**Efficacy of anti-seizure drugs (ASDs) following traumatic brain injury (TBI)**

**A. Purpose of the Study**

Traumatic brain injury (TBI) is a leading cause of death and disability (Ghajar, 2000; Greenwald, 2003). TBI can cause several complications (Chauhan, 2014; Wortzel and Arciniegas, 2014), one of which is epilepsy (Frey, 2003). Seizures after TBI can be divided into three kinds - impact seizures (seizures that occur within 24 hours of the injury), early seizures (occurring within a week of the initial injury) and late seizures (seizures that occur after the first week following the initial injury; Annegers et al., 1980; Iudice and Murri, 2000). The current practice for TBI is administration of a prophylactic anti-seizure drug (ASD) for 7 days after the initial injury. This is because early seizures can increase one’s chances of having another seizure within the next two years (Haltiner et al., 1997; Frey, 2003). However, there is no documented evidence-based data showing that prophylactic ASD administration actually reduces seizure frequency later on (Temkin et al., 1990; Iudice and Murri, 2000); on the other hand, there is evidence that ASDs may be detrimental (Teasell, 2007).

Whether or not there is any long-term impact of ASD administration in subjects with TBI is not known. Hence, the purpose of this study is to examine whether prophylactic ASD administration actually decreases seizure frequency in the first week (acute) and later (chronic) after TBI, to provide evidence-based data for management of individuals with TBI.

**B. Background**

TBI is the leading cause of death worldwide (Greenwald et al., 2003; Maas et al., 2008) and disability (Zink, 2001). TBI can be mild, moderate or severe – approximately 10% of the cases are of severe TBI, whereas the rest are mild (Narayan et al., 2002; Meyer et al., 2008). TBI is associated with numerous complications, one of which is epilepsy (D'Ambrosio and Perucca, 2004). The incidence of seizures post-trauma ranges from 4.4 to 53% depending on the population and severity of the injury (Frey, 2003; Annegers and Coan, 2000). As many as 20% of all acquired epilepsy cases are due to TBI (Anegers, 1991; Lowenstein, 2000; Jabbari et al., 2002; Beghi et al., 2010). Over half of the population who has suffered a TBI develops post-traumatic seizures within 2 years, although the risk of seizures remains high as long as 10 years after the injury (Haltiner et al., 1997). As expected, the incidence of seizures after severe TBI is much higher than that after mild TBI (Haddad and Arabi, 2012).

Current practice parameters by the American Academy of Neurology (AAN; Chang and Lowenstein, 2003) and other studies (Temkin, 2009) suggest that administration of prophylactic ASD during the first week after traumatic injury reduces frequency of early post-traumatic seizures, but not late seizures, but other studies have shown that prophylactic ASD may be detrimental (Teasell, 2007).

The practice of administering ASD prophylactially is to prevent early seizures- this is under the premise that there is no ability to evaluate and monitor for seizures except clinical events. The majority of seizures in an ICU setting are subclinical. To know if a patient is truly seizing, one would need continuous EEG (cEEG) monitoring to examine the potential for early seizures. The AAN guideline recommendation (Chang and Lowenstein, 2003) of 1 week of ASD prophylaxis represents a reasonable compromise. The goal of this study is to use cEEG monitoring to provide evidence-based data on the use of ASDs in TBI to allow for better management and care of individuals with TBI. Another issue is the discrepancy in choice and dose of ASD prescribed – commonly used ASDs are Keppra (levetiracetam) and Cerebyx (fosphenytoin sodium), but which agent is most beneficial is not fully understood.

**C. Description of Methodology**

Patients admitted to Morristown Medical Center (a Level I Trauma center) with a diagnosis of TBI (and who provide with consent in the affirmative) will undergo cEEG monitoring for 7 days in addition to the routine standard of care provided for TBI. They will be administered an ASD (the control groups will not be administered ASD), and seizure frequency will be examined at regular intervals for 5 years following the TBI.

**D. Participant Selection**

(1) Eligibility Criteria - Any adult patient (18+ years of age) admitted to Morristown Medical Hospital with a diagnosis of TBI suspected within the previous 48 hours of admission.

(2) Exclusion Criteria - Patients admitted with a known history of epilepsy.

(3) Recruitment - Any patient meeting eligibility criteria will be offered an opportunity to participate in the study.

(4) Informed Consent

a. On admission, the purposes of the study will be explained to the patient and/or family members.

b. Patient and /or family members will be provided a copy of the consent form document (or provide rationale for waiver of consent documentation).

**E. Description of Agent(s) involved:**

All patients will undergo cEEG monitoring for 7 days in addition to the standard care. Half of the patients will be administered an ASD, whereas the other half will not be given an ASD. An ASD - Keppra (levetiracetam) or Cerebyx (fosphenytoin sodium) - will be given for 7 days by weight.

**F. Description of Potential Risks and (or) Adverse Effects:**

EEG monitoring is associated with an increased risk of skin breakdown or irritation; however, this is minor and quickly heals. Since all patients will undergo cEEG monitoring, we expect to detect subclinical seizures. If we observe such seizures in the ASD group, we will escalate the dose of ASD. If we observe subclinical seizures in the control group, they will be administered an ASD and seizure frequency will be monitored as planned.

**G. Description of Potential Benefits:**

Individuals who are admitted with TBI are administered prophylactic anti-seizure drugs (ASDs) for 7 days without a thorough understanding of whether AEDs in this situation are actually beneficial – actually, they may be detrimental. The reason this is the case is because most seizures in the ICU setting are observed seizures. This will enable us to better understand whether ASDs are actually beneficial in the long-term to prevent seizures in patients with TBI.

**References**

Ghajar J (2000) Traumatic brain injury, 356: 923–929.

Greenwald BD, Burnett DM, Miller MA (2003) Congenital and acquired brain injury. 1. Brain injury: epidemiology and pathophysiology. Arch Phys Med Rehabil. 84(3 Suppl 1):S3-7.

Chauhan NB (2014) Chronic neurodegenerative consequences of traumatic brain injury. Restor Neurol Neurosci. 32:337-365.

Wortzel HS, Arciniegas DB (2014) The DSM-5 approach to the evaluation of traumatic brain injury and its neuropsychiatric sequelae. NeuroRehabilitation. 34:613-623.

Frey LC (2003) Epidemiology of posttraumatic epilepsy: a critical review. Epilepsia 44 Suppl 10:11-7.

Annegers JF, Grabow JD, Groover RV, Laws ER Jr, Elveback LR, Kurland LT (1980) Seizures after head trauma: a population study 30:683-689.

Iudice A, Murri L (2000) Pharmacological prophylaxis of post-traumatic epilepsy. Drugs 59:1091-1099.

Haltiner AM, Temkin NR, Dikmen SS (1997) Risk of seizure recurrence after the first late posttraumatic seizure. Arch Phys Med Rehabil. 78:835-840.

Temkin NR, Dikmen SS, Wilensky AJ, Keihm J, Chabal S, Winn HR (1990) A randomized, double-blind study of phenytoin for the prevention of post-traumatic seizures. N Engl J Med.323:497-502.

Teasell R, Bayona N, Lippert C, Villamere J, Hellings C (2007) Post-traumatic seizure disorder following acquired brain injury Brain Injury 21: 201–214.

Maas AI, Stocchetti N, Bullock R (2008) Moderate and severe traumatic brain injury in adults. Lancet Neurol. 7:728-741.

Zink BJ (2001) Traumatic brain injury outcome: concepts for emergency care. Ann Emerg Med. 37:318-332.

Narayan RK, Michel ME, Ansell B, Baethmann A, Biegon A, Bracken MB, Bullock MR, Choi SC, Clifton GL, Contant CF, Coplin WM, Dietrich WD, Ghajar J, Grady SM, Grossman RG, Hall ED, Heetderks W, Hovda DA, Jallo J, Katz RL, Knoller N, Kochanek PM, Maas AI, Majde J, Marion DW, Marmarou A, Marshall LF, McIntosh TK, Miller E, Mohberg N, Muizelaar JP, Pitts LH, Quinn P, Riesenfeld G, Robertson CS, Strauss KI, Teasdale G, Temkin N, Tuma R, Wade C, Walker MD, Weinrich M, Whyte J, Wilberger J, Young AB, Yurkewicz L (2002) Clinical trials in head injury. J Neurotrauma. 19:503-557.

Meyer K, Helmick K, Doncevic S, Park R (2008) Severe and penetrating traumatic brain injury in the context of war. J Trauma Nurs. 15:185-189.

D'Ambrosio R, Perucca E (2004) Epilepsy after head injury. Curr Opin Neurol. 17:731-735.

Annegers J, Coan SP (2000) The risks of epilepsy after traumatic brain injury. Seizure 7:453-457.

Beghi E, Carpio A, Forsgren L, Hesdorffer DC, Malmgren K, Sander JW, Tomson T, Hauser WA (2010) Recommendation for a definition of acute symptomatic seizure. Epilepsia 51:671-675

Jabbari B, Prokhorenko O, Khajavi K, Mena H (2002) Intractable epilepsy and mild brain injury: incidence, pathology and surgical outcome. Brain Inj. 16:463-467.

Lowenstein DH (2011) Interview: the National Institute of Neurological Diseases and Stroke/American Epilepsy Society benchmarks and research priorities for epilepsy research. Biomark Med. 5:531-535.

Haddad SH, Arabi YM (2012) Critical care management of severe traumatic brain injury in adults. Scand J Trauma Resusc Emerg Med. 3; 20:12.

Chang BS, Lowenstein DH (2003) Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: antiepileptic drug prophylaxis in severe traumatic brain injury: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 60:10-16.

Teasell R, Bayona N, Marshall S, Cullen N, Bayley M, Chundamala J, Villamere J, Mackie D, Rees L, Hartridge C, Lippert C, Hilditch M, Welch-West P, Weiser M, Ferri C, McCabe P, McCormick A, Aubut JA, Comper P, Salter K, Van Reekum R, Collins D, Foley N, Nowak J, Jutai J, Speechley M, Hellings C, Tu L (2007) [A systematic review of the rehabilitation of moderate to severe acquired brain injuries.](http://www.ncbi.nlm.nih.gov/pubmed/17364527) Brain Inj. 21:107-112.

Temkin NR (2009) Preventing and treating posttraumatic seizures: the human experience. Epilepsia 50 Suppl 2:10-13.