10. Seizure Disorders Post ABI

On behalf of the ERABI Research Group

10.1 Classification of Post-Traumatic Seizures and Epilepsy

In 2010, there were approximately 2.5 million traumatic brain injuries (TBI), either in combination with other injuries or as an isolated injury (National Hospital Discharge Survey 2010)**.** Post-traumatic seizures (PTS), although identified as a serious consequence of TBI, remain an understudied problem (Ferguson et al. 2010). PTS disorders have been defined in the Practice Parameter on the Antiepileptic Drug Treatment of Post-traumatic Seizures by the Brain Injury Special Interest Group of the American Academy of Physical Medicine and Rehabilitation (1998; Table 1).

Table 1. Definitions of Post-Traumatic Seizures (p.595; Brain Injury Special Interest Group 1998)

Seizure	Discrete clinical events that reflect a temporary physiologic dysfunction of the brain characterized by excessive and hypersynchronous discharge of cortical neurons.
Post-Traumatic Seizure	An initial or recurrent seizure episode not attributable to another obvious cause after penetrating or non-penetrating TBI. The term *post-traumatic seizure* is preferred over *post-traumatic epilepsy* because the former encompasses both single and recurrent events.
Immediate Post-Traumatic Seizure	A seizure due to TBI occurring within the first 24 hours of injury.
Early Post-Traumatic Seizure	A seizure due to TBI occurring within the first week of injury.
Late Post-Traumatic Seizure	A seizure due to TBI occurring after the first week of injury.
Post-Traumatic Epilepsy	A disorder characterized by recurrent late seizure episodes not attributable to another obvious cause in patients following TBI. The term should be reserved for *recurrent*, late post-traumatic seizures.
Non-Epileptic Seizures	Episodic behavioural events that superficially resemble epileptic attacks but are not associated with paroxysmal activity within the brain.
Epilepsy	A condition characterized by recurrent unprovoked seizures.

10.2 Incidence of Post-Traumatic Seizures

Q. What is the incidence of post-traumatic seizures?

Answer

- 5–7% of all hospitalized patients with TBI
- 11% of patients with severe non-penetrating TBI
- 35–50% of patients with penetrating TBI

It is believed that up to 20% of symptomatic epilepsy in the general population is a result of TBI (Bushnik et al. 2012). Of all patients with TBI who are hospitalized, 5–7% will experience PTS. However, the incidence of PTS is much higher on rehabilitation units (as high as 17%) which is reflective of the increased severity of the injury and a higher number of risk factors in this population (Armstrong et al. 1990; Bontke et al. 1993; Cohen & Groswasser 1991; Kalisky et al. 1985; Sazbon & Groswasser 1990; Wang et al. 2013). The incidence of late post-traumatic seizures (LPTS) ranges from 5 to 19% for the general population (Bushnik et al. 2012). A recent study has shown that when seizures occur, 0.4% were acute seizures, 0.5% were early PTS, and 88.7% were LPTS (Zhao et al. 2012). A study examining 236,164 individuals with TBI found that 2.4% had pre-existing epilepsy or a seizure disorder (Wilson & Selassie 2014). Unfortunately, the consequences of the TBI may be more severe in this population.

For those who sustain a severe non-penetrating TBI approximately 11% will experience seizures post injury and for those who have a TBI as the result of a penetrating injury, the numbers increase to 35–50% (Yablon 1993; Ascroft 1941; Caveness & Liss 1961). In young adults TBI is the leading cause of epilepsy (Annegers 1996).

10.3 Risk Factors for Post-Traumatic Seizures

Identification of the High-Risk Patient

Following TBI or acquired brain injury (ABI) seizures have been associated with secondary accidental injury, depression, a loss of independence (driving privileges), and a reduction in employability (Andelic et al. 2009; Brain Injury Special Interest Group 1998). It is important to identify patients who are at high-risk of developing PTS since these patients may benefit from pharmacological seizure prophylaxis. According to Yablon and Dostrow (2001) the clinical characteristics of the patient, the injury, and information obtained from neuroimaging and electrophysiologic assessment techniques can be used to identify those at high risk for developing seizure disorders post injury.

Q. What factors are predictive of seizures following an ABI?

Answer

- Patient characteristics: age, alcohol use, and family history.
- Injury characteristics: Bone/ metal fragments, depressed skull fracture, focal contusions/injury, focal neurologic deficits, lesion location, dural penetration, intracranial hemorrhage, and injury severity.
- Early post-traumatic seizures.

There are several patient and injury characteristics that increase the likelihood of developing PTS. These include increased injury severity (Glasgow Coma Scale score of less than 10, prolonged length of coma, prolonged length of post-traumatic amnesia), depressed skull fractures, cortical contusions, subdural hematomas, epidural hematomas, intracerebral hematomas, penetrating injuries and wounds with dural penetration, a seizure within the first week of injury, male gender, age, and multiple neurosurgical procedures (Brain Injury Special Interest Group 1998; Dikmen et al. 1991; Englander et al. 2003; Wang et al. 2013; Yablon 1993; Yeh et al. 2013; Zhao et al. 2012; Bushnik et al. 2012; Di Luca & de Lacerda 2013;

Diamond et al. 2014). Ferguson et al. (2010) also found those who had other concomitant injuries or comorbid conditions, previous head injuries, stroke, or depression were more likely to develop LPTS. These findings mirrored the results of previous studies (Andelic et al. 2009; Annegers et al. 1998; Weiss et al. 1983). In a cohort study conducted by Ferguson et al. (2010), the incidence of post-traumatic epilepsy (PTE) was highest in individuals 30 to 54 years of age. However, higher rates of PTE have also been reported for those 50 to 59 and 60 to 69 years of age (Zhao et al. 2012).

The first year post injury is often when PTE develops (Di Luca & de Lacerda 2013). Moreover, Diamond et al. (2014) recently explored genetic variance and PTE development in 256 individuals with moderate to severe TBI. The study found that higher cerebrospinal fluid and serum IL-1β (a potential biomarker for epilepsy) ratios were associated with an increased risk of PTE (Diamond et al. 2014). Due to this study being one of the first studies exploring this gene variability, more studies are needed before firm conclusions can be made.

Table 2. Studies of Risk Factors for Late Post-Traumatic Seizures (p.310; Yablon & Dostrow 2001)

Patient Characteristics	**References**
Age	Annegers et al. 1980; Asikainen et al. 1999; Hahn et al. 1988; Kollevold 1979
Alcohol use	Evans 1962; Heikkinen et al. 1990; Japan Follow-up Group for Posttraumatic Epilepsy 1991; Kollevold 1978
Family history	Caveness 1963; Evans 1962; Heikkinen et al. 1990; Hendrick 1968
Injury Characteristics	
Bone/metal fragments	Ascroft 1941; Salazar et al. 1985; Walker et al. 1959
Depressed skull fracture	Hahn et al. 1988; Jennett 1975; Phillips 1954; Wiederholt et al. 1989
Focal contusions/injury	da Silva et al. 1992; De Santis et al. 1992; Eide & Tysnes 1992; Glötzner et al. 1983; Heikkinen et al. 1990
Focal neurologic deficits	da Silva et al. 1992; Jennett 1975; Salazar et al. 1985
Lesion location	da Silva et al. 1992; Evans 1962; Grafman 1992
Dural penetration	Caveness & Liss 1961; Evans 1962; Salazar et al. 1985
Intracranial hemorrhage	Glötzner et al. 1983; Hahn et al. 1988; Japan Follow-up Group for Posttraumatic Epilepsy 1991
Injury severity	Evans 1962; Jennett 1975; Salazar et al. 1985; Walker & Yablon 1961
Other	
Early post-traumatic seizures	Heikkinen et al. 1990; Jennett 1975; Salazar et al. 1985

10.4 Natural History of Post-Traumatic Seizures

Q. Describe the natural history of post-traumatic seizures.

Answer

- Approximately 50–67% of patients with post-traumatic seizure will experience seizure within the first 12 months and 75–80% by the end of the second year following a TBI.
- Patients with moderate to severe TBI or penetrating TBI remain at increased risk for more than 5 years post TBI.
- Those with penetrating TBI experience first unprovoked seizures sooner than those with blunt TBI.
- Approximately half of those subjects with post-traumatic seizure will experience a seizure recurrence.

Onset

The risk of epilepsy is highest within the first 2 years following brain trauma (Brain Injury Special Interset Group 1998; Dikmen et al. 1991; Englander et al. 2003; Yablon 1993). Yablon and Dostrow (2001) have noted that one-half to two-thirds of individuals who suffer PTS will experience seizure onset within the first 12 months, and 75-80% will have seizures within 2 years of their TBI (Caveness et al. 1979; da Silva et al. 1992; da Silva et al. 1990; Pohlmann-Eden & Bruckmeir 1997; Walker & Yablon 1959; Walker & Yablon 1961). Similarly, of those patients with PTE, Zhao et al. (2012) reported that 66% developed seizures within the first 6 months, 9.9% between 7 and 12 months, 11.7% between 13 and 24 months, and 8.5% between 25 and 36 months. Further, Wang et al. (2013) examined 3,039 individuals with TBI and of the 9.8% that experienced PTS within the first 2 years, occurrence rates at 6 months and 1 year were 59.9% and 78.1%, respectively.

Although the risk of developing PTS is highest within months after the injury (Temkin 2001), the risk remains high for a period of years. As brain injury severity increases, the period of time for which a survivor is at risk of developing PTS also increases. After 5 years, adults with mild TBI no longer have a significantly increased risk relative to the general population (Annegers et al. 1998), whereas those with moderate or severe TBI or penetrating TBI remain at increased risk for more than 5 years post injury (Annegers et al. 1998; da Silva et al. 1992; Pagni 1990; Salazar et al. 1985. Moreover, military personnel suffering severe penetrating missile brain injuries show an elevated risk for more than 15 years after the injury (Annegers et al. 1998; Caveness et al. 1979; Feeney & Walker 1979; Salazar et al. 1985; Weiss et al. 1983). The incidence of seizures beginning later than 3 years post injury is 5% (Zhao et al. 2012).

Those with penetrating trauma typically have their first unprovoked seizure sooner than those patients with non-penetrating trauma (Kazemi et al. 2012). Unprovoked seizures occurred at a median time of one year post injury in a study of 50 participants (Di Luca & de Lacerda 2013); the former was influenced by injury severity, as well as age at the time of injury (Di Luca & de Lacerda 2013). In contrast, a study by Kazemi et al. (2012) found that for those with penetrating trauma, 78% had their first seizure within 1 year and 22% after 1 year. The mean latency to epilepsy onset was found to be shorter for mesial temporal sclerosis compared to lesional neocortical trauma (Gupta et al. 2014).

Recurrence

Seizure recurrence is an important factor in the determination of disability, likelihood of employment, and quality of life, and has been associated with increased health care costs (Baker et al. 1997; Van Hout et al. 1997; Yablon & Dostrow 2001). Some studies have reported that in patients who experienced early PTS, only one-half had a recurrence while another quarter experienced a total of only two to three seizures (De Santis et al. 1979; Kollevold 1979). In a recent study by Zhao et al. (2012) 5.7% of patients with TBI experienced seizures more than once a week, 69.5% more than once a month, and 24.8% had a seizure frequency greater than once a year. After Vagus Nerve Stimulation, patients with PTE demonstrated a greater reduction in seizure frequency, with 50% fewer seizures occurring at the 3 months and 7% fewer at 2 years compared to individuals with non-PTE after Vagnus Nerve Stimulation (Englot et al. 2012).

10.5 Clinical Picture of Post-Traumatic Seizures

Wiedemayer et al. (2002) retrospectively analyzed a consecutive series of 1868 adult patients with head injury and found that the first epileptic seizure was generalized in 69 patients (63.3%) and partial in 40 patients (36.7%). Fifty-eight patients (53.2%) experienced a second early seizure during the follow-up period. Based on multiple studies, the incidence by seizure type is as follows: complex or simple partial seizures with secondary generalization, 16%-77% (Di Luca & de Lacerda 2013; Kazemi et al. 2012; Zhao et al. 2012); generalized tonic-clonic seizures, 30 and 38% (Di Luca & de Lacerda 2013; Zhao et al. 2012); generalized atonic seizures, 2% (Di Luca & de Lacerda 2013); simple partial seizures, 14%; and complex partial seizures, 8.5% (Zhao et al. 2012).

There has also been a correlation found between the type and frequency of seizures; more specifically, those with simple or complex partial seizures experience a higher frequency of seizures (Kazemi et al. 2012). In a study examining 66 individuals who developed LPTS, it was determined that 79% had generalized seizures and 21% had focal seizures (Englander et al. 2003). Another study found focal epilepsy was the most common subtype of PTE, diagnosed in 93% of patients and arising most commonly from the temporal lobes and frontal lobes (Gupta et al. 2014). More specifically, 57% had temporal lobe epilepsy, 35% had frontal lobe epilepsy, 3% had parietal lobe epilepsy, and another 3% had occipital lobe epilepsy (Gupta et al. 2014).

Complications of Post-Traumatic Seizures

Seizures following TBI may themselves be a source of significant morbidity and it has been noted that the recurrence of seizures is an important cause of non-elective hospitalization in patients with severe TBI (Cifu et al. 1999). Potential complications include deterioration in cognitive and behavioural functioning and overall functional status, impaired neurological recovery, status epilepticus and death.

Q. List some of the complications of post-traumatic seizures.

Answer

- Deterioration in cognitive and behavioural functioning
- Negative impact on neurologic recovery
- Deterioration in overall functional status
- Status epilepticus
- Mortality
- Non-elective hospitalization
- Accidental injuries
- Reduction in employability
- Loss of driving privileges

Cognitive and Behavioural Function

Post-traumatic seizure disorders may lead to cognitive and behavioural disorders (Yablon & Dostrow 2001). Cognitive problems may arise during the interictal state in the absence of active seizures (Aarts et al. 1984; Binnie & Marston 1992). Patients with PTS can experience persistent behavioural abnormalities and a higher incidence of psychiatric-related hospitalizations even compared to patients with penetrating TBI who do not experience PTS (Swanson et al. 1995).

Influence on Neurologic Recovery

Neurological recovery can be influenced by PTS (Hernandez & Naritoku 1997; S. Yablon & Dostrow 2001). Yablon and Dostrow (2001) have noted that, in rodent models, brief and infrequent PTS occurring early after brain damage do not appear to impact functional recovery; however, more severe and widespread seizures occurring within the first 6 days post brain injury result in permanent impairments of functional recovery. Seizures occurring after the 6 day mark result in no change in somatosensory recovery (Hernandez & Naritoku 1997).

Functional Status

Recurrent PTS may exert a negative impact on functional status following TBI, an adverse effect independent of the severity of the injury (Barlow et al. 2000; Schwab et al. 1993). In the case of penetrating TBI, PTS have been reported to be an important and independent factor which affects both employment status and cognitive performance (Schwab et al. 1993). However, in the case of non-penetrating TBI, the impact of PTS on functional prognosis and cognition is less clear (Armstrong et al. 1990; Asikainen et al. 1999). Haltiner et al. (1997) found no significant differences at 1 year as a consequence of LPTS in terms of neuropsychological performance and psychosocial functioning when adjusting for injury severity. Asikainen et al. (1999) found that patients with PTS did have poorer outcomes on the Glasgow Outcome Scale, although there were no significant differences in employment outcome associated with the presence of PTS.

Status Epilepticus

Status epilepticus can be defined as either more than five minutes of continuous seizure activity or two or more sequential seizures without full recovery of consciousness between seizures. Status epilepticus is regarded as the most serious of the complications of PTS and may actually lead to additional neurological damage. Fortunately, clinically apparent status epilepticus is an infrequent complication of PTS (Kollevold 1979).

Mortality

In earlier studies mortality among those who sustain a TBI and develop PTS was reported to be high (Corkin et al. 1984; Walker & Blumer 1989; Walker & Erculei 1970). Recently, Englander et al. (2009) found mortality rates to be higher for those TBI patients who had been diagnosed with LPTS when compared with those who had no recorded history of LPTS. Those in the LPTS group who died tended to be younger than individuals who did not have LPTS. Earlier studies found that those patients with penetrating TBIs had a higher risk of dying; however, this is more likely due to the initial trauma rather than PTS (Rish & Caveness 1973; Rish et al. 1983). Yablon and Dostrow (2001) have noted that the complications of a single LPTS are no different than those seen after any seizure, and are generally minimal. However, increased seizure frequency and severity are associated with an increased risk of mortality and morbidity in the form of worsened cognition and overall function.

.10.6 Treatment of Post-Traumatic Seizures

Schierhout and Roberts (2001) reported that a seizure occurring soon after head injury may cause secondary brain damage by increasing the metabolic demands of the brain, increasing intracranial pressure, and leading to excessive amounts of neurotransmitter release. For this reason, the primary therapeutic objective in the use of anticonvulsant drugs has been the prevention of early seizures in an attempt to minimize the extent of secondary brain damage following TBI.

Some anticonvulsant drugs have been shown to have neuroprotective properties in animal studies. For example, following hypoxia, phenytoin has been linked with reduced neuronal damage in neonatal rats (Vartanian et al. 1996) and in rat hippocampal cell cultures (Tasker et al. 1992). Experimental evidence suggests that the neuroprotective effects of phenytoin are related to a blockage of voltage dependent sodium channels during hypoxia (Tasker et al. 1992; Vartanian et al. 1996) which would be expected to decrease the spread of calcium induced neurotoxicity following hypoxic brain injury. As noted by Schierhout and Roberts (2001), this suggests that anti-epileptics may have beneficial properties which may be independent of their proposed anti-seizure activity. Conversely, anti-epileptic drugs have shown toxic effects in stable patients, with impaired mental and motor function being the most common adverse effects; serious adverse effects including deaths as a result of hematological reactions have been also reported (Reynolds et al. 1998). Schierhout and Roberts (2001) have suggested that the injured brain's response to anticonvulsants may be such that toxic effects could be more pronounced and neurological recovery may be delayed.

Seizure Prevention or Prophylaxis

Initially, retrospective and non-randomized clinical trials in humans showed favourable results for the efficacy of anticonvulsant drug prophylaxis; however, prospective investigations of chronic prophylaxis for LPTS have been less impressive.

Q. What evidence is available regarding the prophylactic use of anticonvulsants after ABI?

Answer

- There is Level 1b evidence to suggest that levetiracetam is as safe and effective as phenytoin in the treatment and prevention of early seizures in individuals in the intensive care unit post ABI.
- There is Level 1b evidence that anticonvulsants given during the first 24 hours post ABI reduce the occurrence of early seizures (within the first week post injury).
- There is Level 1a evidence that anticonvulsants given shortly after the onset of injury do not reduce mortality or persistent vegetative state or the occurrence of late seizures (>1 week post injury).
- There is Level 1a evidence that seizure prophylactic treatment with either phenytoin or valproate results in similar incidences of early or late seizures and similar mortality rates.

When it comes to seizure prophylaxis, phenytoin is the most commonly studied medication. When the administration of phenytoin is compared to a placebo, its effect on the occurrence of early seizures is inconclusive; (Bhullar et al. (2014); Temkin et al. (1990)), found it to be effective but Young et al. (1983a) did not. However, Phenytoin was found to be no more effective than placebo in preventing late seizures (McQueen et al. 1983; Temkin et al. 1990; Young et al. 1983b). In fact, Formisano et al. (2007) found that the occurance of late seizures was significantly higher in patients treated with anti-epileptic medications than those who were not. It should be noted that Phenytoin has been shown to have a negative impact on recovery. Dikmen et al. (1991) found that severely injured individuals receiving phenytoin performed more poorly on neuropsychological measures than controls at 1 month but no significant differences were found at 1 year. The following year (12 to 24 months), phenytoin was shown to have a small but negative effect on cognition (Dikmen et al. 1991). Further, those taking phenytoin were shown to have longer hospital stays and worse functional outcomes at discharge than individuals receiving no treatment (Bhullar et al. 2014). Overall, there is not favourable evidence for the use of phenytoin for prevention of seizures.

A systematic review by Schierhout and Roberts (1998) found that the pooled relative risk for early seizure prevention was 0.34 (95% CI, 0.21-0.54, p=0.000). Based on that estimate, 10 people would need to be treated in the acute phase to keep one patient seizure free (Schierhout & Roberts 1998). Further, a Cochrane review that included 1218 patients considered to be at higher risk of PTE found that prophylactic anti-epileptics are effective in reducing early seizures (Schierhout & Roberts 2001).

When Phenytoin was compared to Levetiracetam, the two drugs were comparable in terms of seizure rates (Inaba et al. 2013; Kruer et al. 2013)(Jones et al. 2008), complications, adverse drug reactions, mortality rates (Inaba et al. 2013) and length of hospital stay (Kruer et al. 2013). An Randomized Controlled Trial (RCT) by Szaflarski et al. (2010) found similar results in terms of there being no

difference for early seizure rates, death or adverse events between the two drugs; however, the authors found that those on Levetiracetam performed significantly better on the Disability Rating Scale at 3 and 6months (p=0.042), and the Glasgow Outcome Scale at 6 months (p=0.039) post intervention compared to the Phenytoin group. A meta-analysis by Zafar et al. (2012) also concluded that there was no superiority of either drug at preventing early seizures.

Table 3. Summary of Randomized Controlled Trials Studying Prophylaxis for Early and Late Seizures

Authors/Year	N	Methods	Results	
			Early Seizures	Late Seizures
Temkin et al. (1990)	123	Phenytoin vs. Placebo	+	ND
Young et al. (1983a)a	244	Phenytoin vs. Placebo	ND	NA
Young et al. (1983b)b	179	Phenytoin vs. Placebo	NA	ND
McQueen et al. (1983)	164	Phenytoin vs. Placebo	NA	ND
Szaflarski et al. (2010)	52	Phenytoin vs. Levetiracetam	ND	NA
Temkin et al. (1999)	379	Phenytoin (1wk) vs. Valproate (1mo) vs. Valproate (6mo)	ND	ND
Manaka (1992)	191	Phenobarbital vs. No treatment	NA	ND

ND = No difference between groups; + = Improvement compared with control; - = Impairments compared with control; NA= Not applicable.

Table 4. Summary of Non-Randomized Controlled Trials Studying Prophylaxis of Early and Late Seizures

Authors/Year	N	Methods	Results	
			Early Seizures	Late Seizures
Gabriel et al. (2014)	19	Phenytoin vs. Levetiracetam **groups were not similar at baseline*	ND	ND
Inaba et al. (2013)	813	Phenytoin vs. Levetiracetam	ND	NA
Kruer et al. (2013)	109	Phenytoin vs. Levetiracetam	ND	NA
Jones et al. (2008)	27	Phenytoin vs. Levetiracetam	ND	NA
Bhullar et al. (2014)	93	Phenytoin vs. No prophylaxis	ND	NA
Formisano et al. (2007)	137	Anti-epileptic medication vs. no medication	NA	-
Watson et al. (2004)	404	Glucocorticoids (within 1d) vs. No glucocorticoids	NA	-

Note: ND=No difference between groups; +=Improvement compared with control; -=Impairment compared with control; NA=Not applicable.

Methylphenidate and Risk of Increased Seizures Post ABI

Q. Does methylphenidate used for the treatment of cognitive and behavioural problems post ABI increase the risk of seizures?

Answer

- There is Level 4 evidence that methylphenidate for the treatment of cognitive and behavioural problems can be safely used in patients with brain injury at risk for post-traumatic seizures as it is not associated with an increase in seizure frequency.

Wroblewski et al. (1992) conducted a case series involving 30 individuals with LPTS who had received methylphenidate. The authors found a trend toward a lesser incidence of seizures in patients receiving the methylphenidate treatment (p=0.063), with 13 patients reporting lower frequency of seizures during the medication period. During this time, 20 patients experienced no seizures, and 4 experienced an increase in seizure frequency.

Surgical Treatment of Post-Traumatic Seizures

Yablon and Dostrow (2001) noted the recent interest in a subgroup of patients with ABI who experience continued PTS despite treatment with multiple anticonvulsant drugs. For this special group of patients, surgical treatment may be a viable option.

Some studies have reported a decrease in seizures following surgical resection among a selected group of PTE patients (Diaz-Arrastia et al. 2000; Doyle et al. 1996). The major challenge in this treatment approach is the accurate localization of the exact region responsible for the development of seizures. This is particularly true for patients with severe ABI who frequently show multiple and bilateral sites of brain injury (Diaz-Arrastia et al. 2000).

Q. What evidence is available regarding the efficacy of surgical treatment of post-traumatic seizures?

Answer

- There is Level 4 evidence that a subgroup of patients with ABI (*those where the seizure focus can be accurately localized*) would benefit from surgical resection for post-traumatic seizures.
- There is Level 4 evidence that extratemporal resection is effective in controlling post-traumatic epilepsy.

Marks et al. (1995) reported that, in a cohort of 25 patients with PTS, it was possible to successfully localize the seizure focus in less than half of the sample. Subsequent surgical excision of the area presumed to be the seizure focus resulted in seizure reduction in all treated patients. In those patients who showed a favourable result, the brain injury lesion was specifically limited to the hippocampus or neocortex (Marks et al. 1995); thus, making the identification and surgical resection more accurate. This study supports that surgical excision of the seizure focus may only be a viable treatment option for a subgroup of ABI patients in whom the site of brain injury can be accurately identified. Therefore patients suffering severe ABI with multiple and bilateral localizations would not be suitable.

In a more recent study, Hakimian et al. (2012) retrospectively examined patients with TBI who had an extratemporal resection for PTE. The resection resulted in 28% of patients being seizure free, 50% had a reduction in seizure frequency, and 19% did not benefit from treatment. Overall, good to excellent outcomes were achieved and the risk of complications was found to be minimal.

Reference List

Aarts, J. H. P., Binnie, C. D., Smit, A. M., & Wilkins, A. J. (1984). Selective cognitive impairment during focal and generalized epileptic form EEG activity. *Brain, 107*(1), 293-308.

Aldenkamp, A. P. (1997). Effect of seizures and epileptiform discharges on cognitive function. *Epilepsia*, 38(Suppl 1), S52-S55.

Andelic, N., Hammergren, N., Bautz-Holter, E., Sveen, U., Brunborg, C., & Roe, C. (2009). Functional outcome and health-related quality of life 10 years after moderate-to-severe traumatic brain injury. *Acta Neurol Scand, 120*(1), 16-23.

Annegers, J. F. (1996). The epidemiology of epilepsy. In E. Wyllie (Ed.), *The treatment of epilepsy: principles and practice* (2 ed., pp. 165-172). Baltimore: Williams & Wilkins.

Annegers, J. F., Grabow, J. D., Groover, R. V., Laws, E. R., Jr., Elveback, L. R., & Kurland, L. T. (1980). Seizures after head trauma: a population study. *Neurology, 30*(7 Pt 1), 683-689.

Annegers, J. F., Hauser, W. A., Coan, S. P., & Rocca, W. A. (1998). A population-based study of seizures after traumatic brain injuries. *N Eng J Med, 338*(1), 20-24.

Armstrong, K. K., Sahgal, V., Bloch, R., Armstrong, K. J., & Heinemann, A. (1990). Rehabilitation outcomes in patients with posttraumatic epilepsy. *Arch Phys Med Rehabil, 71*(2), 156-160.

Ascroft, P. B. (1941). Traumatic Epilepsy After Gunshot Wounds of the Head. *Br Med J, 1*(4193), 739-744.

Asikainen, I., Kaste, M., & Sarna, S. (1999). Early and late posttraumatic seizures in traumatic brain injury rehabilitation patients: Brain injury factors causing late seizures and influence of seizures on long-term outcome. *Epilepsia, 40*(5), 584-589.

Baker, G. A., Nashef, L., & Van Hout, B. A. (1997). Current issues in the management of epilepsy: The impact of frequent seizures on cost of illness, quality of life, and mortality. *Epilepsia, 38*(Suppl.1), S1-S8.

Barlow, K. M., Spowart, J. J., & Minns, R. A. (2000). Early posttraumatic seizures in non-accidental head injury: Relation to outcome. *Dev Med Child Neurol, 42*(9), 591-594.

Bhullar, I. S., Johnson, D., Paul, J. P., Kerwin, A. J., Tepas, J. J., & Frykberg, E. R. (2014). More harm than good: Antiseizure prophylaxis after traumatic brain injury does not decrease seizure rates but may inhibit functional recovery. *J Trauma Acute Care Surg, 76*(1), 54-61.

Binnie, C. D., & Marston, D. (1992). Cognitive correlates of interictal discharges. *Epilepsia, 33*(Suppl. 6), S11-S17.

Bontke, C. F., Don Lehmkuhl, L., Englander, J., Mann, N., Ragnarsson, K. T., Zasler, N. D., . . . , Jung, C. (1993). Medical complications and associated injuries of persons treated in the traumatic brain injury model systems programs. *J Head Trauma Rehabil, 8*(2), 34-46.

Brain Injury Special Interest Group. (1998). Practice parameter: antiepileptic drug treatment of posttraumatic seizures. *Arch Phys Med Rehabil, 79*(5), 594-597.

Bushnik, T., Englander, J., Wright, J., & Kolakowsky-Hayner, S. A. (2012). Traumatic brain injury with and without late posttraumatic seizures: what are the impacts in the post-acute phase: a NIDRR Traumatic Brain Injury Model Systems study. *J Head Trauma Rehabil, 27*(6), E36-44.

Caveness, W. F. (1963). Onset and Cessation of Fits Following Craniocerebral Trauma. *J Neurosurg, 20*, 570-583.

Caveness, W. F., & Liss, H. R. (1961). Incidence of Post-traumatic Epilepsy. *Epilepsia, 2*(2), 123-129.

Caveness, W. F., Meirowsky, A. M., Rish, B. L., Mohr, J. P., Kistler, J. P., Dillon, J. D., & Weiss, G. H. (1979). The nature of posttraumatic epilepsy. *J Neurosurg, 50*(5), 545-553.

Cifu, D. X., Kreutzer, J. S., Marwitz, J. H., Miller, M., Hsu, G. M., Seel, R. T., . . . Zafonte, R. (1999). Etiology and incidence of rehospitalization after traumatic brain injury: A multicenter analysis. *Arch Phys Med Rehabil, 80*(1), 85-90.

Cohen, M., & Groswasser, Z. (1991). Epilepsy in traumatic brain-injured patients. *Epilepsia*, 32(Supp.1), S55.

Corkin, S., Sullivan, E. V., & Carr, F. A. (1984). Prognostic factors for life expectancy after penetrating head injury. *Arch Neurol, 41*(9), 975-977.

da Silva, A. M., Nunes, B., Vaz, A. R., & Mendonça, D. (1992). Posttraumatic epilepsy in civilians: clinical and electroencephalographic studies. *Acta Neurochir Suppl, 55*, 56-63.

da Silva, A. M., Vaz, A. R., Ribeiro, I., Melo, A. R., Nune, B., & Correia, M. (1990). Controversies in posttraumatic epilepsy. *Acta Neurochir Suppl, 50*, 48-51.

De Santis, A., Cappricci, E., & Granata, G. (1979). Early post traumatic seizures in adults. Study of 84 cases. *J Neurosurg Sci, 23*(3), 207-210.

De Santis, A., Sganzerla, E., Spagnoli, D., Bello, L., & Tiberio, F. (1992). Risk factors for late posttraumatic epilepsy. *Acta Neurochir Suppl , 55*, 64-67.

Di Luca, D. G., & de Lacerda, G. C. B. (2013). Time interval between traumatic brain injury and Post Traumatic Epilepsy. *Rev Neurocienc, 21*(2), 222-228.

Diamond, M. L., Ritter, A. C., Failla, M. D., Boles, J. A., Conley, Y. P., Kochanek, P. M., & Wagner, A. K. (2014). IL-1beta associations with posttraumatic epilepsy development: a genetics and biomarker cohort study. *Epilepsia, 55*(7), 1109-1119.

Diaz-Arrastia, R., Agostini, M. A., Frol, A. B., Mickey, B., Fleckenstein, J., Bigio, E., & Van Ness, P. C. (2000). Neurophysiologic and neuroradiologic features of intractable epilepsy after traumatic brain injury in adults. *Arch Neurol, 57*(11), 1611-1616.

Dikmen, S. S., Temkin, N. R., Miller, B., Machamer, J., & Winn, H. R. (1991). Neurobehavioral effects of phenytoin prophylaxis of posttraumatic seizures. *JAMA, 265*(10), 1271-1277.

Doyle, W. K., Devinsky, O., Perrine, K., Pacia, S., Vasquez, B., & Luciano, D. (1996). Surgical management of post-traumatic epilepsy who underwent surgical management. *Epilepsia, 37*(supp 5), 185.

Eide, P. K., & Tysnes, O. B. (1992). Early and late outcome in head injury patients with radiological evidence of brain damage. *Acta Neurol Scand, 86*(2), 194-198.

Englander, J., Bushnik, T., Duong, T. T., Cifu, D. X., Zafonte, R., Wright, J., . . . Bergman, W. (2003). Analyzing risk factors for late posttraumatic seizures: a prospective, multicenter investigation. *Arch Phys Med Rehabil, 84*(3), 365-373.

Englander, J., Bushnik, T., Wright, J. M., Jamison, L., & Duong, T. T. (2009). Mortality in late post-traumatic seizures. *J Neurotrauma, 26*(9), 1471-1477.

Englot, D. J., Rolston, J. D., Wang, D. D., Hassnain, K. H., Gordon, C. M., & Chang, E. F. (2012). Efficacy of vagus nerve stimulation in posttraumatic versus nontraumatic epilepsy. *J Neurosurg, 117*(5), 970-977.

Evans, J. (1962). Post-traumatic epilepsy. *Neurology, 12*, 665-674.

Feeney, D. M., & Walker, A. (1979). The prediction of posttraumatic epilepsy: A mathematical approach. *Arch Neurol, 36*(1), 8-12.

Ferguson, P. L., Smith, G. M., Wannamaker, B. B., Thurman, D. J., Pickelsimer, E. E., & Selassie, A. W. (2010). A population-based study of risk of epilepsy after hospitalization for traumatic brain injury. *Epilepsia, 51*(5), 891-898.

Formisano, R., Barba, C., Buzzi, M. G., Newcomb-Fernandez, J., Menniti-Ippolito, F., Zafonte, R., . . . Spanedda, F. (2007). The impact of prophylactic treatment on post-traumatic epilepsy after severe traumatic brain injury. *Brain Inj, 21*(5), 499-504.

Gabriel, W. M., & Rowe, A. S. (2014). Long-Term Comparison of GOS-E Scores in Patients Treated With Phenytoin or Levetiracetam for Posttraumatic Seizure Prophylaxis After Traumatic Brain Injury. *Ann Pharmacother, 48*(11), 1440-1444.

Glötzner, F. L., Haubitz, I., Miltner, F., Kapp, G., & Pflughaupt, K. W. (1983). Seizure prevention using carbamazepine following severe brain injuries. *Neurochirurgia, 26*(3), 66-79.

Grafman, J., Jonas, B., Salazar, A. (1992). Epilepsy following penetrating head injury to the frontal lobes. In D. E. A. Chauvel, E. Halgren, J. Bancaud (Ed.), *Advances in neurology* (Vol. 57 pp. 369-378). New York: Raven Press.

Gupta, P. K., Sayed, N., Ding, K., Agostini, M. A., Van Ness, P. C., Yablon, S., . . . Diaz-Arrastia, R. (2014). Subtypes of post-traumatic epilepsy: Clinical, electrophysiological, and imaging features. *J Neurotrauma, 31*(16), 1439-1443.

Hahn, Y. S., Fuchs, S., Flannery, A. M., Barthel, M. J., & McLone, D. G. (1988). Factors influencing posttraumatic seizures in children. *Neurosurgery, 22*(5), 864-867.

Hakimian, S., Kershenovich, A., Miller, J. W., Ojemann, J. G., Hebb, A. O., D'Ambrosio, R., & Ojemann, G. A. (2012). Long-term outcome of extratemporal resection in posttraumatic epilepsy. *Neurosurg Focus, 32*(3), E10.

Haltiner, A. M., Temkin, N. R., & Dikmen, S. S. (1997). Risk of seizure recurrence after the first late posttraumatic seizure. *Arch Phys Med Rehabil, 78*(8), 835-840.

Heikkinen, E. R., Rönty, H. S., Tolonen, U., & Pyhtinen, J. (1990). Development of Posttraumatic Epilepsy. *Stereotact Funct Neurosurg, 54*(1-8), 25-33.

Hendrick, E., Harris, L. (1968). Post-traumatic epilepsy in children. *J Trauma, 8*, 547-556.

Hernandez, T. D., & Naritoku, D. K. (1997). Seizures, epilepsy, and functional recovery after traumatic brain injury: A reappraisal. *Neurology, 48*(4), 803-806.

Inaba, K., Menaker, J., Branco, B. C., Gooch, J., Okoye, O. T., Herrold, J., . . . Demetriades, D. (2013). A prospective multicenter comparison of levetiracetam versus phenytoin for early posttraumatic seizure prophylaxis. *J Trauma Acute Care Surg, 74*(3), 766-771.

Japan Follow-up Group for Posttraumatic Epilepsy. (1991). The factors influencing posttraumatic epilepsy: multicentric cooperative study. . *No Shinkei Geka, 19*(12), 1151-1159.

Jennett, B. (1975). *Epilepsy after non-missile head injuries*. Chicago: William Heinemann.

Jennett, B., & Van De Sande, J. (1975). EEG prediction of post-traumatic epilepsy. *Epilepsia, 16*, 251-256.

Jones, K. E., Puccio, A. M., Harshman, K. J., Falcione, B., Benedict, N., Jankowitz, B. T., . . . Okonkwo, D. O. (2008). Levetiracetam versus phenytoin for seizure prophylaxis in severe traumatic brain injury. *Neurosurg Focus, 25*(4), E3.

Kalisky, Z., Morrison, D. P., Meyers, C. A., & Von Laufen, A. (1985). Medical problems encountered during rehabilitation of patients with head injury. *Arch Phys Med Rehabil, 66*(1), 25-29.

Kazemi, H., Hashemi-Fesharaki, S., Razaghi, S., Najafi, M., Kolivand, P. H., Kovac, S., & Gorji, A. (2012). Intractable epilepsy and craniocerebral trauma: analysis of 163 patients with blunt and penetrating head injuries sustained in war. *Injury, 43*(12), 2132-2135.

Kollevold, T. (1978). Immediate and early cerebral seizures after head injuries. Part III. *J Oslo City Hosp, 28*(6), 77-86.

Kollevold, T. (1979). Immediate and early cerebral seizures after head injuries. Part IV. *J Oslo City Hosp, 29*(4), 35-47.

Kruer, R. M., Harris, L. H., Goodwin, H., Kornbluth, J., Thomas, K. P., Slater, L. A., & Haut, E. R. (2013). Changing trends in the use of seizure prophylaxis after traumatic brain injury: a shift from phenytoin to levetiracetam. *J Crit Care, 28*(5), 883.

Manaka, S. (1992). Cooperative prospective study on posttraumatic epilepsy: risk factors and the effect of prophylactic anticonvulsant. *Jpn J Psychiatry Neurol, 46*(2), 311-315.

Marks, D. A., Kim, J., Spencer, D. D., & Spencer, S. S. (1995). Seizure localization and pathology following head injury in patients with uncontrolled epilepsy. *Neurology, 45*(11), 2051-2057.

McCrory, P. R., Bladin, P. F., & Berkovic, S. F. (1997). Retrospective study of concussive convulsions in elite Australian rules and rugby league footballers: phenomenology, aetiology, and outcome. *BMJ, 314*(7075), 171-174.

McQueen, J. K., Blackwood, D. H. R., Harris, P., Kalbag, R. M., & Johnson, A. L. (1983). Low risk of late post-traumatic seizures following severe head injury: Implications for clinical trials of prophylaxis. *J Neurol Neurosurg Psychiatry, 46*(10), 899-904.

National Hospital Discharge Survey. (2010). National Hospital Ambulatory Medical Care Survey (NHAMCS). *National Vital Statistics System (NVSS), CDC National Center for Health Statistics*.

Pagni, C. A. (1990). Posttraumatic epilepsy. Incidence and prophylaxis. *Acta Neurochir Suppl, 50*, 38-47.

Phillips, G. (1954). Traumatic Epilepsy After Closed Head Injury. *J Neurol Neurosurg Psychiatry, 17*(1), 1-10.

Pohlmann-Eden, B., & Bruckmeir, J. (1997). Predictors and dynamics of posttraumatic epilepsy. *Acta Neurol Scand, 95*(5), 257-262.

Reynolds, P. S., Gilbert, L., Good, D. C., Knappertz, V. A., Crenshaw, C., Wayne, S. L., . . . Tegeler, C. H. (1998). Pneumonia in dysphagic stroke patients: Effect on outcomes and identification of high risk patients. *Neurorehabil Neural Repair, 12*(1), 15-21.

Rish, B. L., & Caveness, W. F. (1973). Relation of prophylactic medication to the occurrence of early seizures following craniocerebral trauma. *J Neurosurg, 38*(2), 155-158.

Rish, B. L., Dillon, J. D., & Weiss, G. H. (1983). Mortality following penetrating craniocerebral injuries. An analysis of the deaths in the Vietnam Head Injury Registry population. *J Neurosurg, 59*(5), 775-780.

Salazar, A. M., Jabbari, B., Vance, S. C., Grafman, J., Amin, D., & Dillon, J. D. (1985). Epilepsy after penetrating head injury. I. Clinical correlates: A report of the Vietnam Head Injury Study. *Neurology, 35*(10), 1406-1414.

Sazbon, L., & Groswasser, Z. (1990). Outcome in 134 patients with prolonged posttraumatic unawareness. Part 1: Parameters determining late recovery of consciousness. *J Neurosurg, 72*(1), 75-80.

Schierhout, G., & Roberts, I. (1998). Prophylactic antiepileptic agents after head injury: A systematic review. *J Neurol Neurosurg Psychiatry, 64*(1), 108-112.

Schierhout, G., & Roberts, I. (2001). Anti-epileptic drugs for preventing seizures following acute traumatic brain injury. *Cochrane Database Syst Rev,* 4, CD000173.

Schwab, K., Grafman, J., Salazar, A. M., & Kraft, J. (1993). Residual impairments and work status 15 years after penetrating head injury: Report from the Vietnam head injury study. *Neurology, 43*(1), 95-103.

Swanson, S. J., Rao, S. M., Grafman, J., Salazar, A. M., & Kraft, J. (1995). The relationship between seizure subtype and interictal personality: Results from the Vietnam head injury study. *Brain, 118*(1), 91-103.

Szaflarski, J. P., Sangha, K. S., Lindsell, C. J., & Shutter, L. A. (2010). Prospective, randomized, single-blinded comparative trial of intravenous levetiracetam versus phenytoin for seizure prophylaxis. *Neurocrit Care, 12*(2), 165-172.

Tasker, R. C., Coyle, J. T., & Vornov, J. J. (1992). The regional vulnerability to hypoglycemia-induced neurotoxicity in organotypic hippocampal culture: Protection by early tetrodotoxin or delayed MK-801. *J Neurosci, 12*(11), 4298-4308.

Temkin, N. R. (2001). Antiepileptogenesis and seizure prevention trials with antiepileptic drugs: Meta-analysis of controlled trials. *Epilepsia, 42*(4), 515-524.

Temkin, N. R., Dikmen, S. S., Anderson, G. D., Wilensky, A. J., Holmes, M. D., Cohen, W., . . . Winn, H. R. (1999). Valproate therapy for prevention of posttraumatic seizures: A randomized trial. *J Neurosurg, 91*(4), 593-600.

Temkin, N. R., Dikmen, S. S., Wilensky, A. J., Keihm, J., Chabal, S., & Winn, H. R. (1990). A randomized, double-blind study of phenytoin for the prevention of post-traumatic seizures. *N Engl J Med, 323*(8), 497-502.

Van Hout, B., Gagnon, D., Souêtre, E., Ried, S., Remy, C., Baker, G., . . . McNulty, P. (1997). Relationship between seizure frequency and costs and quality of life of outpatients with partial epilepsy in France, Germany, and the United Kingdom. *Epilepsia, 38*(11), 1221-1226.

Vartanian, M. G., Cordon, J. J., Kupina, N. C., Schielke, G. P., Posner, A., Raser, K. J., . . . Taylor, C. P. (1996). Phenytoin pretreatment prevents hypoxic-ischemic brain damage in neonatal rats. *Brain Res, 95*(2), 169-175.

Walker, A. E., & Blumer, D. (1989). The fate of World War II veterans with posttraumatic seizures. *Arch Neurol, 46*(1), 23-26.

Walker, A. E., & Erculei, F. (1970). Post-traumatic epilepsy 15 years later. *Epilepsia, 11*(1), 17-26.

Walker, A. E., & Yablon, S. A. (1959). A follow-up of head injured men of Wordl War II. *J Neurosurg, 16*, 600-610.

Walker, A. E., & Yablon, S. A. (1961). *A follow-up study of head wound in World Ward II. Veterans administration medical monograph.* Washington DC: Us Government Printing Office.

Wang, H., Xin, T., Sun, X., Wang, S., Guo, H., Holton-Burke, C., & Pang, Q. (2013). Post-traumatic seizures-A prospective, multicenter, large case study after head injury in China. *Epilepsy Res, 107*(3), 272-278.

Watson, N. F., Barber, J. K., Doherty, M. J., Miller, J. W., & Temkin, N. R. (2004). Does glucocorticoid administration prevent late seizures after head injury? *Epilepsia, 45*(6), 690-694.

Weiss, G. H., Feeney, D. M., Caveness, W. F., Dillon, D., Kistler, J. P., Mohr, J. P., & Rish, B. L. (1983). Prognostic factors for the occurrence of posttraumatic epilepsy. *Arch Neurol, 40*(1), 7-10.

Wiedemayer, H., Triesch, K., Schäfer, H., & Stolke, D. (2002). Early seizures following non-penetrating traumatic brain injury in adults: Risk factors and clinical significance. *Brain Inj, 16*(4), 323-330.

Wiederholt, W. C., Melton, L. J., Annegers, J. F., Grabow, J. D., Laws, E. R., Jr., & Ilstrup, D. M. (1989). Short-term outcomes of skull fracture: a population-based study of survival and neurologic complications. *Neurology, 39*(1), 96-102.

Wroblewski, B. A., Leary, J. M., Phelan, A. M., Whyte, J., & Manning, K. (1992). Methylphenidate and seizure frequency in brain injured patients with seizure disorders. *J Clin Psychiatry, 53*(3), 86-89.

Yablon, S., & Dostrow, V. (2001). Post-traumatic seizures and epilepsy. In J. McDeavitt (ed.). *State of the Art Reviews in Physical Medicine and Rehabilitation: Traumatic Brain Injury (pp.301-318).* Philidelphia, Hanley, and Belfus.

Yablon, S. A. (1993). Posttraumatic seizures. *Arch Phys Med Rehabil, 74*(9), 983-1001.

Yeh, C. C., Chen, T. L., Hu, C. J., Chiu, W. T., & Liao, C. C. (2013). Risk of epilepsy after traumatic brain injury: A retrospective population-based cohort study. *J Neurol Neurosurg Psychiatry, 84*(4), 441-445.

Young, B., Rapp, R. P., Norton, J. A., Haack, D., Tibbs, P. A., & Bean, J. R. (1983a). Failure of prophylactically administered phenytoin to prevent early posttraumatic seizures. *J Neurosurg, 58*(2), 231-235.

Young, B., Rapp, R. P., Norton, J. A., Haack, D., Tibbs, P. A., & Bean, J. R. (1983b). Failure of prophylactically administered phenytoin to prevent late posttraumatic seizures. *J Neurosurg, 58*(2), 236-241.

Zafar, S. N., Khan, A. A., Ghauri, A. A., & Shamim, M. S. (2012). Phenytoin versus Leviteracetam for seizure prophylaxis after brain injury—A meta analysis. *BMC Neurol, 12, 30*.

Zhao, Y., Wu, H., Wang, X., Li, J., & Zhang, S. (2012). Clinical epidemiology of posttraumatic epilepsy in a group of Chinese patients. *Seizure, 21*(5), 322-326.