comatose) or 8 hr/ day (conscious) for 3 mo. Outcome Measures: Cerebral Perfusion Pressure (CPP), Dopamine levels.	3. Dopamine levels were elevated in the majority of patients following RMNS. 4. Younger patients (<40 yr) had better improvement than older patients.

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

Three studies investigating the efficacy of median nerve electrical stimulation in promoting emergence from coma were identified. In the first of these studies, the authors reported that patients treated with stimulation showed better improvements on the GCS and GOS as well as shorter lengths of stay in the intensive care unit when compared to sham-stimulated controls (Cooper et al., 1999). However, the lack of statistical group comparisons weakens any conclusions that could be drawn from these findings. In a high quality RCT, Peri et al. (2001) found that median nerve electrical stimulation did not significantly improve the duration of coma, GOS scores, or functional independence/assessment measure scores over sham stimulation. The differences in results between the studies could be attributed to either the lack of statistical analysis of the Cooper et al. study and/or the difference in protocols employed by the groups. Further RCTs with greater sample sizes are required to appropriately draw conclusions regarding median nerve electrical stimulation and consciousness/ arousal outcomes.

One study comparing the efficacy of median nerve electrical stimulation to standard care in promoting emergence from coma was identified. Lei et al. (2015) determined that patients who received median nerve electrical stimulation showed no more improvement after two weeks than patients who received standard care. However, six-month follow-up data showed that a significantly higher proportion of patients who received stimulation regained consciousness and had improved FIM scores. These results suggest median nerve electrical stimulation improves consciousness more significantly than standard care alone, however, future studies are encouraged to utilize an RCT design.

Liu et al. (2003) employed a single group design and reported that median nerve electrical stimulation caused considerable increments in CPP. They also found elevations in dopamine levels, a compound which may be involved in the regulation of consciousness (Krimchansky et al., 2004). However, the authors failed to demonstrate a direct correlation between dopamine levels and increased levels of consciousness.

Conclusions

There is conflicting (level 1b and level 2) evidence that compared to a sham treatment, median nerve electrical stimulation improves consciousness and arousal post ABI. The level 1b evidence suggests there is no difference, and no improvement.

There is level 2 evidence that compared to standard care, median nerve electrical stimulation is no different at 2 weeks but is superior at 6 mo in terms of improving consciousness and function post ABI.

There is level 4 evidence that median nerve electrical stimulation may increase cerebral perfusion pressure and dopamine levels in individuals in a coma post ABI.

The effects of median nerve electrical stimulation on consciousness and arousal from coma in individuals post ABI is unclear, however, the strongest evidence suggests there are no benefits.

Median nerve electrical stimulation may be superior to standard care at improving consciousness and function long-term.

Median nerve stimulation may increase cerebral perfusion pressure and dopamine levels in individuals in a coma post ABI.

15.2.1.4 Physiotherapy

The physical rehabilitation of patients has been found to be vital in the recovery of movement, balance, coordination and cognitive function post ABI (Aboulafia-Brakha & Ptak, 2016; Lendraitiene et al., 2016). In addition, physical therapy has the benefit of serving as a preventative measure against complications such as pneumonia and thromboembolisms (Lendraitiene et al., 2016). We identified one study which observed the effects of physiotherapy on patient outcomes in both the acute and post-acute phase of ABI.

Table 15.28 Physiotherapy for Recovery of Consciousness Post ABI

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Lendraitiene et al. (2016) Lithuania RCT PEDro=4 N=52	Population: Severe TBI; Gender: Male=39, Female=13; GCS=3-8. Intervention: Patients underwent individually tailored sessions of physical therapy every day in the acute phase post injury. Patients were divided into 2 groups based on duration of coma (group 1: up to 1 wk; group 2: ≥2 wk.) Outcome Measures: Motor Assessment Scale (MAS), Mini-Mental State Examination (MMSE).	<ol style="list-style-type: none"> Group 2 showed significant improvement in motor function via MAS scores after physical therapy compared to before (p<0.05). When comparing the 2 groups, group 1 showed better improvement in MAS scores than those in group 2 (p<0.05). After acute physical therapy, a significant improvement in mental status via MMSE scores were observed in both groups (both p<0.05). Specifically, group 1 MMSE scores went from 1.4 to 2.2, and group 2 improved from 0.8 to 1.7.

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

Physical rehabilitation has been credited with improving both motor and cognitive outcomes post ABI. A RCT by Lendraitiene et al. (2016) found that patients who spent 1 or 2 weeks in a coma, significantly improved their motor (MAS) and cognitive (MMSE) scores after physiotherapy. Interestingly, MAS scores

were improved significantly more in the group of patients who had been in a coma for up to one week, compared to those who had been in a coma for 2 weeks or more.

Conclusions

There is level 2 evidence that individually tailored physical therapy sessions in the acute phase post ABI improves motor and cognitive function.

Physical therapy in the acute phase post ABI may improve motor and cognitive function.

15.2.2 Pharmacological Interventions

15.2.2.1 Amantadine

Amantadine is a dopamine agonist that acts both pre- and post-synaptically to upregulate dopamine activity (Meythaler et al., 2002). Dopamine is thought to be involved in frontal lobe stimulation and plays a role in behavior, mood, language, motor control, hypothalamic function and arousal (Sawyer et al., 2008). Amantadine was initially developed for prophylactic use as an antiviral agent in the prevention of influenza A but has been used in the treatment of Parkinson’s disease. Its properties as a potential neuroactive agent were quickly recognized (Zafonte et al., 2001), and there is interest in its use as a potential treatment in the management of ABI (Schneider et al., 1999). Researchers believe that amantadine could significantly improve arousal in patients who are comatose. Potential side effects include over-stimulation, peripheral edema, livedo reticularis, and lowering of the seizure threshold, however, these are easily reversible (Schneider et al., 1999). The favorable risk-benefit profile of amantadine suggests that it may be an attractive treatment option for inducing arousal from coma (Hughes et al., 2005).

The RCP reported that the preliminary research on amantadine was positive, but suggested that its longer-term effects required further exploration (*Prolonged disorders of consciousness: National clinical guidelines*, 2013). The authors concluded that there was insufficient evidence to make formal recommendations regarding its use in enhancing recovery of consciousness. However, if medication is prescribed for patients with DOC, it was recommended that it be done in the setting of a clinical trial with formal monitoring and blinded assessors.

Table 15.29 Amantadine for Recovery of Consciousness Post ABI

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Giacino et al. (2012) USA RCT PEDro=7 N=184	Population: TBI; <i>Amantadine Group</i> (n=87): Mean Age=35.5 yr; Gender: Male=64, Female=23; Median Time Post Injury=48 days. <i>Placebo Group</i> (n=97): Mean Age=37.2 yr; Gender: Male=69, Female=28; Median Time Post Injury=47 days. Intervention: Participants were randomized to	1. DRS scores improved significantly more in the amantadine group compared to the placebo group at 4 wk (p=0.007). 2. Rate of improvement on DRS was significantly slowed from 4-6 wk (p=0.02).

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
	<p>receive either amantadine (100 mg, 2x/ days, 14 days. Dose increased to 150 mg 2x/ day at week 3, and to 200 mg 2x/ day at week 4 if DRS score had not improved by at least 2 points from baseline) or a placebo for 4 wk. Outcomes were assessed at baseline, 4 wk and 6 wk.</p> <p>Outcome Measure: Disability Rating Scale (DRS).</p>	<p>3. The overall improvement on DRS from baseline to 6 wk was not statistically different between groups ($p>0.05$).</p>
<p>Meythaler et al. (2002) USA RCT Crossover PEDro=6 N=35</p>	<p>Population: TBI; Mean Age=31 yr; Gender: Male=26, Female=9; Time Post Injury<6 wk; Mean GCS=5.4. Intervention: Patients received amantadine at 200 mg/ day (Group 1, n=15) or placebo (Group 2, n=20) for 6 wk, after which they received the alternate treatment for 6 wk. Outcome Measures: Mini Mental Status Exam (MMSE), Disability Rating Scale (DRS), Functional Independence Measure-Cognitive (FIM-cog), Galveston Orientation and Amnesia Test (GOAT).</p>	<ol style="list-style-type: none"> 1. In Group 1, there was a mean improvement in scores on MMSE (+14.3, $p=0.0185$), DRS (-9.8, $p=0.0022$), GOS (+0.8, $p=0.0077$), and FIM-cog (+15.1, $p=0.0033$) with amantadine. 2. No improvements were observed in Group 1 with placebo administration ($p>0.05$). 3. In Group 2, there was a mean improvement in scores on MMSE (+10.5, $p=0.0015$), DRS (-9.4, $p=0.0006$), GOS (+0.5, $p=0.0231$), and FIM-cog (+11.3, $p=0.003$) with placebo. 4. Group 2 continued to make significant gains in mean scores for MMSE (+6.3, $p=0.0409$), DRS (-3.8, $p=0.0099$), and FIM-cog (+5.2, $p=0.0173$) with amantadine.
<p>Hughes et al. (2005) Canada Case Control N=123</p>	<p>Population: TBI; <i>Amantadine Group</i> ($n=28$): Mean Age=37.36 yr; Gender: Male=17, Female=11; Mean Time Post Injury=6 wk; Mean GCS=4.14. <i>Control Group</i> ($n=95$): Mean Age=38.76; Gender: Male=58, Female=37; Mean Time Post Injury=6 wk; Mean GCS=4.18. Intervention: Patients were compared based on whether they received amantadine or not (control). Most patients received an initial dose of 100 mg 2x/ day that increased to 200 mg 2x/ day if there was no improvement. Treatment was discontinued 3wk after emergence from coma. Outcome Measure: Emergence from coma.</p>	<ol style="list-style-type: none"> 1. The proportion of patients emerging from coma between amantadine and control groups was similar (46% versus 38%, $p=0.42$). 2. Survival analysis identified age ($p=0.004$), GCS ($p=0.008$), and somatosensory evoked potential ($p=0.0002$) to be significant predictors of time to emerge from coma. 3. After controlling for these variables, amantadine did not significantly contribute to patient's emergence from coma.
<p>Saniova et al. (2004) Slovakia Case Control N=74</p>	<p>Population: TBI; <i>Amantadine Group</i> ($n=41$): Mean Age=42.12 yr; Gender: Male=35, Female=6; Mean GCS=4.74. <i>Control Group</i> ($n=33$): Mean Age=43.91 yr; Gender: Male=30, Female=3; Mean GCS=4.70. Intervention: Patients were compared based on whether they had received standard therapy and amantadine (200 mg, 2x/ day) or standard therapy alone (control). Outcome Measures: Glasgow Coma Scale (GCS), Mortality.</p>	<ol style="list-style-type: none"> 1. At discharge, patients treated with amantadine showed significantly higher GCS scores (9.76 versus 5.73, $p<0.0001$). 2. At discharge, patients treated with amantadine had a significantly lower mortality rate (6.06% versus 51.51%, $p<0.001$) than controls.

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

One retrospective study that assessed amantadine was identified. The results of the study found that there was no difference in emergence from coma after amantadine administration (Hughes et al., 2005). Upon further analysis, it was found that the only predictors for emergence from coma were age, GCS score, and somatosensory evoked potential.

Two RCTs identified evaluated the effectiveness of amantadine in improving consciousness in adults. Using a crossover design, Meythaler et al. (2002) assessed patients for orientation, cognitive function, functional independence and disability. The authors found that patients who received amantadine significantly improved on all outcome measures over six weeks but made no further gains when switched to placebo for another six weeks. Patients initially receiving placebo made small gains but went on to make further improvements after amantadine administration. While patients made some natural recovery on placebo, the authors noted that patients made more pronounced improvements on amantadine. In addition, the authors went on to suggest that amantadine aids in recovery regardless of the time of administration. Similarly, a trial by Giacino et al. (2012) found a significant reduction in the disability of participants who received amantadine over four weeks when compared to placebo. However, following a two-week follow-up without amantadine treatment, their recovery slowed such that overall improvements were similar between the two groups (Giacino et al., 2012). The authors recommended that amantadine treatment should be continued until recovery goals are reached, although it should be approached with caution.

In a chart review, patients who were treated with amantadine showed significant improvements in consciousness at discharge and decreased mortality rates when compared to those who received standard therapy (Saniova et al., 2004). While the retrospective nature of this study makes it difficult to draw conclusions, the author recommends amantadine as a safe intervention with promising potential but suggested that further research was warranted.

Conclusions

There is level 1a evidence that amantadine effectively improves consciousness, cognitive function, and disability when compared to placebo post ABI.

There is level 3 evidence that amantadine treatment does not improve emergence from coma compared to control in patients post ABI.

There is level 3 evidence that amantadine is superior to standard care at improving consciousness in patients in a coma post ABI.

Amantadine improves consciousness, cognitive function, and disability; however, it might not affect emergence from coma post ABI. It is important to note that these benefits are only seen during amantadine administration, and so treatment must be continued to sustain the improvements made.

Amantadine may be more effective than standard care at improving consciousness and decreasing mortality in patients in a coma post ABI.

15.2.2.2 Other Medications

In addition to amantadine, other pharmacological interventions have been evaluated for effectiveness in restoring consciousness post ABI.

Table 15.30 Other Medications for Recovery of Consciousness Post ABI

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Shokouhi et al. (2014) Iran RCT PEDro=5 N=58	Population: TBI; Mean Age=30.94 yr; Gender: Male=65, Female=13; GCS Range=3-8. Intervention: Patients were randomized to receive either citicoline (500 mg) every 6 hr for 15 days (n=29) or no treatment (control, n=29) Outcome Measure: Glasgow Coma Scale (GCS).	1. GCS scores improved in both groups, and there was no statistical significance between groups (p>0.05).
Bagnato et al. (2013) Italy PCT N=103	Population: TBI=45, Stroke=35, Hypoxia=23. Antiepileptic Drugs Group (n=54): Mean Age=42.6 yr; Gender: Male=39, Female=15; Mean Time Post Injury=57.9 d. Control Group (n=49): Mean Age=49.5 yr; Gender: Male=27, Female=22; Mean Time Post Injury=50.7 d. Intervention: Patients who received Antiepileptic Drugs (AED) were compared to those who did not (controls). Outcomes were assessed at baseline and 3mo. Outcome Measure: Levels of Cognitive Functioning (LCF).	1. There was no significant difference between AED and control groups in LCF from baseline (2.2 versus 2.3) to 3 mo (3.8 versus 3.7, p>0.05).

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

Two clinical trials have evaluated other pharmacological interventions for restoring consciousness post ABI: citicoline (Shokouhi et al., 2014) and antiepileptics (Bagnato et al., 2013). In both trials, consciousness improved similarly in both the treated and untreated control groups over time, and thus the medications provided no discernable benefit. Given the limited research on each of these medications, additional clinical trials are required prior to making firm conclusions.

Conclusions

There is level 2 evidence that citicoline or antiepileptics are not effective at restoring consciousness post ABI compared to controls.

Citicoline and antiepileptics may not be effective interventions for restoring consciousness post ABI, however, further research is required.

15.3 Miscellaneous Outcomes

15.3.1 Osmolar Interventions

Osmolar therapy is a major treatment approach in controlling intracranial hypertension and edema following ABI. Although mannitol is most commonly used to control ICP, results from some studies have called for its replacement as the primary osmolar intervention with saline; a safer and more effective compound (Horn et al., 1999; Ware et al., 2005).

Table 15.31 Miscellaneous Outcomes - Osmolar Therapy for Acute Management Post ABI

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Baker et al. (2009) Canada RCT PEDro=10 N=64	<p>Population: TBI; <i>Hypertonic Saline (HTS, n=33)</i>: Mean Age=42.3 yr; Gender: Male=23, Female=10; Mean GCS=5.8. <i>Hypertonic Saline and Dextran (HSD, n=31)</i>: Mean Age=42.5 yr; Gender: Male=18, Female=13; Mean GCS=5.2.</p> <p>Intervention: Participants were randomized to receive intravenous infusions of 0.9% HTS (250mL) or 7.5% HTS (250 mL) with 6% dextran-70 (HSD). Outcomes were assessed during the first 48 hr and at discharge.</p> <p>Outcome Measures: Glasgow Outcome Scale (GOS), GOS Extended (GOSE), Disability Rating Scale (DRS), Functional Independence Measure (FIM), Mortality, Biomarkers.</p>	<ol style="list-style-type: none"> 1. There was no significant difference between groups in GOS, GOSE, DRS, FIM, or mortality. 2. Peak levels of biomarkers were significantly correlated with unfavorable outcomes measured by the GOS and GOSE.
Myburgh et al. (2007) Australia RCT PEDro=10 N=460	<p>Population: TBI; Hypertonic Saline (HTS, n=229): Median Age=35 yr; Gender: Male=169, Female=60; Median GCS=7. Albumin (ALB, n=231): Median Age=37 yr; Gender: Male=179, Female=52; Median GCS=7.</p> <p>Intervention: Participants were randomized to receive intravenous infusions of 0.9% HTS or 4% ALB. Outcomes were assessed at 24 mo.</p> <p>Outcome Measures: Glasgow Outcome Scale Extended (GOSE), Mortality.</p>	<ol style="list-style-type: none"> 1. At 24 mo, there was a significantly higher rate of mortality in ALB than HTS (33.2% versus 20.4%, RR=1.63, p=0.003). 2. Among those with severe TBI (GCS<9), there was a significantly higher rate of mortality in ALB than HTS (41.8% versus 22.2%, RR=1.88, p<0.001). 3. Among those with mild TBI (GCS=9-12), there was a lower rate of mortality in ALB than HTS, but it was not significant (16.0% versus 21.6%, RR=0.74, p=0.50). 4. There were no significant differences in GOSE between groups.
Sayre et al. (1996) USA RCT PEDro=7 N=41	<p>Population: TBI; <i>Mannitol (MAN, n=20)</i>: Mean Age=29yr; Gender: Male=19, Female=1; Mean GCS=7.1. <i>Hypertonic Saline (HTS, n=21)</i>: Mean Age=27 yr; Gender: Male=20, Female=1; Mean GCS=6.4.</p> <p>Intervention: Patients were randomized to receive either intravenous infusion of 20% MAN (5 mL/kg) or 0.9% HTS (5 mL/kg).</p> <p>Outcome Measures: Systolic Blood Pressure (SBP), Mortality, Urine Output (UO), Serum Sodium.</p>	<ol style="list-style-type: none"> 1. Mortality was 25% in MAN and 14% in HTS (p=0.38). 2. Mean SBP was significantly lower in MAN than in HTS (116 mmHg versus 142 mmHg, p<0.003) 2 hr after admission; however, when all time periods were compared there was no overall difference between groups.

		3. UO was significantly greater ($p<0.001$) and serum sodium was significantly lower ($p<0.00001$) in MAN compared with HTS.
Coritsidis et al. (2015) USA Case Control N=205	Population: TBI; Mean Age=53.12 yr; Gender: Male=157, Female=48; Mean GCS=8.75. Intervention: Participants who received hypertonic saline (HTS, n=96) or did not (n=109) were compared in retrospective analysis. Outcome Measures: Infections, Length of Stay (LOS), Blood Pressure (BP), Deep Venous Thrombosis (DVT), Acute Kidney Injury (AKI), Neurological Benefits.	1. After correction for GCS, pulmonary infections ($p=0.001$) and LOS ($p=0.0048$) were significantly higher in HTS patients. 2. HTS did not result in increased BP, DVT, AKI or neurological benefits. 3. HTS significantly increased the odds for all infections ($p<0.05$), most specifically pulmonary infections, in patients with GCS<8.

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

In a trial by Baker et al. (2009), HTS-dextran solution was similar to normal saline solution infusion in all morbidity (GOS, GOSE, FIM, DRS) and mortality outcomes measured. However, peak levels of brain injury biomarkers (neuron-specific enolase, myelin-basic protein) were associated with unfavourable GOS, GOSE scores in the HTS-dextran group.

Three studies were analyzed comparing HTS to either mannitol (Sayre et al., 1996), albumin (Myburgh et al., 2007) or a control group (Coritsidis et al., 2015). Although HTS has gained traction as an effective treatment of ICP post ABI, a case control study found increases in hospital LOS, and rates of infections after HTS use in patients post ABI (Coritsidis et al., 2015). Furthermore, the authors suggest that treatment should be administered with caution in patients with severe TBI (GCS<8), as they had significantly increased odds for developing pulmonary infections.

Sayre et al. (1996) conducted a RCT to investigate the effects of early mannitol administration in an out-of-hospital emergency care setting. The authors reported that mannitol administration was associated with increased urine output, lower serum sodium, and a transient (2 hour) decrease in systolic blood pressure when compared to HTS. Despite the improved side effect profile associated with HTS administration, mortality between groups was the same.

Finally, a very high quality RCT compared HTS to albumin in patients post ABI (Myburgh et al., 2007). The study noted an increase in mortality, especially in GCS<9 patients, but no differences in GOSE scores in the albumin group compared to those receiving HTS. The results from this study suggest that HTS is safer than albumin and should be considered first when administering an osmolar therapy to treat patients post ABI.

Conclusions

There is level 1b evidence that hypertonic saline and dextran infusion is the same as normal saline alone at improving morbidity and mortality outcomes.

There is level 1b evidence that elevated serum brain injury markers are associated with unfavourable outcomes post TBI.

There is level 1b evidence that mannitol may increase urine output, lowers serum sodium, transiently decreases systolic blood pressure, but may have the same effect on mortality compared to hypertonic solution post ABI.

There is level 1b evidence that albumin may increase mortality, specifically in individuals with an ABI and a Glasgow Coma Scale score less than 9, compared to hypertonic solution.

There is level 1b evidence that albumin may not differ from hypertonic solution for improving Glasgow Outcome Scale Extended scores in patients post ABI.

There is level 3 evidence that hypertonic solution may increase hospital length of stay and rates of infections compared to controls post ABI.

There is level 3 evidence that compared to a control group, administration of a hypertonic solution may increase the risk of pulmonary infections in individuals with an ABI and a Glasgow Coma Scale score <8.

A hypertonic saline and dextran infusion combination is likely the same as normal saline at improving mortality and morbidity outcomes in patients post TBI. Brain injury serum markers may predict the development of unfavourable outcomes.

Hypertonic saline may increase hospital length of stay and rates of infections, especially in patients with severe TBIs.

Mannitol may increase urine output, lower serum sodium, transiently decrease systolic blood pressure, but has the same mortality compared to hypertonic solution.

Albumin may increase mortality, especially in patients with severe TBI, compared to hypertonic solution; however, there may be no difference in neurological outcomes between treatments.

15.3.2 Erythropoietin

Erythropoietin (EPO) is a hormone produced by the kidneys and functions as the main factor driving red blood cell formation, or erythropoiesis. Erythropoietin has been found to promote neurogenesis, angiogenesis, and reduce apoptotic and inflammatory responses; properties which have garnered interest for its use as a neuroprotective agent in ABI (Kumral et al., 2011; Li et al., 2016; Simon et al., 2017; Wang et al., 2015). While animal models have shown the benefit of recombinant EPO use in TBI models, the benefit in humans post ABI is unclear (Matejkova et al., 2013; Peng et al., 2016; Wang et al., 2015).

The AANS and the EBIC made no recommendations regarding EPO in acute ABI.

Table 15.32 Miscellaneous Outcomes - Erythropoietin for Acute Management Post ABI

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Skrifvars et al. (2017) Australia Secondary Analysis to RCT PEDro=9 N=606	Population: TBI. Intervention: Patients received either weekly doses of 40,000IU of subcutaneous epoetin alfa (EPO) or placebo for a maximum of 3 doses or until discharge from the ICU. Outcome Measure: Subgroup Analysis.	<ol style="list-style-type: none"> 1. Most TBI deaths were from cerebral causes in the first 2wk and were related to withdrawal of care. 2. There was a difference in EPO effect in patients who had undergone a neurosurgical procedure prior to randomization compared with those who had not. EPO decreased mortality more in the group who had not undergone a previous neurosurgical operation (p=0.01) compared with those who had (p=0.37).
Li et al. (2016) China & Australia RCT PEDro=9 N _{initial} =159 N _{final} =146	Population: Severe TBI; <i>Treatment Group (n=75):</i> Mean Age=43.4 yr; Gender: Male=49, Female=26; Time Post Injury≤6h; Mean GCS=6.8. <i>Control Group (n=71):</i> Mean Age=41.1 yr; Gender: Male=41, Female=30; Time Post Injury≤6h; Mean GCS=7.1. Intervention: Patients received 100U/kg subcutaneous injections of recombinant human erythropoietin on days 1, 3, 6, 9 and 12 following TBI. The control group received the same volumes of saline injections on the same days post injury. Outcome Measures: Biochemical and Physiological Parameters, Glasgow Outcome Scale (GOS).	<ol style="list-style-type: none"> 1. There were no significant differences between groups in blood pressure, hemoglobin levels, infection rates, or thromboembolic events 3mo after treatment. On day 7, the treatment group had significantly lower serum NSE and S-100β protein levels (p<0.05). 2. At 3 mo follow-up, patients in the treatment group had better recovery based on itemized GOS analysis. Specifically, the treatment group had significantly more individuals in itemized GOS categories of good recovery and moderate disability, and significantly fewer individuals in the categories of severe disability and vegetative state (all p<0.05).

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

Two studies were identified evaluating the effects of recombinant human EPO (rhEPO) in patients post ABI. Compared to a control (saline) population, patients receiving rhEPO were found to have improved neurological outcomes (GOS), as well as decreased markers of brain cell destruction (Li et al., 2016). However, it is important to note that the decreased brain destruction markers were only present on day 7 of the treatment protocol, and not again at 3 months. In a follow up to a separate RCT, Skrifvars and colleagues (2017) found a decrease in mortality in patients receiving EPO, especially those who underwent a neurosurgical operation before treatment with EPO. Based on the available data, rEPO administration appears to provide an appreciable mortality and neurological benefit in patients post ABI, however further studies are required to support these findings.

Conclusions

There is level 1b evidence that recombinant erythropoietin administration may improve neurological outcomes and transiently decreases markers of brain cell destruction compared to saline post ABI.

There is level 1b evidence that recombinant erythropoietin administration may decrease mortality compared to saline, especially in patients who have undergone an operation previously, post ABI.

Recombinant erythropoietin administration likely improves mortality and neurological outcomes, and acutely lowers brain cell destruction markers in patients post ABI.

15.3.3 Other Medications

In addition to the aforementioned medications, other pharmacological interventions have been evaluated for the treatment of ABI and complications resulting from ABIs. These interventions include antifibrinolytic agents, dyslipidemia drugs, nonsteroidal anti-inflammatory drugs, sedatives, beta blockers, and selenium.

Table 15.33 Miscellaneous Outcomes - Other Medications for Acute Management Post ABI

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Jokar et al. (2017) Iran RCT PEDro=7 N=80	<p>Population: TBI; <i>Tranexamic Acid (TA)</i> (n=40): Mean Age=35.4 yr; Gender: Male=32, Female=8. <i>Placebo</i> (n=40): Mean Age=36.2 yr; Gender: Male=28, Female=12.</p> <p>Intervention: Patients were randomized to receive either tranexamic acid (a bolus of 1 g over 10min followed by a continuous infusion of 1 g over 8 hr) or placebo in addition to standard ICH care.</p> <p>Outcome Measures: Extent of Intracranial Hemorrhage (ICH) growth, Initial ICH volume.</p>	<ol style="list-style-type: none"> Initial ICH volume was similar for both groups (TA=21.6 ml, placebo=22.2 ml; p=0.83). However, 48 h after treatment began ICH volume was significantly less in the TA group compared to placebo (TA=23.3 ml, placebo=26.5 ml; p=0.04). ICH growth was significantly larger in the placebo group compared to the TA group (p<0.001).
Moghaddam et al. (2017) Iran RCT PEDro=8 N=113	<p>Population: TBI; <i>Selenium Group</i> (n=57): Mean Age=40.07 yr; Gender: Male=45, Female=12. <i>Control Group</i> (n=56): Mean Age=42.93 yr; Gender: Male=45, Female=11.</p> <p>Intervention: Patients were randomized to receive either selenium (within 8h after injury) plus standard treatment, or standard treatment alone (control).</p> <p>Outcome Measures: Glasgow Outcome Scale Extended (GOS-E), Full Outline of Unresponsiveness (FOUR), Sequential Organ Failure Assessment (SOFA), Acute Physiology and Chronic Health Evaluation III (APACHE), Side Effects, Length of Stay</p>	<ol style="list-style-type: none"> There were no significant between group differences for any of the outcome measures. For side effects in the selenium group, 1 patient reported nausea and 3 patients had facial flushing.

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
	(LOS).	
Humble et al. (2016) USA Case Series N=85	Population: Severe TBI; Median Age=35; Gender: Male=73, Female=12; Median GCS=3. Intervention: Medical records for patients who received dexmedetomidine infusions were identified. Outcome Measures: Blood Pressure (BP), Heart Rate (HR), Glasgow Coma Scale (GCS), Richmond Agitation-Sedation Scale (RASS), Opioid Dosage.	<ol style="list-style-type: none"> 1. BP and HR decreased during dexmedetomidine infusion and returned to baseline levels after infusion. 2. GCS increased from 8 to 9.5 pre-infusion to infusion ($p<0.01$), and from 9.5 to 10 infusion to post-infusion ($p<0.01$). 3. RASS scores increased significantly from pre-infusion to infusion and from infusion to post-infusion ($p<0.01$ and $p<0.05$, respectively). 4. Fifty-one patients received propofol and 35 received midazolam during the study period.
Ko et al. (2016) USA Case Control N=440	Population: TBI; <i>Early propranolol</i> ($n=109$): Mean Age=57.7 yr; Gender: Male=293, Female=137; Mean GCS=12.2. <i>Control</i> ($n=331$): Mean Age=60.4 yr; Gender: Male=216, Female=115; Mean GCS=12.4. Intervention: Patients were administered low-dose intravenous propranolol (1 mg every 6 hr) in the early stages post-TBI and compared with controls. Outcome Measures: Days on a Ventilator, Mortality, Length of Stay (LOS).	<ol style="list-style-type: none"> 1. The early propranolol group had significantly more days on a ventilator than the control group ($p<0.001$). 2. When controlling for associated risk factors, early propranolol was independently associated with lower mortality ($p=0.012$). 3. No significant differences were found between groups for LOS.
Neilson et al. (2016) Singapore Case Control N=118	Population: Severe TBI; Mean Age=70.2; Median GCS=5. Intervention: Patient records were identified from a database of patients with severe TBI who were admitted with head injury from 2006-2009. Each patient that was taking statin prior to injury was matched to a patient with no prior statin use. Outcome Measures: Mortality, Glasgow Outcome Scale (GOS).	<ol style="list-style-type: none"> 1. Based on the Kaplan-Meier curve, the median survival at 14 days between statin users and non-statin users was not significantly different ($p=0.13$). The same result was found for survival at 6mo ($p=0.14$). 2. At 6 mo, there was no significant between group difference in median GOS ($p=0.11$).
Picetti et al. (2016) Italy Pre-Post Test N=30	Population: ABI; Mean Age=50.1 yr; Gender: Male=17, Female=13; Median GCS=6. Intervention: Patients received Diclofenac Sodium (DCFS, 12.5 mg) intramuscularly for fever control. The study duration was 2 hr. Outcome Measures: Core Body Temperature (T_c), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Mean Arterial Pressure (MAP), Heart Rate (HR), Cerebral Perfusion Pressure (CPP).	<ol style="list-style-type: none"> 1. Two hours after DCFS administration, T_c ($p<0.001$), SBP ($p<0.001$), DBP ($p<0.001$), MAP ($p<0.001$), HR ($p<0.001$), and CPP ($p<0.001$) were all significantly decreased compared to baseline.

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

A number of pharmacological agents have been studied by different groups for the treatment of ABI. Tranexamic acid, an antifibrinolytic agent, was examined for its efficacy in treating ICH when used in

combination with standard care (Jokar et al., 2017). The researchers found that patients who only received standard care had significantly larger ICH growth compared to the group who additionally received tranexamic acid. Further research is required to make definitive conclusions on the efficacy of tranexamic acid in ICH treatment, however early results show promise of its use in limiting ICH growth.

Selenium, an element in the periodic table, is a compound used today for the treatment of a vast range of conditions including cardiovascular diseases, osteoarthritis, neurological diseases, and depression. A group led by Moghaddan (2017) compared patients receiving standard care to those receiving selenium in addition to standard care on number of morbidity (SOFA, APACHE, side effects, LOS) and neurological outcomes measures (GOSE, FOUR). There were no significant differences between groups in any outcome measure, however patients in the selenium group reported nausea (n=1) as well as facial flushing (n=3). These results suggest that selenium may not be beneficial in the treatment of ABI, and while not alarming, can be associated with side effects that affect quality of life.

Patient records were identified from a database and patients with severe TBI taking a statin prior to injury were matched to patients with severe TBI with no prior statin use (Neilson et al., 2016). After analysis, it was determined that no differences existed between the groups in terms of GOS scores, or survival (14 days and 6 months). The results of this study suggest that statins, a class of drug used to lower the risk of cardiovascular disease and treat dyslipidemia, are not effective agents in the treatment of TBI.

In a separate case control study, researchers administered propranolol in the early stages post-TBI to determine its effects on morbidity and mortality (Ko et al., 2016). The group reported that patients who received propranolol had a lower mortality but spent more days on a ventilator compared to patients who did not receive propranolol. No difference was noted between groups in the length of time they stayed in the hospital. Further randomized studies are required to determine the effects of early propranolol intervention in patients with TBI.

Dexmedetomidine, an alpha-2 receptor agonist, is a sedative commonly used in the ICU to intubate patients. However, Humble et al. (2016) retrospectively analyzed patients who received dexmedetomidine acutely after sustaining a severe TBI. The researchers noted that dexmedetomidine infusion was associated with increased sedation (decreased blood pressure, heart rate, and increased RASS score), increased GCS scores, and decreased opioid use. While caution must be taken when drawing conclusions from a single retrospective study, these results suggest that dexmedetomidine infusion post TBI can effectively sedate patients and reduce the need for further sedation by opioid administration. High quality RCTs involving dexmedetomidine are required to properly study its effects in patients post TBI.

Diclofenac Sodium (DCFS) is a non-steroidal anti-inflammatory drug (NSAID) used to reduce fever in patients in the ICU. A group out of Italy studied the effects of intramuscular DCFS administration to control fever in patients with ABI, and noted a decrease in core temperature, systolic blood pressure, diastolic blood pressure, MAP, heart rate and CPP (Picetti et al., 2016). While DCFS effectively reduced core body temperature, it also compromised patient blood pressure and blood flow to the brain. Further studies are required to study the full effects of DCFS in patients with TBI; however, early results do not support its use as a fever control agent.

Conclusions

There is level 1b evidence that tranexamic acid in combination with standard care is superior to standard care alone at reducing intracranial hemorrhage growth in patients post TBI.

There is level 1b evidence that selenium in addition to standard care is not different than standard care alone at improving morbidity and neurological outcomes in patients post TBI.

There is level 3 evidence that statin use prior to injury does not improve mortality or neurological outcomes compared to no prior statin use in patients post TBI.

There is level 3 evidence that early propranolol intervention decreases mortality, increases time spent on a ventilator, but has no effect on hospital length of stay compared to controls in patients post TBI.

There is level 4 evidence that dexmedetomidine decreases blood pressure and heart rate, increases Glasgow Coma Scale and Richmond Agitation-Sedation Scale scores, and reduces the need for opioid administration in patients post TBI.

There is level 4 evidence that diclofenac sodium decreases core body temperature, blood pressure, heart rate, and cerebral perfusion pressure in patients post TBI.

Tranexamic acid in combination with standard care is likely superior to standard care alone at reducing intracranial hemorrhage growth in patients post TBI.

Selenium in addition to standard care is likely not different than standard care at improving morbidity and neurological outcomes in patients post TBI and may even be associated with nausea and facial flushing.

Prophylactic statin use may not improve mortality or neurological outcomes in patients post TBI.

Early propranolol intervention may decrease mortality, but increase time spent on a ventilator in patients post TBI.

Dexmedetomidine might improve sedation, neurological outcomes and decrease the need for opioid administration, however caution should be taken due to its ability to lower blood pressure.

Diclofenac Sodium might decrease core body temperature, however its benefit in preventing fever is outweighed by its ability to compromise systemic and cerebral perfusion.

15.3.4 Tracheostomy

Patients with ABI enter the ICU with varying degrees of consciousness, frequently requiring mechanical assistance from a ventilator to maintain adequate respiration. While patients often arrive to the ICU with an endotracheal tube, ventilation through a tracheostomy tube is the preferred method of ventilation in patients requiring assistance for a prolonged period of time (Cheung & Napolitano, 2014; Durbin, 2010). Conflicting results exist regarding the potential benefits of a tracheostomy in patients post ABI. While some studies have reported shorter duration of ventilation (Teoh et al., 2001) and hospital LOS (D'Amelio

et al., 1994), others have associated tracheostomies with detrimental effects, such as increases in ICP (Kocaeli et al., 2008; Stocchetti et al., 2000).

Table 15.34 Miscellaneous Outcomes - Tracheostomy for Acute Management Post ABI

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Baron et al. (2016) Austria Case Control N=2,156	<p>Population: TBI; <i>Endotracheal Tube (n=1603):</i> Median Age=58 yr; Gender: Male=1167, Female=436; Median GCS Score=6. <i>Endotracheal Tube, then Tracheostomy (n=553):</i> Median Age=62 yr; Gender: Male=394, Female=159; Median GCS=6.</p> <p>Intervention: Patient data was retrospectively gathered from 87 Austrian ICUs. Outcomes of TBI intubated patients who underwent tracheostomy were compared with intubated patients who did not undergo tracheostomy.</p> <p>Outcome Measures: Mortality, Abbreviated Injury Scale (AIS).</p>	<ol style="list-style-type: none"> 1. Patients who underwent tracheostomy were older, more often intubated, had longer a longer ICU stay, exhibited a higher level of treatment, and displayed AIS head scores ≥ 4 more often. 2. Mortality ratio (observed:expected mortality) was significantly lower in patients who underwent tracheostomy (0.62 [0.53-0.72]) compared with patients who remained intubated (1.00 [0.95-1.05]).

Discussion

Intubated ABI patients who underwent a tracheostomy were compared to intubated patients who did not undergo a tracheostomy (Baron et al., 2016). The researchers found that compared to those who did not undergo a tracheostomy, patients who did receive the intervention had a lower mortality ratio, required more treatment, were older, and had more severe injuries. While drawing conclusions from a single study is difficult, these results suggest that a tracheostomy may provide a greater survival benefit to ABI patients who are in worse condition.

Conclusions

There is level 3 evidence that individuals with an ABI receiving a tracheostomy may have improved mortality compared to individuals not receiving a tracheostomy.

Tracheostomies might improve mortality in individuals post ABI; however, individuals undergoing the procedure are generally older, more injured, and require more treatment.

15.4 Guideline Implementation

Guideline adherence is an inherently difficult parameter to quantify given the reliance on self-reporting and the relative heterogeneity of available guidelines – this is especially true in European countries (Volovici et al., 2019). However, The Brain Trauma Foundation guidelines for management of ABIs have

long been considered the standard for best practice and are used by a number of countries around the world. Despite being well accepted and believed to improve outcomes, adherence rates are suboptimal with reports of in-center adherence hovering around 60% (Khormi et al., 2018). Adherence rates have not been found to be influenced by region; however, a number of factors have been associated with lower levels of guideline adherence, ranging from center-specific factors (level of trauma center, volume of trauma), guideline specific factors (higher adherence rates in specific guideline subsections with higher levels of evidence) and even procedure specific factors (surgical interventions tend to have lower levels of adherence compared to medical ones) (Hirschi et al., 2018; Khormi et al., 2018). Guideline adherence has increased since 1997; however, it has plateaued at the current rate which was achieved in 2002.

This section will examine the existing literature on the efficacy of guideline adherence in the treatment of patients post ABI.

Table 15.35 Guideline implementation for the Acute Management of Patients Post ABI

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
<p>Gupta et al. (2016) India& USA Cohort N=400</p>	<p>Population: TBI=400. <i>India (HPNATC) Site (n=200):</i> Mean Age=36 yr; Gender: Male=169, Female=31. Mean ISS=31.4. <i>USA (HMC) Site (n=200):</i> Mean Age=44.1 yr; Gender: Male=145, Female= 55. Mean ISS=38.5. Intervention: At HMC, 200 patients with TBI were retrospectively analyzed to asses the institution’s adherence to ICU TBI treatment guidelines. At HPNATC, 200 patients with TBI were prospectively analyzed to assess similar parameters. Outcomes were measured at 3, 6 and 12 mo post discharge. Outcome Measures: In-Hospital Mortality, Glasgow Outcome Scale (GOS), Guideline Adherence.</p>	<ol style="list-style-type: none"> 1. At JPNATC, in-hospital mortality was 24%, compared to 24.3% at HMC. 2. Guideline adherence rates were reported to be 74.9% at JPNATC, compared to a 71.6% rate at HMC. 3. Highest adherence rates in both sites were found in: achieving target temperature, not using prophylactic barbiturates, starting of nutritional support and avoidance of IV steroids. 4. At the JPNATC, a 1% increase in guideline adherence was associated with a 3% in-hospital mortality decrease [0.97; 95% CI, 0.95-0.99]. 5. Adherence rates below 65% were significantly associated with an increase in mortality [1.92; 95% CI, 1.11-3.33]. 6. At JPNATC, 60% of patients had improved GOS scores compared to discharge.
<p>Lele et al. (2018) India Secondary Analysis N=200</p>	<p>Population: TBI=200. <i>ICP Monitor group (n=126):</i> Mean Age=34.8 yr; Gender: Male=108, Female=18. <i>No ICP Monitor group (n=74):</i> Mean Age=38 yr; Gender: Male=60, Female=14. Intervention: ICP monitor placement was retrospectively analyzed in patients with TBI. Those receiving an ICP monitor were compared to those without. Outcomes were assessed at discharge, 3, 6, and 12 mo post TBI. Outcome Measures: In-Hospital Mortality, Glasgow Outcome Scale (GOS).</p>	<ol style="list-style-type: none"> 1. In-hospital mortality was significantly lower in the ICP monitoring group when compared to the other group (0.50; 95% CI, 0.29-0.87). 2. There was no significance difference in mortality (in-hospital) between groups at 3 (0.65; 95% CI, 0.40-1.05), 6 (0.70; 95% CI, 0.45-1.11), and 12mo (0.78; 95% CI, 0.51-1.18). 3. There was no significance difference between groups in GOS scores at discharge (1.20; 95% CI, 0.58-2.49), 3 (0.87; 95% CI, 0.50-1.51), or 6 mo (0.99; 95% CI, 0.44-2.25). 4. Amongst patients receiving ICP monitors, absence of cerebral edema (0.54; 95% CI, 0.35-0.84), and absence of IVH (0.53; 95% CI, 0.33-0.82) were associated with the best outcomes.

Discussion

One large, multi-center, cohort study was reviewed to analyze the effect of guideline adherence on morbidity and mortality outcomes in patients post TBI (Gupta et al., 2016). Across both centers, guideline adherence (74.9% JPNATC, 71.6% HMC) and in-hospital mortality (24% JPNATC, 24.3% HMC) were the same. Interestingly, guideline adherence at both sites were highest in the same parameters (achieving

target temperature, etc). At the JPNATC site, guideline adherence rates below 65% were found to be associated with a significant increase in mortality; however, there did not seem to be any improvement in mortality rates with higher levels of adherence. This finding is particularly noteworthy given that the average hospital guideline adherence rate is 60%, indicating that this may be the minimum level of adherence required to not significantly affect patient mortality.

A secondary analysis of the Gupta et al. (2016) study analyzed ICP monitor placement in patients at the Indian JPNATC site (Lele et al., 2018). The group noting a decrease in mortality while in-hospital, but not at any other time when the ICP monitoring group was compared to the control (no monitor) group. Further, there were no difference in GOS scores at discharge or up to 6 mos post intervention.

Conclusions

There is level 2 evidence that guideline adherence rates below 60% are associated with an increase in mortality rates in patients post TBI.

There is level 2 evidence that when compared to no monitor placement, intracranial pressure monitor placement improves mortality in-hospital, but not at any other time in patients post TBI.

These is level 2 evidence that there is no difference in Glasgow outcome scale scores between patients treated with an intracranial pressure monitor and patients treated without one post TBI.

Adherence to TBI treatment guidelines below 60% may be associated with increased patient mortality

Intracranial pressure monitor placement may improve short-term mortality, but not long-term mortality or morbidity outcomes

15.5 Conclusion

This acute intervention chapter focuses on interventions which were initiated within 14 days of ABI incident or diagnosis. The majority of interventions focus on the management of ICP, this secondary insult post ABI can be catastrophic if not addressed and managed properly. Other focuses include prompting emergence from coma and surgical interventions.

15.6 Summary

There is level 1b evidence that intracranial pressure monitoring is not different to imaging/clinical based monitoring at improving mortality, hospital length of stay, or neurological worsening in patients post TBI.

There is level 1b evidence that there is a higher rate of decubitus ulcers in the intracranial pressure monitoring group when compared to imaging/clinical based monitoring group in patients post TBI.

There is level 1b evidence that patients in the imaging/clinical based monitoring group receive high-dose barbiturates, hypertonic saline infusion and hyperventilation interventions at a higher frequency when compared to the intracranial pressure monitoring group post TBI.

There is level 2 evidence that intracranial pressure monitoring may improve mortality in-hospital, and 6 months post-discharge in patients post ABI compared to no monitoring.

There is level 2 evidence that intracranial pressure monitoring may not improve Glasgow Outcome Scale scores in patients post ABI compared to no monitoring.

There is level 3 evidence that an intraparenchymal fiberoptic monitor may yield lower intensive care unit length of stay, device complications, need for surgical decompressions, and need for intracranial pressure monitoring compared to an external ventricular drainage post ABI.

There is level 2 evidence that head elevations of 15° compared to 0° can effectively reduce elevated intracranial pressure post ABI when compared to a flat position.

There is conflicting (level 2) evidence that head elevations 30° compared to 0° can effectively reduce elevated intracranial pressure post ABI when compared to a flat position.

There is conflicting (level 2) evidence regarding whether or not head elevation can improve cerebral perfusion pressure post ABI.

There is conflicting (level 2 and level 4) evidence whether increasing the head elevation angle is correlated with greater intracranial pressure improvement post ABI. Level 2 evidence suggests that there is no angle-dependent benefit.

There is level 4 evidence that head elevation of 45° and 60° may effectively reduce elevated intracranial pressure post ABI when compared to a flat position.

There is level 4 evidence that head elevation of 10°-60° may decrease mean arterial pressure post ABI.

There is level 2 evidence that head elevation of 30° from a flat position may effectively reduces elevated intracranial pressure compared to head elevation of 0° in individuals post ABI.

There is level 4 evidence that head elevation of 60° from a flat position may effectively reduce elevated ICP post ABI.

There is conflicting (level 2 and level 4) evidence regarding whether or not head elevation of 30° effectively improves cerebral perfusion pressure post ABI. With level 2 evidence supporting the use of head elevation to improve cerebral perfusion pressure.

There is conflicting (level 1a) evidence regarding whether or not therapeutic hypothermia (32-35°C) effectively reduces elevated intracranial pressure post ABI compared to normothermia.

There is conflicting level 1a evidence whether or not therapeutic hypothermia (32-35°C) is associated with more favourable Glasgow Outcome Scale (extended) scores or mortality rates post ABI compared to normothermia treatment.

There is level 1a evidence that therapeutic hypothermia (32-35°C) increases the risk of complications such as pneumonia during treatment in patients post ABI.

There is level 1b evidence that very mild hypothermia (35-37°C) is just as effective as mild hypothermia (32-34°C) at lowering intracranial pressure in ABI patients.

There is conflicting (level 1b and level 2) evidence that very mild hypothermia (35-37°C) improves long term outcomes and mortality rates to a greater extent than mild hypothermia (32-34°C) in ABI patients. There is level 1b evidence that outcomes are the same.

There is level 1b evidence that very mild hypothermia (35-37°C) is effective at lowering intracranial pressure in diffuse II ABI patients, but increases mortality in diffuse III ABI patients.

There is level 1b evidence that hypothermia interventions may be more effective at decreasing intracranial pressure and improving long-term outcomes when administered for long-term (120 hours) compared to short term (48 hours)

There is conflicting (level 1b and level 2) evidence that therapeutic hypothermia may improve intracranial pressure and mortality and long-term outcomes when compared to standard therapy in ABI patients. The higher quality level 1b evidence suggests there is no improvement in intracranial pressure, and there is a negative impact in long-term outcomes and mortality.

There is level 1b evidence that intracranial pressure/cerebral perfusion pressure and brain tissue oxygen managed hypothermia are similar at reducing intracranial pressure in individuals with an ABI when compared to controls.

There is level 2 evidence that selective hypothermia may be superior to systemic hypothermia in improving intracranial pressure post ABI.

There is level 2 evidence that systemic hypothermia improves favourable outcomes (Glasgow Outcome Scale score >4) and reduces mortality compared to conventional treatment post ABI.

There is level 2 evidence that very mild hypothermia (35-36°C) may more effective than mild hypothermia (32-34°C) at improving neurological outcomes with fewer complications in patients post ABI.

There is level 4 evidence that hypothermia treatment combined with mannitol may be more effective at sustaining improved intracranial pressure, cerebral perfusion pressure, and oxygenations compared to hypothermia alone post ABI.

There is level 1b evidence that hyperventilation plus intravenous tromethamine is superior than hyperventilation alone at improving long-term outcomes in patients post ABI.

There is level 4 evidence that hyperventilation may lower elevated intracranial pressure post TBI.

There is level 4 evidence that brief (40 min) periods of hyperventilation can decrease cerebral blood flow and cerebral oxygen saturation in patients post TBI.

There is level 4 evidence that hyperoxia (PaO₂=200-250 mmHg) can improve cerebral oxygenation following hyperventilation post ABI.

There is level 2 evidence that conventional physiotherapy alone, or in combination with verticalization may improve Glasgow Coma Scale, Coma Recovery Scale-Revised, Level of Cognitive Functioning, and Disability Rating Scale scores compared to controls in patients post ABI.

There is level 2 evidence that verticalization plus conventional physiotherapy may be superior to conventional physiotherapy alone at improving Coma Recovery Scale-Revised scores in patients post ABI.

There is level 2 evidence that verticalization using the Erigo robot may cause less sympathetic stress in patients with ABI compared to the verticalization using the MOTomed machine, or conventional therapy.

There is level 4 evidence that continuous rotational therapy does not improve intracranial pressure following severe TBI.

There is level 4 evidence that the prone position may increase intracranial pressure but improve cerebral oxygenation post ABI.

There is conflicting (level 4) evidence that prone positioning improves cerebral perfusion and mean arterial pressure in patients post ABI.

There is level 4 evidence that the positions supine with head down 30°; 75% supine; and 75% prone may increase intracranial pressure more than the supine position in patients post ABI.

There is level 4 evidence that non-invasive active intrathoracic pressure regulation for 120 min improves intracranial and cerebral perfusion pressure but has no effect on mean arterial pressure in patients post TBI.

There is level 4 evidence that non-invasive active intrathoracic pressure regulation for 120 min is not associated with any serious adverse effects in patients post TBI.

There is level 4 evidence that propofol may improve intracranial pressure and cerebral perfusion pressure, with no associated adverse outcomes post ABI.

There is level 4 evidence that propofol and vasopressor treatment may increase the risk of developing propofol infusion syndrome post ABI.

There is level 1b evidence that propofol is more effective than morphine at improving favourable outcomes and reducing intracranial pressure post TBI- specially at higher doses.

There is level 2 evidence that propofol is similar to midazolam and morphine with regards to sedation, morbidity, changes in intracranial pressure, cerebral perfusion, and mean arterial pressure post ABI.

There is level 2 evidence that propofol may not differ from dexmedetomidine in its effect on intracranial pressure and cerebral perfusion pressure post ABI.

There is level 1b evidence that midazolam is no different than propofol at improving Glasgow Outcome Scale scores, mortality, or disability in patients post ABI.

There is level 2 evidence that midazolam is not different from propofol in its effect on intracranial pressure or cerebral perfusion pressure post ABI.

There is level 4 evidence that high doses of midazolam are associated with decreases in systolic blood pressure and hypotension following intubation in patients post ABI.

There is level 4 evidence that midazolam has no effect on intracranial pressure but decreases mean arterial pressure and cerebral perfusion pressure post TBI.

There is level 4 evidence that remifentanyl may not improve intracranial pressure, cerebral perfusion pressure, mean arterial pressure, or cerebral blood flow velocity post ABI.

There is level 4 evidence that sufentanil may decrease mean arterial pressure, cerebral perfusion pressure, and heart rate post ABI.

There is level 4 evidence that sufentanil may transiently increase intracranial pressure post ABI.

There is level 4 evidence that sufentanil may increase intracranial pressure in patients with low mean arterial pressure post ABI.

There is conflicting (level 1a and level 2) evidence as to whether fentanyl, morphine, or sufentanil increase intracranial pressure, and decrease cerebral perfusion pressure post ABI. The level 1a evidence suggests that it increases intracranial pressure and decreases cerebral perfusion pressure.

There is level 1b evidence that propofol is more effective than morphine at improving favourable outcomes and reducing intracranial pressure post TBI- specially at higher doses.

There is level 2 evidence that alfentanil may result in a decrease in cerebral perfusion pressure and mean arterial pressure, and a transient increase in intracranial pressure, post ABI compared to controls.

There is level 2 evidence that remifentanyl may not affect intracranial pressure post ABI compared to controls.

There is level 4 evidence that sufentanyl with midazolam decreases intracranial pressure and mean arterial pressure for 2 days post ABI.

There is level 2 evidence that thiopental is more effective than pentobarbital for controlling elevated intracranial pressure refractory to conventional treatment, and less likely to induce adrenal insufficiency post ABI.

There is level 2 evidence that thiopental in combination with mild hypothermia has better one-year clinical outcomes compared to conventional management post ABI.

There is level 3 evidence that thiopental induces leukopenia and granulocytopenia in patients post ABI.

There is level 4 evidence that thiopental decreases intracranial pressure, cerebral perfusion pressure, and mean arterial pressure post ABI.

There is conflicting (level 1b and level 2) evidence regarding whether or not pentobarbital improves intracranial pressure compared to conventional management measures post ABI. Level 1b evidence suggests there is no difference.

There is level 2 evidence that barbiturate use is associated with development of hypotension in patients post ABI.

There is level 2 evidence that pentobarbital decreases energy expenditure, total urinary nitrogen excretion, improves nitrogen balance, but has no effect on 3-methylhistidine excretion compared to controls in individuals with an ABI refractory to standard therapy.

There is conflicting (level 1b) evidence as to whether dexanabinol in cremophor-ethanol solution effectively lowers intracranial pressure, increases cerebral perfusion pressure, and improves long-term clinical outcomes post TBI when compared to placebo.

There is level 1b evidence that high-dose KN38-7271 (a dual cannabinoid agonist) may improve intracranial pressure and cerebral perfusion pressure and improves survival post TBI compared to low-dose KN38-7271.

There is level 1a evidence that progesterone treatment is no better than placebo at improving Glasgow outcome scale scores at 3 and 6 mo post TBI.

There is level 1b evidence that progesterone is superior to placebo at improving Glasgow outcome scale scores in patients with an initial Glasgow coma scale score ≥ 5 post TBI.

There is level 1b evidence that progesterone treatment may be associated with adverse events such as phlebitis and thrombophlebitis.

There is level 1a evidence that progesterone does not improve intracranial pressure compared to placebo post ABI.

There is level 1a evidence that progesterone improves mortality and Glasgow outcome scale scores compared to placebo in patients post ABI.

There is level 1b evidence that Anatiab, regardless of dose, has no effect on serious adverse events, mortality, Glasgow Coma Scale, Modified Oxford Handicap Scale, or Disability Rating Scale scores in individuals post ABI.

There is level 2 evidence that high-dose anatiab is superior to low-dose anatiab and placebo at improving Glasgow outcome scale scores at 3 and 6 mos post TBI.

There is level 1a evidence that Bradycor is effective at preventing acute elevations intracranial pressure and reducing therapeutic intensity levels post ABI when compared to placebo.

There is conflicting (level 1b) evidence that Bradycor improves mortality and Glasgow outcome scale scores in patients post ABI.

There is level 4 evidence that dimethyl sulfoxide temporarily reduces intracranial pressure elevations and increases cerebral perfusion pressure post ABI.

There is level 4 evidence that increasing concentrations of DMSO provide longer intracranial pressure reduction but are accompanied by an increase in electrolyte imbalances post ABI.

There is conflicting (level 1b) evidence that methylprednisolone increases mortality rates compared to placebo in individuals post ABI. The largest trial strongly recommends against its use due to increased mortality.

There is level 1b evidence that high (60 mg loading dose, 24 mg every 6 hr) and low (10 mg loading dose, 4 mg every 6 hr) dose dexamethasone are the same as placebo at improving intracranial pressure, and neurological outcomes (6 mo) post TBI.

There is conflicting (level 2) evidence that dexamethasone increases mortality and the rate of complications (hyperglycemia, cerebral spinal fluid infections) when compared to placebo post ABI.

There is level 1b evidence that triamcinolone may improve outcomes compared to placebo in individuals post ABI with a Glasgow Coma Scale score less than 8 and a focal lesion.

There is level 2 evidence that glucocorticoid administration on the first day post-injury may increase the risk of developing first late seizures compared to placebo.

There is level 4 evidence that methylprednisolone improves mortality rates in patients with acute respiratory distress syndrome secondary to sepsis post ABI.

There is level 1b evidence that conivaptan is superior to standard care (e.g. osmolar therapy, sedation, analgesia) in lowering elevated intracranial pressure post ABI.

There is level 1b evidence that vasopressin and catecholamine treatment are likely similar in lowering elevated intracranial pressure, improving hospital length of stay and mortality post ABI.

There is level 4 evidence that paracetamol may lower elevated intracranial pressure, cerebral perfusion pressure, mean arterial pressure, and core body temperature post ABI.

There is level 3 evidence that hypertonic saline lowers elevated intracranial pressure post ABI.

There is level 3 evidence that hypertonic saline causes an increase in serum sodium, days spent in the ICU, but not mortality in patients post ABI

There is level 4 evidence that hypertonic saline lowers elevated intracranial pressure up to 12 hours post ABI.

There is level 4 evidence that hypertonic saline increases cerebral perfusion pressure and cerebral blood flow post ABI.

There is level 4 evidence that 3 days post TBI contused brain tissue increases in volume after administration of hypertonic saline.

There is level 1a evidence that hypertonic saline is similar to mannitol in terms of mortality or Glasgow outcome scale (extended) scores in patients post TBI.

There is conflicting (level 1b) evidence as to whether hypertonic solution lowers elevated intracranial pressure more effectively than mannitol post ABI.

There is level 1b evidence that the use of hypertonic solution results in similar intracranial pressure control and clinical outcomes (cognition, mortality, functional independence, return to work) when compared to Ringer's lactate solution post ABI.

There is level 1b evidence that sodium bicarbonate is the same as hypertonic saline at lowering intracranial pressure; however, it sustains this improvement longer in patients post ABI.

There is conflicting (level 2 and level 3) evidence that hypertonic saline lowers intracranial pressure for longer compared to mannitol post ABI. The level 2 evidence suggest that it does.

There is level 2 evidence that hypertonic saline is superior to mannitol at improving cerebral perfusion pressure, cerebral blood flow, and blood-glucose control in patients post ABI.

There is level 2 evidence that urinary sodium excretion is higher in hypertonic saline patients compared to those receiving mannitol post ABI.

There is level 4 evidence that hypertonic saline is superior to barbiturates, propofol, and fentanyl at lowering intracranial pressure post ABI.

There is level 4 evidence that mannitol may be effective in controlling elevated intracranial pressure post ABI.

There is level 4 evidence that mannitol may be effective in increasing cerebral perfusion pressure post ABI.

There is level 4 evidence that mannitol may only improve intracranial pressure and cerebral perfusion pressure post ABI in hypertensive patients (Intracranial pressure > 20 mmHg).

There is level 1a evidence that hypertonic saline is similar to mannitol in terms of mortality or Glasgow outcome scale (extended) scores in patients post TBI.

There is conflicting (level 1b) evidence as to whether hypertonic solution lowers elevated intracranial pressure more effectively than mannitol post ABI.

There is level 1a evidence that mannitol effectively reduces elevated intracranial pressure in patients post TBI.

There is level 1b evidence that mannitol is no more effective than hypertonic saline in improving intracranial pressure or cerebral perfusion pressure in individuals with an ABI.

There is level 1b evidence that mannitol is less effective than Ringer's (sodium) lactate in controlling elevated intracranial pressure post ABI.

There is level 2 evidence that early versus late administration of mannitol is the same at lowering elevated intracranial pressure in individuals with an ABI.

There is level 2 evidence that higher doses of mannitol (1.4 g/kg) are more effective than lower doses (0.7 g/kg) at reducing intracranial pressure in patients post TBI.

There is level 4 evidence that enteral urea may lower elevated intracranial pressure in patients with ABI and syndrome of inappropriate antidiuretic hormone secretion.

There is level 2 evidence that platelet transfusion in patients concurrently on anti-platelet therapy improves platelet dysfunction but has no effect on morbidity or mortality post ABI.

There is level 3 evidence that thawed plasma may be superior to packed red blood cells at improving neurological function and disability at both discharge and follow up in patients with multiple injuries post TBI.

There is level 1b evidence that ventricular cerebrospinal fluid drainage, regardless of amount drained, effectively lowers elevated intracranial pressure, and increases cerebral perfusion pressure post ABI.

There is level 3 evidence that continuous cerebrospinal fluid drainage is superior to intermittent cerebrospinal fluid drainage at lowering intracranial pressure, but the same at improving long-term outcomes and therapeutic intensity post ABI.

There is level 4 evidence that ventricular cerebrospinal fluid drainage lowers elevated intracranial pressure post ABI.

There is conflicting (level 4) evidence that ventricular cerebrospinal fluid drainage lowers elevated intracranial pressure for prolonged periods (24 hours) post ABI.

There is level 4 evidence that ventricular cerebrospinal fluid drainage increases cerebral perfusion pressure and cerebral blood flow post ABI.

There is level 4 evidence that lumbar cerebrospinal fluid drainage lowers elevated intracranial pressure post ABI.

There is level 4 evidence that continuous cerebrospinal fluid extractions through an external lumbar device lowers intracranial pressure in patient's refractory to standard intracranial pressure treatment.

There is level 1a evidence that a decompressive craniectomy is more effective than standard care at reducing elevated intracranial pressure, while producing poorer outcomes (Glasgow outcome scale extended scores < 4) post ABI.

There is conflicting (level 1b) evidence that a decompressive craniectomy is superior at improving mortality compared to standard care in patients post ABI.

There is level 1b evidence that a decompressive craniectomy with a unilateral frontotemporoparietal bone flap (12x15 cm) may be superior to a limited decompressive craniectomy with a temporoparietal bone flap (6x8 cm) in lowering intracranial pressure and improving Glasgow Outcome Scale scores post ABI.

There is level 2 evidence that a decompressive craniectomy is just as effective as a controlled decompression at reducing intracranial pressure and improving Glasgow outcome scale scores in patients post ABI.

There is level 2 evidence that the surface area of the bone flap removed in a decompressive craniectomy does not affect intracranial pressure or Glasgow coma scale scores post TBI.

There is level 3 evidence that decompressive craniectomy and craniotomy interventions are similar at decreasing intracranial pressure post ABI.

There is conflicting (level 3) evidence as to whether decompressive craniectomies have better mortality outcomes compared than a craniotomy post ABI.

There is level 4 evidence that patient's initial GCS score is correlated with favourable outcomes post decompressive craniectomy.

There is conflicting (level 3 and level 4) evidence as to the effect of a decompressive craniectomy on mortality and long-term outcomes. There is level 3 evidence that an earlier intervention is associated with positive long-term outcomes.

There is conflicting (level 4) evidence whether or not a decompressive craniectomy effectively reduces elevated intracranial pressure post ABI compared to no treatment.

There is conflicting (level 4) evidence regarding whether or not a decompressive craniectomy effectively improves cerebral perfusion pressure post ABI.

There is level 4 evidence that younger age, higher Glasgow coma scale score and larger decompressive craniectomy are associated with improved long-term outcomes in patients receiving decompressive craniectomies post ABI.

There is level 2 evidence that a decompressive craniectomy with expansile duraplasty is not different than a decompressive craniectomy with dural-slits with respect to mortality or Glasgow Outcome Scale scores in patients post acute subdural hematoma.

There is level 3 evidence that a larger decompressive craniectomy may be associated with positive long-term outcomes compared to routine care in patients post ABI.

There is conflicting (level 3) evidence as to whether decompressive craniectomy is superior to craniotomy at improving mortality, long-term outcomes, and hospital length of stay in patients post ABI.

There is level 3 evidence that an intracranial hemorrhage evacuation with a decompressive craniectomy may increase the need for additional treatment but is not different in terms of mortality and neurological outcomes than an intracranial hemorrhage evacuation with a craniotomy post ABI.

There is level 3 evidence that a hematoma evacuation may be superior to a hematoma evacuation combined with decompressive craniectomy at producing favourable outcomes in patients post ABI.

There is conflicting (level 3) evidence as to whether a decompressive craniectomy is associated with higher Glasgow Outcome Scale scores and lower mortality than standard care post ABI.

There is level 4 evidence that a decompressive craniectomy may be associated with increased mortality, low recovery rates, and expansion of hemorrhagic contusions in patients post ABI.

There is level 4 evidence that younger age, higher initial Glasgow Coma Scale score, and earlier decompressive craniectomy may be associated with positive long-term outcomes in patients post ABI.

There is level 4 evidence that trepanation in patients with thick subdural intracranial hemorrhages may increase mortality post ABI.

These is level 4 evidence that the use of synthetic skin substitution in patients where skin closure is not possible post decompressive craniectomy is associated with high rates of infections and mortality post TBI.

There is level 1a evidence that multisensory stimulation may be more effective than standard care at improving consciousness and cognitive function post ABI.

There is level 1b evidence that familiar auditory stimulation may be more effective than standard care at improving consciousness post ABI.

There is level 1b evidence that multisensory stimulation delivered five times per day may be more effective at improving consciousness and cognitive function post ABI than stimulation delivered twice a day.

There is level 1b evidence that multisensory stimulation delivered by a family member may be more effective at improving consciousness and cognitive function post ABI when compared to stimulation delivered by a nurse.

There is level 2 evidence that specific, directed, and regulated sensory stimulation may be more effective at improving consciousness and cognitive function post ABI than indiscriminate stimulation.

There is level 2 evidence that multimodal stimulation may be superior to standard care at reducing coma duration post ABI.

There is level 4 evidence that multimodal stimulation is superior to unimodal stimulation at increasing behaviours corresponding with arousal post ABI.

There is level 2 evidence that structured auditory sensory stimulation improves Sensory Stimulation Assessment Measure and Disability Rating Scale, but not Glasgow Outcome Scale scores compared to controls in individuals in a coma post ABI.

There is conflicting (level 2 and level 4) evidence that multi-sensory stimulation may reduce heart rate in patients in a coma post ABI. The level 2 evidence suggests there is no increase in heart rate of physical signs of patient arousal, but only biochemical ones.

There is level 3 evidence that multi-sensory stimulation has no effect on emergence from coma, Glasgow Outcome Scale scores, or recovery post ABI compared to controls.

There is level 4 evidence that the use of biographically meaningful objects for sensory stimulation post ABI transiently improves motor behaviours.

There is level 2 evidence that musical therapy is superior to silence at improving consciousness and brain activity in individuals in a coma 1 mo post ABI.

There is conflicting (level 1b and level 2) evidence that compared to a sham treatment, median nerve electrical stimulation improves consciousness and arousal post ABI. The level 1b evidence suggests there is no difference, and no improvement.

There is level 2 evidence that compared to standard care, median nerve electrical stimulation is no different at 2 weeks but is superior at 6 mo in terms of improving consciousness and function post ABI.

There is level 4 evidence that median nerve electrical stimulation may increase cerebral perfusion pressure and dopamine levels in individuals in a coma post ABI.

There is level 2 evidence that individually tailored physical therapy sessions in the acute phase post ABI improves motor and cognitive function.

There is level 1a evidence that amantadine effectively improves consciousness, cognitive function, and disability when compared to placebo post ABI.

There is level 3 evidence that amantadine treatment does not improve emergence from coma compared to control in patients post ABI.

There is level 3 evidence that amantadine is superior to standard care at improving consciousness in patients in a coma post ABI.

There is level 2 evidence that citicoline or antiepileptics are not effective at restoring consciousness post ABI compared to controls.

There is level 1b evidence that hypertonic saline and dextran infusion is the same as normal saline alone at improving morbidity and mortality outcomes.

There is level 1b evidence that elevated serum brain injury markers are associated with unfavourable outcomes post TBI.

There is level 1b evidence that mannitol may increase urine output, lowers serum sodium, transiently decreases systolic blood pressure, but may have the same effect on mortality compared to hypertonic solution post ABI.

There is level 1b evidence that albumin may increase mortality, specifically in individuals with an ABI and a Glasgow Coma Scale score less than 9, compared to hypertonic solution.

There is level 1b evidence that albumin may not differ from hypertonic solution for improving Glasgow Outcome Scale Extended scores in patients post ABI.

There is level 3 evidence that hypertonic solution may increase hospital length of stay and rates of infections compared to controls post ABI.

There is level 3 evidence that compared to a control group, administration of a hypertonic solution may increase the risk of pulmonary infections in individuals with an ABI and a Glasgow Coma Scale score <8.

There is level 1b evidence that recombinant erythropoietin administration may improve neurological outcomes and transiently decreases markers of brain cell destruction compared to saline post ABI.

There is level 1b evidence that recombinant erythropoietin administration may decrease mortality compared to saline, especially in patients who have undergone an operation previously, post ABI.

There is level 1b evidence that tranexamic acid in combination with standard care is superior to standard care alone at reducing intracranial hemorrhage growth in patients post TBI.

There is level 1b evidence that selenium in addition to standard care is not different than standard care alone at improving morbidity and neurological outcomes in patients post TBI.

There is level 3 evidence that statin use prior to injury does not improve mortality or neurological outcomes compared to no prior statin use in patients post TBI.

There is level 3 evidence that early propranolol intervention decreases mortality, increases time spent on a ventilator, but has no effect on hospital length of stay compared to controls in patients post TBI.

There is level 4 evidence that dexmedetomidine decreases blood pressure and heart rate, increases Glasgow Coma Scale and Richmond Agitation-Sedation Scale scores, and reduces the need for opioid administration in patients post TBI.

There is level 4 evidence that diclofenac sodium decreases core body temperature, blood pressure, heart rate, and cerebral perfusion pressure in patients post TBI.

There is level 3 evidence that individuals with an ABI receiving a tracheostomy may have improved mortality compared to individuals not receiving a tracheostomy.

There is level 2 evidence that guideline adherence rates below 60% are associated with an increase in mortality rates in patients post TBI.

There is level 2 evidence that when compared to no monitor placement, intracranial pressure monitor placement improves mortality in-hospital, but not at any other time in patients post TBI.

These is level 2 evidence that there is no difference in Glasgow outcome scale scores between patients treated with an intracranial pressure monitor and patients treated without one post TBI.

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