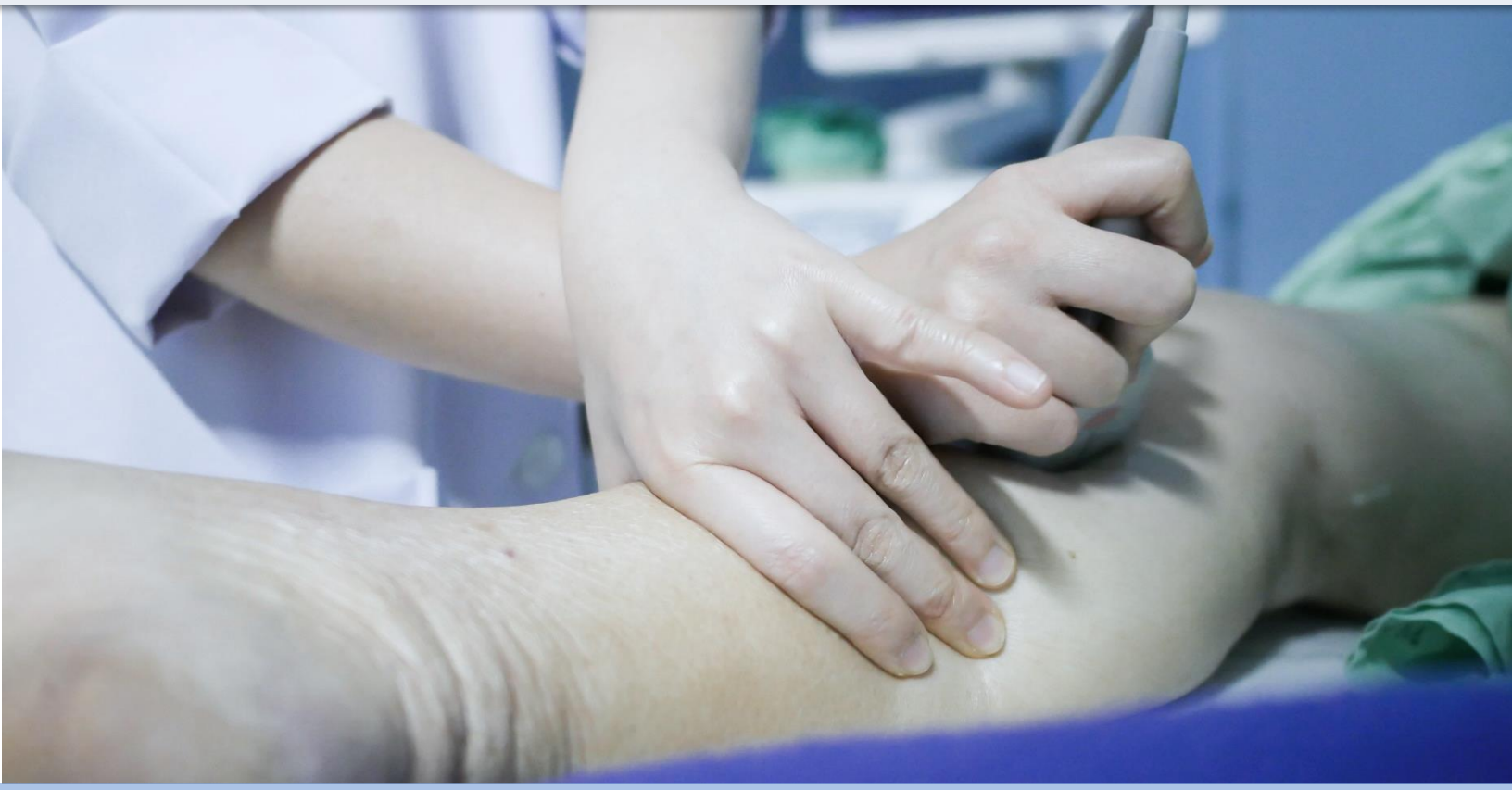
ERABI EVIDENCE-BASED REVIEW of moderate to severe ACQUIRED BRAIN INJURY



VENOUS THROMBOEMBOLISM

POST ACQUIRED BRAN INJURY

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Disclaimer

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Conflict of Interest

In the context of ERABI development, the term "conflict of interest" (COI) refers to situations in which an author or ERABI staff member's financial, professional, intellectual, personal, organizational or other relationships may compromise their ability to independently conduct this evidence-based review. No limiting conflicts were identified.

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Greetings from Dr. Robert Teasell,

Professor and Chair-Chief of Physical Medicine and Rehabilitation

The Collaboration of Rehabilitation Research Evidence (CORRE) team is delighted to present the Evidence-Based Review of Moderate to Severe Acquired Brain Injury (ERABI) *Venous Thromboembolism post Acquired Brain Injury.* Through the collaboration of researchers and clinicians and supported by the Ontario Neurotrauma Foundation/Ontario Ministry of Health, ERABI provides an up-to-date review of the current evidence in brain injury rehabilitation. ERABI synthesizes the research literature into a utilizable format, laying the foundation for effective knowledge transfer to improve healthcare programs and services.

We offer our heartfelt thanks to the many stakeholders who are able to make our vision a reality. Firstly, we would like to thank the Ontario Neurotrauma Foundation, which recognizes ERABI's capacity to lead in the field of brain injury evidence-based reviews and has been committed to funding it. We would also like to thank the co-chairs of ERABI, Dr. Mark Bayley (University of Toronto), Dr. Shawn Marshall (University of Ottawa) and Dr. Nora Cullen (McMaster University) for their invaluable expertise and stewardship of this review. Special thanks to the authors for generously providing their time, knowledge and perspectives to deliver a rigorous and robust review that will guide research, education and practice for a variety of healthcare professionals. We couldn't have done it without you! Together, we are building a culture of evidence-based practice that benefits everyone.

We invite you to share this evidence-based review with your colleagues, patient advisors that are partnering within organizations, and with the government agencies with which you work. We have much to learn from one another. Together, we must ensure that patients with brain injuries receive the best possible care every time they require rehabilitative care – making them the real winners of this great effort!

Robert Teasell, MD FRCPC

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PREFACE

About the Authors

ERABI is internationally recognized and led by a team of clinicians and researchers with the goal of improving patient outcomes through research evidence. Each ERABI module is developed through the collaboration of many healthcare professionals and researchers.

Shannon Janzen, MSc, is a research associate and the project coordinator for the Evidence-Based Review of Acquired Brain Injury (ERABI). Her research interests focus on the integration of best evidence into clinical practice to optimize patient outcomes, with an emphasis on knowledge translation initiatives.

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Dr. Shawn Marshall is a physician specializing in Physical Medicine and Rehabilitation (Physiatrist). He is the Division Head of Physical Medicine and Rehabilitation at the University of Ottawa and The Ottawa Hospital where he manages both in-patients and out-patient clinics for patients with concussion to severe traumatic brain injury. Dr. Marshall has a Master's degree in Clinical Epidemiology and is a Full Professor at the University of Ottawa in the Department of Medicine.

Dr. Robert Teasell is Professor of Physical Medicine and Rehabilitation, Schulich School of Medicine and Dentistry, Western University and a Clinical Researcher at Lawson Research Institute in London, Ontario. He is a clinician at Parkwood Institute, St. Joseph's Health Care London.

Purpose

The Evidence-Based Review of Acquired Brain Injury (ERABI) is a systematic review of the rehabilitation literature of moderate to severe acquired brain injuries (ABI). It is an annually updated, freely accessible online resource that provides level of evidence statements regarding the strength of various rehabilitation interventions based on research studies. The ERABI is a collaboration of researchers in London, Toronto and Ottawa. Our mission is to improve outcomes and efficiencies of the rehabilitation system through research synthesis, as well as from providing the foundational research evidence for guideline development, knowledge translation, and education initiatives to maximize the real-world applications of rehabilitation research evidence.

Key Concepts

Acquired Brain Injury

For the purposes of this evidence-based review, we used the definition of ABI employed by the Toronto Acquired Brain Injury Network (2005). ABI is defined as damage to the brain that occurs after birth and is not related to congenital disorders, developmental disabilities, or processes that progressively damage the brain. ABI is an umbrella term that encompasses traumatic and non-traumatic etiologies (Table 1).

Table 1 | Defining Acquired Brain Injury

Included in ABI definition	Excluded from ABI definition
Traumatic Causes • Motor vehicle accidents • Falls • Assaults • Gunshot wounds • Sport Injuries **Non-traumatic Causes** • Tumours (benign/meningioma only) • Anoxia • Subarachnoid hemorrhage (non-focal) • Meningitis • Encephalitis/encephalopathy (viral, bacterial, drug, hepatic) • Subdural Hematoma	**Vascular and Pathological Incidents** • Intracerebral hemorrhage (focal) • Cerebrovascular accident (i.e., stroke) • Vascular accidents • Malignant/metastatic tumours **Congenital and Developmental Problems** • Cerebral Palsy • Autism • Developmental delay • Down's syndrome • Spina bifida with hydrocephalus **Progressive Processes** • Alzheimer's disease • Pick's disease • Dementia • Amytrophic Lateral Sclerosis • Multiple Sclerosis • Parkinson's disease • Huntington's disease

Given that 'ABI' can have multiple definitions, studies with an 'ABI' population can be equally heterogeneous in terms of the sample composition. Such studies may include any combination of persons with TBI, diffuse cerebrovascular events (i.e., subarachnoid hemorrhage) or diffuse infectious disorders (i.e., encephalitis or meningitis). The vast majority of individuals with ABI have a traumatic etiology; therefore, much of the brain injury literature is specific to TBI. The terms ABI and TBI have been used intentionally throughout ERABI to provide more information about populations where relevant.

Moderate to Severe Injury

ABI severity is usually classified according to the level of altered consciousness experienced by the patient following injury (Table 2). The use of level of consciousness as a measurement arose because the primary outcome to understand the severity of an injury is the Glasgow Coma Scale. Consciousness levels following ABI can range from transient disorientation to deep coma. Patients are classified as having a mild, moderate or severe ABI according to their level of consciousness at the time of initial assessment. Various measures of altered consciousness are used in practice to determine injury severity. Common measures include the Glasgow Coma Scale (GCS), the duration of loss of consciousness (LOC), and the duration of post-traumatic amnesia (PTA).

Table 2 | Defining Severity of Traumatic Brain Injury, adapted from Veterans Affairs Taskforce (2008) and Campbell (2000)

Criteria	Mild	Moderate	Severe	Very Severe
Initial GCS	13-15	9-12	3-8	Not defined

Duration LOC	< 15minutes*	<6 hours	6-48 hours	>48 hours
Duration PTA	< 1hour*	1-24 hours	1-7 days	>7 days
	*This is the upper limit for mild traumatic brain injury; the lower limit is any alteration in mental status (dazed, confused, etc.).			

Methods

An extensive literature search using multiple databases (CINAHL, PubMed/MEDLINE, Scopus, EMBASE, and PsycINFO) was conducted for articles published in the English language between 1980–March 2020 that evaluate the effectiveness of any intervention/treatment related to ABI. The references from key review articles, meta-analyses, and systematic reviews were reviewed to ensure no articles had been overlooked. For certain modules that lacked research evidence the gray literature, as well as additional databases, were searched in order to ensure the topic was covered as comprehensively as possible.

Specific subject headings related to ABI were used as the search terms for each database. The search was broadened by using each specific database's subject headings, this allowed for all other terms in the database's subject heading hierarchy related to ABI to also be included. The consistent search terms used were "head injur*", "brain injur*", and "traumatic brain injur*". Additional keywords were used specific to each module. A medical staff librarian was consulted to ensure the searches were as comprehensive as possible.

Every effort was made to identify all relevant articles that evaluated rehabilitation interventions/ treatments, with no restrictions as to the stage of recovery or the outcome assessed. For each module, the individual database searches were pooled, and all duplicate references were removed. Each article title/abstract was then reviewed; titles that appeared to involve ABI and a treatment/intervention were selected. The remaining articles were reviewed in full.

Studies meeting the following criteria were included: (1) published in the English language, (2) at least 50% of the population included participants with ABI (as defined in Table 1.3) or the study independently reported on a subset of participants with ABI, (3) at least three participants, (4) ≥50% participants had a moderate to severe brain injury, and (5) involved the evaluation of a treatment/intervention with a measurable outcome. Both prospective and retrospective studies were considered. Articles that did not meet our definition of ABI were excluded.

Interpretation of the Evidence

The levels of evidence (Table 3) used to summarize the findings are based on the levels of evidence developed by Sackett et al. (2000). The levels proposed by Sackett et al. (2000) have been modified; specifically, the original ten categories have been reduced to five levels. Level 1 evidence pertains to high

quality RCTs (PEDro ≥6) and has been divided into two subcategories, level 1a and level 1b, based on whether there was one, or more than one, RCT supporting the evidence statement.

The evidence statements made in evidence-based reviews are based on the treatment of groups rather than individuals. There are times when the evidence will not apply to a specific case; however, the majority of patients should be managed according to the evidence. Ultimately, the healthcare professional providing care should determine whether an intervention is appropriate, and the intensity in which it should be provided, based on their assessment of the patient. Furthermore, readers are asked to interpret the findings of studies with caution as evidence can be misinterpreted. The most common scenario occurs when results of a trial are generalized to a wider group than the evidence allows. Evidence is a tool, and as such, the interpretation and implementation of it must always be done with these limitations in mind.

Table 3 | Levels of Evidence

Level	Research Design	Description
1A	Randomized Controlled Trial (RCT)	More than one RCT with PEDro score ≥6. Includes within subject comparisons, with randomized conditions and crossover designs
1B	RCT	One RCT with PEDro ≥6
2	RCT	One RCT with PEDro <6
	PCT	Prospective controlled trial (not randomized)
	Cohort	Prospective longitudinal study using at least two similar groups with one exposed to a particular condition
3	Case Control	A retrospective study comparing conditions including historical controls
4	Pre-Post test	A prospective trial with a baseline measure, intervention, and a post-test using a single group of subjects
	Post-test	A prospective intervention study using a post intervention measure only (no pre-test or baseline measurement) with one or more groups
	Case Series	A retrospective study usually collecting variables from a chart review
5	Observational study	Using cross sectional analysis to interpret relations
	Clinical Consensus	Expert opinion without explicit critical appraisal, or based on physiology, biomechanics or “first principles”
	Case Reports	Pre-post or case series involving one subject

Strength of the Evidence

The methodological quality of each randomized controlled trial (RCT) was assessed using the Physiotherapy Evidence Database (PEDro) rating scale developed by the Centre for Evidence-Based Physiotherapy in Australia (Moseley et al., 2002). The PEDro is an 11-item scale; a point is awarded for ten satisfied criterion yielding a score out of ten. The first criterion relates to external validity, with the remaining ten items relating to the internal validity of the clinical trial. The first criterion, eligibility criteria, is not included in the final score. A higher score is representative of a study with higher methodological quality.

VENOUS THROMBOEMBOLISM

POST ACQUIRED BRAIN INJURY

Summary of the Evidence

Intervention	Key Point Level of Evidence
Non-Pharmacological Interventions	
Mechanical Interventions	Intermittent pneumatic compression devices and low molecular weight heparin may have a similar effect in terms of the prevention of deep vein thrombosis post ABI when compared to each other. - *There is conflicting level 2 evidence (from one cohort study; Praeger et al., 2012; and one prospective controlled trial; Kurtoglu et al., 2004) and level 4 evidence (from one case series; Minshall et al., 2011) regarding the effectiveness of intermittent pneumatic compression devices compared to low-molecular-weight heparin or unfractionated heparin for the prophylaxis of DVT and PE.* Intermittent compression devices may not aggravate intracranial hemodynamics in patients with severe ABI. - *There is level 4 evidence (from one pre-post test; Davidson et al., 1993) that intermittent compression devices do not cause acute elevations in intracranial pressure in patients with severe ABI.* When compared to VTE chemoprophylaxis., prophylactic inferior vena cava filters may worsen outcomes. - *There is level 2 evidence (from one retrospective cohort study; Elkbulki et al., 2020a) that prophylactic inferior vena cava filters are associated with higher rates of DVT, nonfatal PE and longer hospital stays when compared to VTE chemoprophylaxis following severe TBI.* Early placement of inferior vena cava filters (within 48 hours) may shorten hospital length of stay. - *There is level 2 evidence (from one retrospective cohort study; Elkbuli et al., 2020) that IVC filter placement within 48hrs of admission significantly improves ICU and hospital length of stay in adult trauma patients.*
Pharmacological Interventions	
Thromboembolic Prophylaxis	Administration of pharmacological thromboembolic prophylaxis within the first 72 hours post ABI may be effective for reducing the risk of developing venous thromboembolism. - *There is level 3 evidence that prophylactic anticoagulation is more effective than placebo in reducing the risk of developing deep vein thrombosis in patients post ABI.* Enoxaparin is effective for the prevention of venous thromboembolism development after elective neurosurgery and has not been found to cause excessive bleeding.

- *There is level 2 evidence that the administration of enoxaparin within the first 72 hours post ABI reduces the risk of developing deep vein thrombosis and pulmonary embolism post injury compared to unfractionated heparin.*

Introduction

Venous thromboembolism (VTE) is a blood clot that forms within a vein. The most common place for a blood clot to form is a deep vein, which is called a deep venous thrombosis or DVT. If the clot breaks off and travels to the lungs, causing partial or full occlusion, it is called a pulmonary embolism (PE) (Office of the Surgeon et al., 2008). Together, DVT and PE are referred to as VTE. VTE remains a common complication in patients who have sustained an ABI (Raslan et al., 2010; Scudday et al., 2011); however the scientific literature specific to ABI is quite limited. The following section presents ABI specific research regarding the prevention and treatment of VTE. Additional information on clinical presentation and testing practices is presented, however, it should be noted that not all in-text citations refer to research that meets the specific ERABI ABI inclusion criteria (mixed populations, age, mixed ABI severity, etc.) and therefore should be interpreted with caution when considering the application of any tests or indicators of VTE to an ABI population.

Incidence of Venous Thromboembolism Post Head Injury

In a large sample study consisting of 38,984 individuals with TBI, the incidence of VTE at the time of admission was 1.31% (Olufajo et al., 2016). At one-month post injury, the incidence for VTE increased to 1.87% and by one year it was 2.83% (Olufajo et al., 2016). The reported incidence of DVT among patients with TBI ranges from 11% to 54% (Carlile et al., 2010; Cifu et al., 1996; Denson et al., 2007; Geerts et al., 1994). The risk of developing a DVT or PE, in the absence of prophylaxis, is estimated to be approximately 20% post TBI (Haddad & Arabi, 2012). Severity of injury is found to be associated with incidence of VTE in isolated patients with TBI (Van Gent et al., 2014). Decisions on how to treat, and when, are often made on a case-by-case basis (Tang & Lobel, 2009). Experts recommend beginning pharmacological prophylaxis as early as 48 to 72 hours post injury (INESSS-ONF, 2017; Norwood et al., 2001). Unless contraindicated, mechanical thromboprophlaxis and low-molecular-weight heparin (LMWH) are recommened in the acute phase of recovery (Haddad & Arabi, 2012).

Risk Factors for Venous Thromboembolism

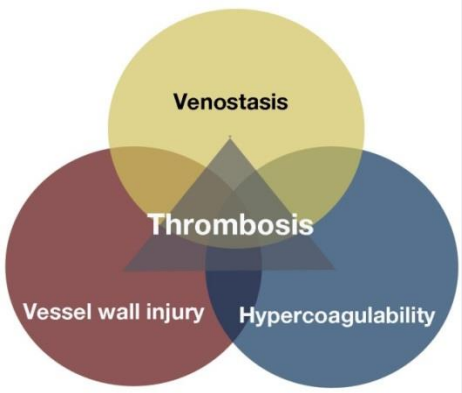

Figure 1 | Virchow's Triad

The most recognized risk factors for VTE are venostasis, intimal damage of the vessel wall, and a hypercoagulable state (Virchow's triad - see Figure 1) (Watanabe & Sant, 2001). Patients with a severe brain injury are commonly immobilized for periods of time as a result of extremity or spine fractures, they experienced at the time of their injury (Vergouwen et al., 2008). The incidence of DVT appears to be impacted by length of stay in the intensive care unit and the number of days a patient is on a ventilator. There does not appear to be a correlation between VTE incidence and initial Glasgow Coma Scale (GCS) scores, Injury Severity Scale scores, or the Abbreviated Injury Scale score (Denson et al., 2007). Those at highest risk post injury are those who remain on a ventilator longer than 3 days (Olufajo et al., 2016; Raslan et al., 2010). At 1-year post injury, risk of VTE is greatest for those discharged to extended care facilities compared to home, and for individuals who undergo an operation (Olufajo et al., 2016). Patients involved in trauma that does not specifically involve vessel injury are still at increased risk of thromboembolism, suggesting a trauma-induced hypercoagulable state (Geerts et al., 1994; Geerts et al., 1996). Therefore, persons who have sustained a TBI appear to be at increased risk of developing VTE for multiple reasons.

Clinical Presentation of Deep Vein Thrombosis and Pulmonary Embolism

A study found that up to 91% of thrombi form below the iliac level (De Maeseneer et al., 2016). The most common symptoms reported when a DVT is present are pain, swelling of the legs, and discoloration of the region (Collins, 2009). The clinical presentation of PE is challenging. Many cases are clinically silent (66%) with only 30% having the clinical features of a DVT (Garcia-Fuster et al., 2014). Asymptomatic PE is discovered in 70% of patients with confirmed clinically symptomatic DVT (Browse, 1974; Corrigan et al., 1974; Hull & Hirsh, 1983). Clinically, PE presents with tachycardia, tachypnea, hemoptysis, pleuritic chest pain and fever. Radiographic findings might include signs of consolidation or pleural effusion (Worku et al., 2014). Massive PE may cause right heart failure, which can progress to cardiovascular collapse, coma, and death.

Diagnostic Testing for Deep Vein Thrombosis

A positive diagnosis of DVT can only be made if a venogram is positive or there is a positive venous ultrasound at two or more sites of the proximal veins. The diagnosis of DVT can be ruled out if there is a

negative venogram, a negative D-dimer test or a normal venous ultrasound in patients with low clinical suspicion of DVT (Carlile et al., 2006).

Venous Ultrasound

Venous ultrasound is often used to diagnose a DVT. There are several types of venous ultrasonography. They include compression ultrasound, duplex ultrasound, and color Doppler imaging. Although these types of venous ultrasonography are sometimes used interchangeably, their sensitivities and specificities for detecting acute DVT vary (Zierler, 2004). The sensitivity and specificity of compression ultrasonography for detecting DVTs is 43% and 85%, respectively (Girard et al., 2005). The weighted mean sensitivity and specificity of venous ultrasonography for the diagnosis of symptomatic proximal DVT are 97% and 94%, respectively; the sensitivity falls to 73% for distal DVT (Kearon et al., 1998; Zierler, 2004). Importantly, distal DVTs do not confer the same risk of extension to PE as do proximal DVTs. Typically, if a distal clot is going to extend proximally, this occurs within one week of its development. Consequently, serial ultrasound could be used in symptomatic patients in whom the test is initially negative as the test would become positive with the clot extension.

Venography

Venography is considered a definitive test for DVT but it is an older, invasive test whereby contrast dye is injected into the leg veins. Diagnosis of DVT is made if an intraluminal-filling defect is noted.

D-Dimer Assay

D-dimer assay is a rapid, non-invasive, and inexpensive test. Fibrin is the main component of thrombus formation and fibrin degradation products include D-dimers (Gill & Nahum, 2000). A positive D-dimer test is highly sensitive for the presence of a thrombus but lacks specificity since D-dimers are found in other disease states, including cancer, congestive heart failure, and inflammatory conditions (Raimondi et al., 1993). As a result, D-dimer assays have a high negative predictive value but a poor positive predictive value. To illustrate, Akman et al. (2004) reported that the sensitivity and negative predictive values of the D-dimer test were high, at 95.2% and 96.2% respectively, in a group of 68 rehabilitation patients (stroke, spinal cord injury, TBI, hip arthroplasty). The specificity and positive predictive values were low at 55.3% and 48.7%, respectively.

Diagnostic Testing for Pulmonary Embolism

The diagnostic work-up for a suspected PE is a step-wise decision algorithm consisting of clinical likelihood and D-dimer testing (Di Nisio et al., 2016; Moore et al., 2018). Patients with low clinical suspicion of PE have D-dimer testing. If the D-dimer is negative, PE is ruled out in patients with low clinical suspicion of PE; if positive, patients move to imaging for PE. Patients with high clinical suspicion of PE do not have D-dimer testing and move straight to imaging. Patients with ABI are most often considered high-risk for PE. Computed Tomography Pulmonary Angiogram (CTPA) is the preferred imaging modality for diagnosis of PE (Di Nisio et al., 2016; Moore et al., 2018). Ventilation/Perfusion

Scanning (V/Q Scan) can be used when CTPA is contraindicated. Combining imaging with pre-test clinical decision rules increases the predictive power in the diagnosis of PE.

Ventilation/Perfusion Scanning

Palmowski et al. (2014) reported the sensitivity and specificity of V/Q scanning as 95.8% and 82.6%, respectively, with false negative rates of 4.2% and false positive rates of 17.3%. Hence, a normal scan virtually excludes a PE (high negative predictive value). Identified perfusion defects are non-specific and only represent true PE in about one-third of cases. The probability that a perfusion defect represents a PE increases with the size, shape, and number of defects as well as the presence of a normal ventilation scan.

TABLE 4 | Probability of Pulmonary Embolism Based on Ventilation-Perfusion Scan Results and Clinical Suspicion in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED Investigators) Study

Ventilation-Perfusion Scan Results	Clinical Suspicion of Pulmonary Embolism*		
	Low	Intermediate	High
High Probability	56%	88%	96%
Intermediate Probability	16%	28%	66%
Low Probability	4%	16%	40%
Normal/Near-Normal Probability	2%	6%	0%

*Percentage of patients with pulmonary embolism; adapted from the PIOPED Investigators (Gill & Nahum, 2000; PIOPED Investigators, 1990).

The Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED Investigators) study demonstrated that a low-probability or normal ventilation-perfusion scan with a low clinical suspicion of PE essentially excludes the diagnosis of PE (negative predictive values of 96% and 98% respectively) (Gill & Nahum, 2000; PIOPED Investigators, 1990). When clinical suspicion is high and the scan indicates a high probability of PE, the positive predictive value is 96% (Gill & Nahum, 2000; PIOPED Investigators, 1990), and these patients should be treated. The majority of ventilation perfusion scans have non-diagnostic results, requiring further testing (PIOPED Investigators, 1990). For this reason, in addition to limited availability of V/Q scans, CTPA is the preferred investigation for PE imaging.

Computed Tomography Pulmonary Angiogram

CTPA is the preferred imaging modality for diagnosing PE (Di Nisio et al., 2016; Moore et al., 2018). It has become first line at most centers because it is fast, highly sensitive and specific, and can detect other causes of chest pain such as pneumonia, musculoskeletal injuries or pericardial abnormalities (Di Nisio et al., 2016). Combined with clinical probability rules there is a very high positive predictive value (Gottschalk et al., 2002; Stein et al., 2006). CTPA carries risks associated with radiation exposure, bleeding, adverse reaction to contrast medium, and is contraindicated in renal insufficiency. V/Q scan is used for investigating potential PE when CTPA is contraindicated (Di Nisio et al., 2016).

Venous Thromboembolism Prophylaxis Post ABI

Several interventions have been examined for the prevention of DVT after an ABI, including mechanical therapy, pharmaceuticals, or a combination of both. In a systematic review, Hachem et al. (2018) found rates of VTE in patients with severe TBI not receiving anticoagulation prophylaxis were near 30%, compared to 5-10% of patients with prophylaxis. However, there is no agreement on the administration of these medications in terms of timing, dose, and/or which anticoagulation medication.

Non-Pharmacological Prophylaxis

Non-pharmacological, mechanical interventions used to prevent the development of DVT post ABI include: the insertion of inferior vena cava filters, thromboembolism deterrent stockings, and intermittent pneumatic compression devices including arteriovenous foot pumps and sequential compression devices (SCDs). These devices operate primarily through two distinct mechanisms of action. The first is mechanical, in which the device increases the velocity of venous return to decrease venous stasis, thus reducing the opportunity for clot formation. The second, and perhaps more important mechanism, involves the systemic activation of the fibrinolytic system which, during compression, leads to the breakdown of fibrin clots associated with thromboembolism (Macatangay et al., 2008). The exception is vena cava filters, which operate by another method of mechanical VTE prevention (Watanabe & Sant, 2001). These filters are inserted into the inferior vena cava to prevent the passage of distal emboli into the lungs. Some reports have demonstrated success rates as high as 96% in the prevention of pulmonary emboli (Greenfield & Michna, 1988). However, the use of vena cava filters carries some associated risks. They can become blocked or dislodged which can increase the risk of an embolism. Some have also reportedly increased risks for repeated DVT compared with patients without such devices (Decousus et al., 1998).

TABLE 5 | Mechanical Interventions for the Prevention of Venous Thromboembolism Post ABI

Author, Year Country Study Design Sample Size	Methods	Outcome
Compression Devices		
Praeger et al. (2012) Australia Cohort N=36	**Population:** TBI; Mean Age=40.3yr; Gender: Male=28, Female=8; Mean GCS=8. **Treatment:** Thromboprophylaxis included compression stockings and/or Low-Molecular-Weight Heparin (LMWH). **Outcome Measures:** Rate of DVT and PE assessed with compression ultrasound.	1. The rate of DVT was 6%, PE was 6%, and total VTE was 11%. 2. Among individuals with severe TBI the rates of DVT, PE, and total VTE were 10%, 10% and 19%, respectively.
Minshall et al. (2011) USA Case Series N=386	**Population**: TBI; Gender: Male=293, Female=93. **Intervention:** Chart review of patients receiving LMWH (30 mg, 2x/day; n=158), unfractionated	1. Mortality in the sequential compression devices alone group was higher (47%) compared to the LMWH (5%) and UFH (16%) groups.

	heparin (UFH; 5000 IU 3x/day; n=171) or sequential compression devices alone (n=57). **Outcome Measures:** Rate of DVT, PE, and intracranial hemorrhage complications.	2. Those in the UFH group had a significantly higher rate of DVT and PE than those in the LMWH group (p<0.05). 3. Five percent of those in the LMWH group and 12% in the UFH group had progression of their intracranial hemorrhage, compared to 25% in the untreated group.
Kurtoglu et al. (2004) Turkey PCT N=120	**Population:** TBI=103, Other=17; Median Age=37.1yr; Gender: Male=47, Female=73. **Intervention:** Patients admitted to the Intensive Care Unit (ICU) were allocated to receive either Intermittent Pneumatic Compression devices (IPC; n=60) placed below the knee or Low-Molecular-Weight Heparin (LMWH) (n=60) (40 mg/day, enoxaparin sodium) for VTE prophylaxis. **Outcome Measures:** Rate of DVT, PE and mortality.	1. In the IPC group, there were 4 (6.6%) and 2 (3.3%) cases of DVT and PE, respectively. 2. In the LMWH group, there were 3 (5%) and 4 (6.6%) cases of DVT and PE, respectively. 3. Overall, 7 (11.6%) and 8 (13.3%) patients died in the IPC and the LMWH group, respectively. 4. There were no significant differences between groups in rates of DVT (p=0.04), PE (p=0.07), or mortality (p=0.08).
Gersin et al. (1994) USA Cohort N=32	**Population:** TBI; *Group 1 (n=14)*: Mean Age=38.3yr; Gender: Male=10, Female=4; Mean GCS Score=7.1. *Group 2 (n=18)*: Mean Age=36.1yr; Gender: Male=14, Female=4; Mean GCS Score=6.8. **Intervention:** Patients admitted to the surgical Intensive care unit (ICU) either received (Group 1) or did not receive (Group 2) prophylactic sequential compression devices (SCDs). Technetium venoscans were conducted along with ventilation/perfusion (V/Q) lung scans within 6 days of admission and repeated weekly for 1 mo. **Outcome Measure:** Incidence of DVT/PE.	1. Of those who were given SCD prophylaxis, 4 developed PE and none developed DVT. 2. Of those who did not receive prophylactic SCD, 2 developed PE and 2 developed DVT. 3. The groups did not differ significantly in the development of DVT and PE (p=0.7).
Davidson et al. (1993) USA Pre-Post N=24	**Population:** TBI=22, Other=2; Gender: Male=20, Female=4; Mean GCS Score=6. **Intervention:** Patients admitted to the surgical or trauma intensive care unit received intermittent sequential pneumatic leg compressions (11s compression phase, 60 sec of deflation). **Outcome Measures:** Mean Arterial Pressure (MAP), heart rate, central venous pressure, intracranial pressure, cerebral perfusion pressure. Measurements were obtained when the compression was initiated (time 0) and at 10, 20, and 30 min into therapy.	1. No significant changes in MAP, central venous pressure, intracranial pressure, or cerebral perfusion pressure occurred during the study period.
IVC Filters		
Elkbuli et al., (2020a) USA Retrospective Cohort $N_{Initial}$=2900, N_{Final}=2900	**Population:** TBI=481; *Inferior Vena Cava Filter (IVCF; n=413):* mean age=51.9±22.3yr; gender: male=310, female=103; time post injury=not reported; severity: mean GCS=10.0±4.8. *Venous Thromboembolism Chemoprophylaxis (VTEC; n=2487):* mean age=51.3±23.4yr; Gender: male=1714, female=31; time post	1. IVCF placement was associated with higher injury severities (p<.001). 2. Patients with IVCFs had significantly increased ICU LOS, incidence of DVT and PE for patients with an injury severity score<35 (p<.001). 3. Injury severity scores >35 were not associated with a change in DVT or PE incidence (p>.05).

	injury=not reported; severity: mean GCS=11.8±4.7. **Intervention:** Retrospective analysis of outcomes related to prophylactic IVCFs or VTE chemoprophylaxis. **Outcome Measures:** Intensive care unit length of stay (ICU LOS), total hospitalization, incidence of pulmonary embolism (PE), incidence of deep vein thrombosis (DVT), in-hospital mortality, home mortality.	4. IVCF was associated with lower in-hospital mortality in patients with AIS-head scores greater than 3. 5. No other significant differences in mortality were observed between groups.
Elkbuli et al., (2020b) USA Retrospective Cohort $N_{Initial}$=513, N_{Final}=513	**Population:** TBI=390; *Early IVCF (0-48hr); n=119: m*ean age=49.9±22.9yr; gender: male=81, female=38; time post injury=not reported; severity: mean GCS=10.5±4.9. *Late IVCF (>48); n=394:* mean age=54.6±22.6yr; gender: male=275, female=119; time post injury=not reported; severity: mean GCS=10.4±4.8. **Intervention:** Adult trauma patients underwent prophylactic inferior vena cava filter (IVCF) placement. Patients were stratified by admission time to IVCF placement: early (0-48hr) and late (>48hr) and the two groups were compared. Outcomes were measured throughout their hospitalization. **Outcome Measures:** Venous thromboembolism (VTE), hemorrhagic complications (HC), intensive care unit length of stay (ICU-LOS), hospitalization length of stay.	1. Early placement of IVCF (first 48hrs) is significantly associated with shorter ICU-LOS(p=.005), and hospital LOS (p=.022). 2. No significant difference in VTE, HC, or mortality was observed between early and late IVCF placement (p>.05).

Discussion

Gersin et al. (1994) investigated the effectiveness of SCDs. Of 32 patients admitted to the surgical intensive care unit with severe TBI, a total of eight patients developed DVT or PE following injury, half of whom had received prophylactic SCDs (showing no significant difference between SCDs and no intervention). The effectiveness of prophylactic SCDs in the prevention of post-TBI DVT or PE thus remains questionable.

Davidson et al. (1993) conducted a study to evaluate the possibility that intermittent pneumatic compression could aggravate intracranial hemodynamics in patients with severe brain injury. The authors reported that the use of intermittent compression devices to prevent the occurrence of DVT was not associated with any significant changes in intracranial pressure or cerebral perfusion pressure in stable patients in whom intracranial pressure was controlled by conventional measures (Davidson et al., 1993). These findings suggest that there is no contraindication to the use of pneumatic compression for the prevention of DVT in severe acute patients with brain injury who are responsive to conventional intracranial management measures.

When intermittent pneumatic compression devices were compared to prophylactic LMWH for the prevention of VTE, no significant differences in the development of PEs or DVTs were found between

groups (Kurtoglu et al., 2004). However, Minshall et al. (2011) found that mortality was higher in the group of patients receiving sequential compression devices alone compared to LMWH or UFH.

Conclusions

There is conflicting level 2 evidence (from one cohort study; Praeger et al., 2012; and one prospective controlled trial; Kurtoglu et al., 2004) and level 4 evidence (from one case series; Minshall et al., 2011) regarding the effectiveness of intermittent pneumatic compression devices compared to low-molecular-weight heparin or unfractionated heparin for the prophylaxis of DVT and PE.

There is level 4 evidence (from one pre-post test; Davidson et al., 1993) that intermittent compression devices do not cause acute elevations in intracranial pressure in patients with severe ABI.

There is level 2 evidence (from one retrospective cohort study; Elkbulki et al., 2020a) that prophylactic inferior vena cava filters are associated with higher rates of DVT, nonfatal PE and longer hospital stays when compared to VTE chemoprophylaxis following severe TBI.

There is level 2 evidence (from one retrospective cohort study; Elkbuli et al., 2020) that IVC filter placement within 48hrs of admission significantly improves ICU and hospital length of stay in adult trauma patients.

KEY POINTS

- Intermittent pneumatic compression devices and low molecular weight heparin may have a similar effect in terms of the prevention of deep vein thrombosis post ABI when compared to each other.
- Intermittent compression devices may not aggravate intracranial hemodynamics in patients with severe ABI.
- When compared to VTE chemoprophylaxis., prophylactic inferior vena cava filters may worsen outcomes.
- Early placement of inferior vena cava filters (within 48 hours) may shorten hospital length of stay.

Pharmacological Prophylaxis

Oral agents have been investigated for their prophylactic potential against DVT. Warfarin (Coumadin), a well-established anticoagulant with a predictable duration of action, is sometimes avoided as a prophylactic alternative for DVT due to its elevated bleeding side effects (Watanabe & Sant, 2001). Albrecht and colleagues (2014) report that warfarin use is associated with lower rates of DVT and PE, but comes at the cost of the risk of increased hemorrhagic bleeding. However, some experts felt the use of warfarin was advisable, especially for high-risk patients due to its benefit in treating undetected

thrombosis; the therapeutic dose range for prophylaxis and treatment of thromboembolism are the same (Hirsh et al., 1992; Hyers et al., 1992; Landefeld & Goldman, 1989).

In a multicenter observational study of DVT prophylaxis with a mixed TBI population sample of 932 patients treated with anticoagulation drugs, 71% were given LMWH, 23% unfractionated heparin, 1% Coumadin, and 3% were given both LMWH and Low-dose unfractionated heparin, none of which were associated with increased intracranial or systemic hemorrhage (Carlile et al., 2010). The Institut national d'excellence en santé et en services sociaux (INESSS) and Ontario Neurotrauma Foundation clinical practice guidelines for the rehabilitation of moderate to severe TBI recommend initiating thromboprophylaxis as soon as medically appropriate (level B evidence), and physical methods of thromboprophylaxis (i.e., compression stockings) should be used when pharmacological prophylaxis is delayed or contraindicated (level B evidence)(INESSS-ONF, 2017). There is also evidence from a meta-analysis that aspirin has positive effects in the reduction of both DVT and PE, by 40% and 60% respectively (BMJ, 1994). A systematic review on anticoagulation in patients with severe TBI found 30% rate of VTE among patients not receiving anticoagulation compared to 5-10% in patients receiving anticoagulation therapy (Hachem et al., 2018).

Overall, there is a lack of persuasive evidence to guide decisions about when to administer anticoagulant prophylaxis in those who sustain traumatic intracranial hemorrhage. Clinicians often make decisions based on their own assessments of the risks and benefits (Scales et al., 2010). To date no national standard of care exists for the administration of the pharmacological prophylaxis treatment of DVT post TBI (Phelan, Eastman, et al., 2012).

Differences in medications used for pharmacological thromboprophylaxis of patients with ABI is another important consideration. Subcutaneous heparin in low doses has been reported to be both safe and effective as prophylaxis against DVT development post ABI (Watanabe & Sant, 2001). The route of delivery may also affect the efficacy of anticoagulant prophylaxis (Watanabe & Sant, 2001). For this reason, intravenously delivered heparin may be more effective in the prevention of thromboembolism compared with subcutaneous administration, although this method of delivery might increase the risk of bleeding (Green et al., 1988). LMWH, which is injected subcutaneously, has gained popularity due to the ease of administration and dosage adjustment. Of note, low-molecular weight variants of unfractionated heparin are more expensive but the advantages are such that they have become the standard of care. Carlile et al. (2006) found that 15 of the 16 rehabilitation centers surveyed reported routinely initiating treatment with either LMWH or Low-dose unfractionated heparin. In a study with a mixed trauma population, low-dose unfractionated heparin was compared to enoxaparin (LMWH) for the treatment of DVT (Geerts et al., 1996). Of those receiving low-dose unfractionated heparin, 44% suffered a DVT compared to 31% of patients receiving enoxaparin (p=0.014) (Geerts et al., 1996). These results are consistent with Byrne et al. (2017) matched analysis in patients with isolated severe TBI, where patients who received LMWH had an adjusted odds ratio of 0.49 (95% CI=0.29-0.82) of developing a PE compared to patients who were treated with unfractionated heparin. The INESSS and Ontario Neurotrauma Foundation clinical practice guidelines for the rehabilitation of moderate to severe TBI

recommends LMWH over unfractionated heparin after TBI (level C evidence), although these guidelines are mostly based on evidence in general trauma patients, and not TBI specifically (INESSS-ONF, 2017).

TABLE 6 | Pharmacological Interventions for the Prophylaxis of Venous Thromboembolism Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Baharvahdat et al., (2019) Iran RCT PEDro=9 $N_{Initial}$=54, N_{Final}=53	**Population:** TBI=54; *Intervention Group (Enoxaparin; n=26): m*ean age=27.2±13.2yr; gender: male=22, female=4; time post injury=<5h; severity: median GCS=7. *Control Group (Placebo; n=27):* mean age=25.9±0.9yr; Gender: male=22, female=5; time post injury=<5h; severity: median GCS=7. **Intervention:** Participants were randomly allocated to receive enoxaparin (0.5mg/kg subcutaneous) or placebo (2mL sterile water subcutaneous) every 6h for a total of six doses. Outcome measures were assessed at baseline and discharge. **Outcome Measures:** Incidence of intracranial hematoma (ICH), Glasgow Outcome Scale (GOS), hospital length of stay, intensive care unit length of stay.	1. There were no significant group differences in the incidence new ICH or ICH size increase (p>.05). 2. Enoxaparin significantly improved favourable outcomes (GOS, p=.019) compared to the placebo group. 3. No significant differences in hospital or ICU length of stay were observed between groups (p>.05).
Phelan et al. (2012) USA RCT PEDro=8 N=62	**Population:** TBI; *Intervention Group (n=34):* Mean Age=40.7yr; Gender: Male=22, Female=12. *Control Group (n=28):* Mean Age=42.6yr; Gender: Male=16, Female=12. **Intervention:** The intervention group received enoxaparin (30 mg, 2x/day) within 24-96hr after injury, whereas the control group received a placebo. **Outcome Measures:** Radiographic worsening of TBI, VTE, and extracranial hemorrhagic complications.	1. One DVT occurred in the control group; however, no mention of DVT occurrence was reported for the intervention group. 2. No clinical TBI progressions were found.
Hachem et al. (2018) Canada PCT N=64	**Population:** TBI; Gender: Male=45, Female=19. Mean Age=44yr; Mean GCS=5. **Intervention:** Prospective evaluation of patients who received enoxaparin within 3 days of admission (Early group), after 3 days (Late group), and no enoxaparin (No treatment group). All patients were provided Thombo-Embolic Deterrent stockings. Doppler ultrasounds (DUS) 7 days (+/- 3d) post admission were used to evaluate DVTs, in addition to care and investigations ordered by the treating clinicians. **Outcome Measures**: VTE events, intracranial hemorrhage (ICH) progression, DUS.	1. Progression of ICH after initiation of enoxaparin was similar between the early (0%) and late (7%) groups. 2. VTE incidence was not significantly different between the early (10%) and late (16%) groups (p=0.99).
Brandi et al., (2020) Switzerland Case Control $N_{Initial}$=177, N_{Final}=177	**Population:** TBI=177; *Patients with Venous Thromboembolism (VTE; n=23):* mean age=51±20yr; gender: male=16, female=7; time post injury=not reported; severity: GCS<13.	1. Delayed onset of PTP was the only independent predictor of VTE (p<.05). 2. No other measures significantly predicted the incidence of VTE (p>.05).

Author Year Country Study Design Sample Size	Methods	Outcome
	Patients without VTE (n=154): mean age=50±22yr; gender: male=114, female=40; time post injury=not reported; severity: GCS<13. **Intervention:** Retrospective analysis of the risk factors associated with developing VTE following moderate to severe TBI. **Outcome Measures:** Hypotension, intensive care unit length of stay, number of days on mechanical ventilation, pharmacological VTE prophylaxis (PTP) initiation.	
Störmann et al., (2019) Germany Retrospective Cohort $N_{Initial}$=292, N_{Final}=292	**Population:** TBI=292; *Intervention Groups (time to chemical VTE prophylaxis):* *Early* (<24hr after hospitalization, n=93*)*: mean age=62.1±19.1yr; Male=61.3%; severity: mean AIS=3.7±0.8. *Intermediate* (24-48hr, n=90): mean age=60.8±21.6yr; Male=66.7%; severity: mean AIS=3.6±0.7. *Late* (>48hr, n=74): mean age=62.1±21.7yr; Male=71.6%; severity: mean AIS=3.4±0.6. No Therapy (n=35): mean age=64.5±19.3yr; Male=60.0%; severity: mean AIS=3.9±0.9. **Intervention:** Participants with severe TBI were given VTE prophylaxis at different times. Outcomes were monitored over the first 7 days of recovery. **Outcome Measures:** Intracranial bleeding progression, venous thromboembolism (VTE), mortality.	1. Early administration of chemical VTE prophylaxis within 24hr after admission did not significantly increase the risk of intracranial bleeding progression(p>.05) in patients with severe blunt TBI.
Seifi et al. (2018) USA Case Control N=155	**Population:** TBI; Gender: Male=119, Female=36. Mean Age=41.6yr. **Intervention:** Retrospective review of patients who received chemical thromboprophylaxis or inferior vena cava (IVC) filter for prevention of VTE. Only patients with clinical suspicion of PE had diagnostic investigations, there was no surveillance for PE. **Outcome Measure:** Incidence of PE.	1. 33 patients did not receive chemical thromboprophylaxis. 2. 60 patients received an IVC filter. 3. 4 patients developed a clinically significant PE. They were all in the group of patients that received chemical thromboprophylaxis. None had an IVC filter prior to developing a PE. 4. There was no significant difference between incidence of PE between patients that received chemical thromboprophylaxis and those who did not (p=0.58).
Byrne et al. (2016) USA Cohort N=3634	**Population**: ABI; Median Age=43yr; Gender: Male=2798, Female=836; Median Time Post Injury=84hr; Median GCS=3. **Intervention**: Participants were included in retrospective analysis after having received either unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) as either early prophylaxis (<72 hr) or late prophylaxis (≥72 hr) for VTE. **Outcome Measures**: Risk of DVT, PE, late neurosurgical intervention and mortality; abbreviate head injury scale (AIS) and incidence of ischemic (ICH) stroke.	1. PE occurred in 1.7% of participants, and DVT in 6.5%. 2. Early prophylaxis was associated with lower odds of PE (OR=0.48) and DVT (OR=0.51) than late prophylaxis. 3. There was no significant difference in risk of late neurosurgical intervention or death between early and late prophylaxis. 4. LMWH was associated with lower odds of VTE (OR=0.6) and mortality (OR=0.59) than UFH.

Author Year Country Study Design Sample Size	Methods	Outcome
		5. Late prophylaxis group had significantly higher AIS score, ICH incidence, and early neurosurgical intervention rate than early prophylaxis group. 6. The late group most commonly received LMWH and early group most commonly received UFH.
Saadi et al., (2018) USA Case Series $N_{Initial}$=96, N_{Final}=96	**Population:** TBI=177; *No Prophylaxis (n=14):* mean age=58.3±21.7yr; gender: male=7, female=7; time post injury=not reported; severity: mean GCS=7.7±3.7. *Prophylaxis within 24h (n=7):* mean age=62.1±27.6yr; gender: male=4, female=3; time post injury=not reported; severity: mean GCS=7.3±4.0. *Prophylaxis within 48h (n=14):* mean age=48.8±19.0yr; gender: male=13, female=1; time post injury=not reported; severity: mean GCS=5.6±3.6. *Prophylaxis after 48h (n=61):* mean age=54.5±20.5yr; gender: male=48, female=13; time post injury=not reported; severity: mean GCS=5.1±3.3. **Intervention:** Retrospective chart review of patients that received pharmacological venous thromboembolism prophylaxis following severe TBI. **Outcome Measures:** Time to prophylaxis initiation, prophylaxis regimen, incidence of VTE, adverse effects.	1. Of the patients included, 14.6% did not receive VTE prophylaxis, 7.3% initiated therapy within 24h, 14.6% within 48h and 63.5% after 48h. 2. Delayed prophylaxis significantly increased the incidence of VTE (p=.038). 3. No significant differences between VTE prophylaxis regimens and incidence of VTE were observed (p>.05). 4. Lack of VTE prophylaxis resulted in significantly higher rates of mortality (p=.006). 5. Earlier VTE prophylaxis was associated with increased minor bleeds (p=.042) but not major bleeds (p>.05).
Dengler et al. (2016) USA Case Series N=155	**Population:** Gender: Male=119, Female=36. **Intervention:** Patients with severe TBI, intracranial hemorrhage (ICH), and invasive intracranial monitoring were retrospectively reviewed. Patient outcomes were correlated with prophylactic treatment (if any) for DVT that patients received. **Outcome Measures:** DVT: incidence, time to detection, time to starting prophylaxis; time to stable head computed tomography (CT); in-hospital mortality.	1. Twelve percent of the cohort experienced at least one DVT during the course of the study. 2. Following admission median time to stable head CT was 2 days, DVT prophylaxis was 4 days, and DVT detection was 8 days. 3. Among patients who did not receive anticoagulation treatment, the incidence of DVT (30.3%) was significantly greater than that of patients who received heparin (8.0%, p<0.01). 4. Among all patients, 28 (18%) experienced in-hospital mortality. 5. Those who did not receive anticoagulation treatment had a significantly increased risk of DVT and in-hospital death. 6. No significant association was observed between DVT formation, and the various doses of unfractionated heparin and low-molecular-weight heparin.
Meyer et al. (2016) USA Case Series N=67	**Population:** TBI=67; *No Early VTC (n=35):* Mean Age=25.2yr; Gender: Male=35; Mean GCS=8.3. *Early VTC (n=32):* Mean Age=24.9yr; Gender: Male=32; Mean GCS=10.3. **Intervention:** A retrospective analysis of patients with	1. The incidence of worsened ICH, DVT or PE, 30-day mortality, or non-elective reoperation were not significantly different between the treatment groups.

Author Year Country Study Design Sample Size	Methods	Outcome
	penetrating brain injury (PBI) was conducted. Patients were grouped based on if they received early VTE chemoprophylaxis (VTC, occurring within 48hr of injury) status. **Outcome Measures:** Intracranial hemorrhage (ICH) worsening; PE; DVT; 30-day mortality; emergent reoperation; VTC: timing, agents used.	2. The mean time of first VTC dose was 24hr from admission. 3. The most commonly used early VTC agent was enoxaparin (30 mg subcutaneously, twice daily; 91%). The other 3 patients who received early VTC were given UFH (5000 units subcutaneously, 3 times daily).
Daley et al. (2015) USA Case Control N=271	**Population:** TBI; *Intervention Group (n=45):* Mean Age=42yr; Gender: Male=38, Female=7; Mean GCS=10. *Control Group (n=226):* Mean Age=47yr; Gender: Male=173, Female=53; Mean GCS=10. **Intervention:** Participants were categorized based on exposure (intervention) or lack of exposure (control) to enoxaparin during the acute phase after undergoing an emergency craniotomy, post-TBI. **Outcome Measures:** Rate of DVT and PE, days on ventilation (DOV), length of stay (LOS), mortality rate.	1. No significant differences between groups (intervention and control) were found in terms of rate of DVT (2% vs 3%, p=0.87) and PE (0% versus 1%, p=0.99), as well as LOS and DOV. 2. The intervention group had a significantly lower rate of mortality in hospital compared to the control group (4% vs 24%, p=0.01).
Kim et al. (2014) USA Case Control N=75	**Population:** TBI; Mean Age=44yr; Gender: Male=59, Female=16; Mean GCS=4. **Intervention:** Participants received heparin prophylaxis at early (<3 days, n=22), intermediate (3-5 days, n=34), or late (>5 days, n=19) time intervals post injury. **Outcome Measures:** Rate of DVT, PE, and morality, number of ventilator and Intensive care unit (ICU) days, Glasgow Coma Scale (GCS), Abbreviated Injury Scale (AIS), Injury Severity Score, Marshall CT score, neurological improvement.	1. There was no significant difference between groups in mean rates of DVT, PE, or mortality; mean days on ventilator or in ICU; or mean scores on GCS, AIS, or Marshall CT score. 2. There was a significant difference in mean ISS score between the early and intermediate groups (28 versus 35, p=0.02) and between the early and late groups (28 versus 36, p=0.007). 3. There was a significant difference in cumulative neurological improvement between the early and late groups (p<0.05), with greater improvement in the early group.
Lin et al. (2013) USA Case Series N=3812	**Population:** TBI, Abbreviated Injury Severity Scale>3. **Intervention:** Patient records were reviewed. Participants were grouped based on intervention without the heparin prophylaxis protocol (n=1970) and treatment after the implementation of a heparin prophylaxis protocol (n=1842). **Outcome Measures:** Rate of DVT and PE.	1. Rate of DVT was 0.97% without the protocol and 1.21% with the heparin prophylaxis protocol. 2. A single patient had PE in each group.
Farooqui et al. (2013) USA Case Control N=236	**Population:** TBI; Gender: Male=146, Female=90. *Group A (n=107):* Mean Age=53.3yr. *Group B (n=129):* Mean Age=57.4yr. **Intervention:** Group A had no routine administration of chemoprophylaxis and Group B received either Lovenox (30 mg, 2x/day) or Heparin (5000 U, 3x/day) 24 hr after stable computed tomography (CT). **Outcome Measures:** Rate of DVT and PE.	1. DVT rate was higher in group A than group B (5.6% versus 0%, p=0.008). 2. PE rate was 3.74% in group A and 0.78% in group B (p=0.18). 3. Progression of intracranial hemorrhage did not differ significantly between groups (p=0.33).
Kwiatt et al. (2012) USA	**Population:** TBI; Gender: Male=836, Female=379. *Control Group (n=995):* Mean Age=52.9yr; Mean	1. Patients receiving LMWH were significantly older and had more severe injuries (p<0.001) than those who did not.

Author Year Country Study Design Sample Size	Methods	Outcome
Case Series N=1215	GCS=11.4. *Treatment Group (n=220):* Mean Age=46.2yr; Mean GCS=8. **Intervention:** Retrospective comparison of patients who received low-molecular-weight heparin (LMWH, *treatment group*) for VTE prophylaxis and those who did not. **Outcome Measure:** Progression of intracranial hemorrhage.	2. LMWH compared to the control had greater hemorrhage progression (42% versus 24%, p<0.001). 3. For those receiving LMWH, when it was initiated did not impact the rate of hemorrhage progression. 4. The LMWH compared to the control group had a greater number of VTE episodes (9.1% versus 3.1%, p<0.001).
Praeger et al. (2012) Australia Cohort N=36	**Population:** TBI; Mean Age=40.3yr; Gender: Male=28, Female=8; Mean GCS=8. **Treatment:** Thromboprophylaxis included compression stockings and/or Low-Molecular-Weight Heparin (LMWH). **Outcome Measures:** Rate of DVT and PE assessed with compression ultrasound.	1. The rate of DVT was 6%, PE was 6%, and total VTE was 11%. 2. Among individuals with severe TBI the rates of DVT, PE, and total VTE were 10%, 10% and 19%, respectively.
Minshall et al. (2011) USA Case Series N=386	**Population**: TBI; Gender: Male=293, Female=93. **Intervention:** Chart review of patients receiving LMWH (30 mg, 2x/day; n=158), unfractionated heparin (UFH; 5000 IU 3x/day; n=171) or sequential compression devices alone (n=57). **Outcome Measures:** Rate of DVT, PE, and intracranial hemorrhage complications.	1. Mortality in the sequential compression devices alone group was higher (47%) compared to the LMWH (5%) and UFH (16%) groups. 2. Those in the UFH group had a significantly higher rate of DVT and PE than those in the LMWH group (p<0.05). 3. Five percent of those in the LMWH group and 12% in the UFH group had progression of their intracranial hemorrhage, compared to 25% in the untreated group.
Koehler et al. (2011) USA Cohort N=669	**Population:** TBI; Gender: Male=487, Female=182. *Early Group (n=268):* Mean Age=39.8yr. *Late Group (n=401):* Mean Age=40.2yr. **Intervention:** Enoxaparin (30 mg 2x/day) was administered to all patients. The early group received the VTE prophylaxis within 0-72 hr and the late group at 73 hr or later. **Outcome Measure:** Incidence of DVT and PE.	1. Those in the early group compared to the late group spent significantly fewer days on a ventilator (p<0.001), fewer days in ICU (p<0.002) and hospital (p<0.004). 2. Intracranial hemorrhage progression for the early vs late groups was 9.38% vs 17.41% (p<0.001) before prophylaxis and 1.46% vs 1.54% after (p=0.912). 3. The proportion of DVTs and PEs were not significantly different (p=0.117 and p=0.49, respectively).
Scudday et al. (2011) USA Case Control N=812	**Population:** TBI; Gender: Male=560, Female=252. *Intervention Group (n=402):* Mean Age=45.2yr. *Control Group (n=410):* Mean Age=51.5yr. **Intervention:** Retrospective review comparing patients that received chemical thromboprophylaxis (91% Heparin, 9% Enoxaparin) to an untreated control group. **Outcome Measure:** Incidence of VTE.	1. A lower incidence of VTE was found in the treated group compared to the untreated group (1% versus 3%, p=0.019).

Author Year Country Study Design Sample Size	Methods	Outcome
Salottolo et al. (2011) USA Case Series N=480	**Population:** TBI; Mean Age=53yr; Gender: Male=296, Female=184; Mean GCS=12.2. **Intervention:** Retrospective review of patients considered for thrombus prophylaxis (lovenox 30 mg 2x/day or heparin 5000 U, 2x/day), timing of administration, and whether or not the intervention was interrupted. **Outcome Measures:** Development of VTE or DVT.	1. Fifty-three percent of patients received pharmacological thromboprophylaxis (PTP); median time to start was 3d and it was continuous in 73.7%. 2. Medications began <72 hr post injury in 108 patients and >72 hr post injury in 147. 3. The no PTP group had 4 DVTs and 2 PEs compared to the PTP group which had 8 DVTs and 3 PEs. 4. Neither the administration of these medications (p=0.29) or the timing of administration (p=0.26) had any effect on the development of VTE. 5. Patients with interrupted PTP has a significant increased odds of developing VTE compared with patients with continuous PTP (OR=7.07, p=0.04).
Norwood et al. (2008) USA Case Series N=525	**Population:** TBI; Mean Age=39.6yr; Gender: Male=387, Female=138; Abbreviated Injury Scale ≥2; Mean Time Post-Injury=36.2hr. **Intervention:** Patients were given Enoxaparin sodium (30 mg, 2x/day). **Outcome Measures:** Incidence of DVT and PE, mortality rates.	1. Four percent of patients died. 2. Of 151 patients that underwent a lower extremity venous Doppler ultrasound, 6 patients were diagnosed with a DVT. 3. No patients within the study group were diagnosed with a PE.
Kurtoglu et al. (2004) Turkey PCT N=120	**Population:** TBI=103, Other=17; Median Age=37.1yr; Gender: Male=47, Female=73. **Intervention:** Patients admitted to the Intensive Care Unit (ICU) were allocated to receive either Intermittent Pneumatic Compression devices (IPC; n=60) placed below the knee or Low-Molecular-Weight Heparin (LMWH) (n=60) (40 mg/day, enoxaparin sodium) for VTE prophylaxis. **Outcome Measures:** Rate of DVT, PE and mortality.	1. In the IPC group, there were 4 (6.6%) and 2 (3.3%) cases of DVT and PE, respectively. 2. In the LMWH group, there were 3 (5%) and 4 (6.6%) cases of DVT and PE, respectively. 3. Overall, 7 (11.6%) and 8 (13.3%) patients died in the IPC and the LMWH group, respectively. 4. There were no significant differences between groups in rates of DVT (p=0.04), PE (p=0.07), or mortality (p=0.08).
Kleindienst et al. (2003) USA Case Series N=940	**Population:** Head Injury=344, Elective Surgery (tumors)=294, Intracranial Hemorrhage (ICH)=302; Mean Age=57.3yr. **Intervention:** A retrospective review of patients either receiving 18 mg/day of Certoparin-sodium (3000 U anti-factor Xa) for prophylaxis on the evening prior to elective neurosurgery (ES) and within 24 hours after surgery, or admission whenever a CT showed an absence of a progressive haematoma. **Outcome Measures:** Incidence of bleeding complications, VTE events, and morbidity/mortality rates.	1. One hundred and fifty-five patients were excluded due to coagulation abnormalities or significant bleeding. 2. Intracranial bleeding was found in 1.5% of the total sample. 3. The incidence of VTE and PE was 0.2% and 0.1% of patients respectively, with no associated mortality. 4. No heparin induced thrombocytopenia was observed.
Norwood et al. (2002) USA Pre-Post	**Population:** Traumatic Intracranial Hemorrhagic injuries (IHI); Mean Age=39.5yr; Mean GCS=10.	1. At discharge (n=106), 2% of patients had a DVT and no PE

Author Year Country Study Design Sample Size	Methods	Outcome
N=150	**Intervention:** Patients received Enaxoparin-sodium (30 mg, 2x/day) beginning 24 hr after initial evaluation. **Outcome Measures:** Incidence of DVT or PE, Progression of IHI, mortality, Glasgow Outcome Scale (GOS).	2. Twenty-three percent of patients had CT progression of IHI pre-treatment. Rate of progression of IHI significantly decreased after initiation of the intervention (p=0.002). 3. Study group mortality was 7%. 4. On the GOS, the majority (76%) of patients showed good recovery.
Kim et al. (2002) USA Case Control N=64	**Population:** ABI; Gender: Male=49, Female=15. *Early Group (n=47):* Mean Age=37.7yr; Mean GCS=9.1. *Late Group (n=17):* Mean Age=44yr; Mean GCS=9.4. **Intervention:** Retrospective review of patients who received unfractionated heparin (UFH) within 72 hours of admission (Early Group) and those who received it after the third day (Late Group). **Outcome Measures:** VTE events, bleeding complications.	1. There was no increase in intracranial bleeding or deterioration on neurological examination due to UFH administration. 2. There was no statistical difference in VTE events between groups.
Agnelli et al. (1998) USA RCT PEDro=6 N=307	**Population:** TBI=261, Other=46; *Intervention Group (n=153)*: Mean Age=55.1yr; Gender: Male=69, Female=84. *Placebo Group (n=154)*: Mean Age=57.5yr; Gender: Male=84, Female=70. **Intervention:** Patients received either enoxaparin (40 mg/day) or placebo administered subcutaneously for no less than 7 days, beginning within 24 hr following elective neurosurgery. All patients were fitted with thigh-length compression stockings, which were worn from the morning of surgery until discharge. **Outcome Measures:** Symptomatic, objectively documented VTE (DVT or PE) or DVT detected by bilateral venography performed at the end of the treatment period.	1. Eighty-four percent of patients receiving placebo and 85% of the patients receiving enoxaparin had venographic studies sufficient for analysis. 2. Thirty-two percent of patients in the placebo group and 17% in the intervention group had DVT, with a relative risk of 0.52 (p=0.004). 3. Six percent of patients in the placebo group had a clinically overt thromboembolic event compared to only 1% in the enoxaparin group. 4. The rates of proximal DVT were 13% in patients taking placebo and 5% in patients taking enoxaparin (p=0.04).

Discussion

Results indicate that early anticoagulation treatment (within the first 72 hours) may reduce the risk of developing DVT post injury (Brandi et al., 2020; Byrne et al., 2016; Farooqui et al., 2013; Kim et al., 2002; Kim et al., 2014; Norwood et al., 2008; Saadi et al., 2018; Salottolo et al., 2011; Scudday et al., 2011) without increasing the risk of intracranial hemorrhagic injury (Baharvahdat et al., 2019; Byrne et al., 2016; Koehler et al., 2011; Scudday et al., 2011; Stormann et al., 2019) or deterioration on neurological examination (Kim et al., 2002). However, these results are in conflict with Meyer et al. (2016) and Hachem et al. (2018), which found no increased risk of ICH worsening, but found no benefit regarding VTE incidence.

Patients with ABI who were started on unfractionated heparin within three days of injury onset, compared to those who started after this time period, did not differ significantly in terms of the number

of thromboembolic events (Kim et al., 2002; Kim et al., 2014). However, those who received heparin earlier had greater cumulative neuro improvement and lower injury severity scale scores (Kim et al., 2014).

Norwood and colleagues conducted two studies examining the benefits of administering enoxaparin (LMWH) prophylaxis to those who sustain a severe ABI within the first 48 hours post injury (Norwood et al., 2008; Norwood et al., 2002). Results from both studies indicate that administering enoxaparin post ABI reduces the risk of developing DVT and PE, without increasing the risk of bleeding post injury. Scudday et al. (2011) also found that patients who received chemical prophylaxis within 72 hours of injury had a significantly lower incidence of developing VTE post ABI ($p<0.019$) compared to those not receiving chemical prophylaxis (Kim et al., 2014). Overall, a meta-analysis by Jamjoom and colleagues (2013) concluded that individuals who begin pharmacological thromboprophylaxis within 72 hours of injury have half the risk of VTE without significantly increased risk of intracranial hemorrhage progression, compared to those who start prophylaxis more than 72 hours after their injuries.

On the contrary, a few studies have demonstrated that these medications may not be beneficial or superior treatments. In one study with individuals who underwent a craniotomy post ABI, indicative of a more severe brain injury, no significant differences were reported for rate of DVT and PE when comparing those who received enoxaparin prophylaxis to those who did not (Daley et al., 2015). Further, Kwiatt et al. (2012) reported that patients receiving LMWH were at higher risk for hemorrhage progression and the risk of using LMWH may exceed its benefit. Similarly for heparin, Lin et al. (2013) did not find a reduction in DVT or PE once individuals with a severe TBI were administered a heparin prophylaxis protocol.

A systematic review of twelve studies reported that overall evidence supported the use of enoxaparin for reduction of DVT and unfractionated heparin for decreased mortality rates compared to no chemoprophylaxis (Chelladurai et al., 2013). Furthermore, a retrospective study of 20 417 patients with isolated TBI reported less likelihood of VTE with LMWH compared to unfractionated heparin (Benjamin et al., 2017).

Conclusions

There is level 3 evidence that prophylactic anticoagulation is more effective than placebo in reducing the risk of developing deep vein thrombosis in patients post ABI.

There is level 2 evidence that the administration of enoxaparin within the first 72 hours post ABI reduces the risk of developing deep vein thrombosis and pulmonary embolism post injury compared to unfractionated heparin.

KEY POINTS

- Administration of pharmacological thromboembolic prophylaxis within the first 72 hours post ABI may be effective for reducing the risk of developing venous thromboembolism.
- Enoxaparin is effective for the prevention of venous thromboembolism development after elective neurosurgery and has not been found to cause excessive bleeding.

Conclusion

The most well studied intervention for the prevention of VTE is pharmacological thromboprophylaxis. There is moderate evidence that pharmacological prophylaxis with heparin, particularly LMWH helps reduce the risk of developing a VTE post ABI, without increasing the risk of intracranial bleeding in patients with TBI. Compression stockings are not more effective than LMWH. Unfortunately, the evidence in ABI specific populations is limited; the timing, agent and methods of anticoagulation therapy would benefit from more research.

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