Surgical Neurology International

OPEN ACCESS

For entire Editorial Board visit : http://www.surgicalneurologyint.com

Editor: **James I. Ausman**, MD, PhD University of California, Los Angeles, CA, USA

Original Article

Anti-epileptic prophylaxis in traumatic brain injury: A retrospective analysis of patients undergoing craniotomy versus decompressive craniectomy

Vivek Ramakrishnan, Robert Dahlin, Omid Hariri, Syed A. Quadri, Saman Farr, Dan Miulli, Javed Siddiqi

Department of Neurosurgery, Arrowhead Regional Medical Center, Colton, California, USA

E-mail: Vivek Ramakrishnan - vivekandhema@gmail.com; Robert Dahlin - robert.dahlin@nv.touro.edu; Omid Hariri - ohaririucla@gmail.com; *Syed A. Quadri - dr.saqader@gmail.com; Saman Farr - samanfarr@gmail.com; Dan Miulli - drdmnsx@compuserve.com; Javed Siddiqi - SiddiqiJ@armc.sbcounty.gov *Corresponding author

Received: 18 April 14 Accepted: 23 October 14 Published: 20 January 15

This article may be cited as:
Ramakrishnan V, Dahlin R, Hariri O, Quadri SA, Farr S, Miulli D, *et al.* Anti-epileptic prophylaxis in traumatic brain injury: A retrospective analysis of patients undergoing craniotomy versus decompressive craniectomy. Surg Neurol Int 2015;6:8.

Available FREE in open access from: http://www.surgicalneurologyint.com/text.asp?2015/6/1/8/149613

Abstract

Background: Seizures account for significant morbidity and mortality early in the course of traumatic brain injury (TBI). Although there is sufficient literature suggesting short-term benefits of antiepileptic drugs (AEDs) in post-TBI patients, there has been no study to suggest a time frame for continuing AEDs in patients who have undergone a decompressive craniectomy for more severe TBI. We examined trends in a levelII trauma center in southern California that may provide guidelines for AED treatment in craniectomy patients.

Methods: A retrospective analysis was performed evaluating patients who underwent decompressive craniectomy and those who underwent a standard craniotomy from 2008 to 2012.

Results: Out of the 153 patients reviewed, 85 were included in the study with 52 (61%) craniotomy and 33 (39%) craniectomy patients. A total of 78.8% of the craniotomy group used phenytoin (Dilantin), 9.6% used levetiracetam (Keppra), 5.8% used a combination of both, and 3.8% used topiramate (Topamax). The craniectomy group used phenytoin 84.8% and levetiracetam 15.2% of the time without any significant difference between the procedural groups. Craniotomy patients had a 30-day seizure rate of 13.5% compared with 21.2% in craniectomy patients (P = 0.35). Seizure onset averaged on postoperative day 5.86 for the craniotomy group and 8.14 for the craniectomy group. There was no significant difference in the average day of seizure onset between the groups P = 0.642.

Conclusion: Our study shows a trend toward increased seizure incidence in craniectomy group, which does not reach significance, but suggests they are at higher risk. Whether this higher risk translates into a benefit on being on AEDs for a longer duration than the current standard of 7 days cannot be concluded as there is no significant difference or trend on the onset date for seizures in either group. Moreover, a prospective study will be necessary to more profoundly evaluate the duration of AED prophylaxis for each one of the stated groups.

Key Words: Craniotomy, craniectomy, levetiracetam, phenytoin, seizure, traumatic brain injury, topiramate

Access this article online

Website: www.surgicalneurologyint.com

DOI: 10.4103/2152-7806.149613

Quick Response Code:

INTRODUCTION

Traumatic brain injury (TBI) remains one of the major causes of death and disability in the industrialized nations of the world. Although several preventive measures have been undertaken both at the government level as well as the private sector to reduce the morbidity and mortality associated with head trauma, it nonetheless continues to have a significant impact on society today.

Actual mortality from TBI has decreased in the past 30 years by approximately half, from 50% to 25%.[2] This reduction is not only due to more aggressive preventive measures to avoid TBI, but also a result of early and aggressive recognition and treatment of secondary factors that play a role in morbidity and mortality of TBI. Seizures in particular are a significant source of morbidity early in the course of TBI. In their study of head trauma patients in 1980, Annegers *et al*. found a 30% incidence of seizures less than 7 days following a severe TBI.[1] This study also found a marked decrease in seizure rates after 7 days, with a 10% seizure rate 2 years after the TBI. In a randomized double-blinded study in 1990, Temkins *et al*. further showed that phenytoin given during the early phase (first 7 days) post-TBI showed a significant reduction in seizure rates.[3] However, this rate reduction did not continue when phenytoin was given beyond 7 days post-TBI.

A further study in 1999 by Haltiner *et al*. found that there were no significant adverse effects of phenytoin when the drug was used for 2 weeks post-TBI.[5] The Brain Trauma Foundation began forming their guidelines in 1995 with continual modification using studies such as these. They also found level II evidence to recommend the use of antiepileptic drugs (AEDs) for 7 days post-TBI. Thus, there is sufficient established literature to suggest a benefit from antiepileptic medication in post-TBI patients for the short term, as well as in patients who have undergone a craniotomy as per a randomized double-blinded study by North *et al*. They found that a maximal benefit from phenytoin therapy was obtained within 2 weeks postoperatively.[6]

Although the literature suggests a benefit from AEDs for TBI patients postcraniotomy, there has been no literature to suggest a time frame for continuing AED in patients who have undergone a decompressive craniectomy for a more severe TBI. Decompressive craniectomy for TBI has been studied most prominently since the 1970s with prospective trials analyzing its usefulness in patients with acute subdural hematoma (SDH). Ransohoff and Benjamin were the first to describe hemicraniectomy in 1971 as a way to reduce overall mortality and morbidity in TBI.[7]

Recently there have been more studies advocating the use of craniectomy in both TBI and in patients suffering from malignant cerebral edema as a consequence of ischemic cerebrovascular accident, most commonly as a lifesaving technique. The use of hemicraniectomy is being reinvestigated now with recent studies such as Ecker *et al*., who retrospectively studied the outcomes of craniectomies in soldiers from the wars in Iraq and Afghanistan. This study found that 60% of patients who underwent a hemicraniectomy for the treatment of penetrating TBI to either bilateral cortex or supratentorial and infratentorial injury showed a "good" Glasgow outcome score.[4]

In light of the amount of literature concerning the use of AEDs in TBI patients, as well as the emerging body of literature on the potential benefits of hemicraniectomy in this same patient population; there is a relative lack of discussion in the literature on the use of AEDs in hemicraniectomy patients. No clear studies have been undertaken to establish the optimal days of therapy for patients with TBI who require a hemicraniectomy. Furthermore, there have been no studies to demonstrate whether the general practice of administering phenytoin for 7 days post-TBI actually applies to patients that have one or more bone flaps removed.

This study questions whether or not there exists a relationship between seizure rates, treatment time, and complications from postTBI patients who have undergone a hemicraniectomy at a busy level-II trauma center in southern California. Our aim is to find any associations in this patient population that may ultimately give more clear guidelines on AED therapy for patients who have had portions of their skull removed. These guidelines would clearly have an impact on the management and complication rates of these patients, both in the hospital as well as the intensive care unit (ICU) setting, with associated costs and financial ramifications for the care of these patients.

MATERIALS AND METHODS

Approval was obtained by our Institutional Review Board (IRB) to conduct a retrospective data analysis of patient information. Our primary database was the hospital patient census of the neurosurgery department from 2008 to 2012. We began by documenting all patients who had undergone a decompressive craniectomy operation with bone flap left off and all patients who had undergone a standard craniotomy operation with bone flap left on. Craniectomy versus craniotomy was decided based on initial computed tomography (CT) of the head and the degree of cerebral edema and contusion associated with the traumaticbrain injury. Moreover, it was determined intraoperatively based on the degree of cerebral swelling and on the surgeon's decision.

The selection criteria from this aforementioned population included trauma patients over the age of

18 years. We excluded all patients who underwent craniectomy or craniotomy for any reason other than head trauma, such as aneurysmal subarachnoid hemorrhage or malignant cerebral edema from an ischemic stroke. We also excluded any patient with a prior history of seizure, any patient with a prior history of taking an AED, and any patient who seized upon initial arrival in the emergency department or trauma bay prior to receiving initial AED. In addition, we excluded patients who expired within 24 h of hospital arrival.

Seizure was defined as any episode of either generalized or partial epileptiform activity who took place in TBI patients. Seizure diagnosis was made on a purely clinical basis without the necessity of EEG verification. EEG was only used in a confirmatory role when the diagnosis was unclear, or when checking for possible 'silent' seizure activity, such as silent status epilepticus.

We then analyzed both groups in terms of seizure incidence (both generalized and partial), day of seizure onset, AED used, initial Glasgow Coma Scale (GCS), discharge GCS, amount of midline shift (MLS) on initial CT scan, whether or not the trauma was penetrating, and 30- day outcome. We based our outcome data primarily on follow up notes conducted in neurosurgery clinic or in other outpatient clinic notes. All information was obtained from medical records as well as radiology department imaging records and documents. Statistical analysis was carried out using SPSS software using *t*-test analysis with a statistical significance level set at $P < 0.05$.

RESULTS

We began with an initial cohort of 153 patients, 88 patients in the craniotomy group and 65 patients in the craniectomy group. After the above-mentioned exclusion criteria were imposed, there were a total of 85 patients included within the study: 52 in the craniotomy group and 33 in the craniectomy group. (See Table 1). The sex distributions between the groups were 80.8% male in the craniotomy group and 81.8% male in the craniectomy group and not statistically significant. However, the craniectomy cohort was significantly younger than the craniotomy group (aged: 35.6 vs. 46.4 years; $P = 0.022$).

Among the two groups, the type and nature of injury (degree of penetration) as well as the side of injury and extent of MLS were noted. The craniotomy group had a 38.5% incidence of isolated epidural hematoma (EDH), 1.9% had combined EDH and traumatic intraparenchymal hemorrhage (IPH), 3.8% had combined EDH and SDH, 9.6% had isolated IPH, and 46.2% had isolated SDH. The craniectomy group had a 15.2% incidence of isolated EDH, 3.0% combined EDH and SDH, 9.1% isolated IPH, and 72.7% isolated SDH. The craniectomy group had greater MLS than the craniotomy group (9.33 vs. 6.33 mm, $P = 0.009$). The stated 15.2% of craniectomies performed for isolated EDH included cerebral edema as well as cerebral contusion associated with EDH.

Table 1: Trends in patient population undergone craniotomy versus decompressive craniectomy

	Craniotomy	Craniectomy	*P*
N	52	33	
Gender			
Male	80.8%	81.8%	0.9
Female	19.2%	18%	0.63
Age	46.4	35.6	0.022
Penetrating	7.7%	6.1%	0.77
Side			
Left	44.2%	42.4%	0.87
Right	48.1%	54.5%	0.56
Bilateral	7.7%	3.0%	0.37
MLS	6.33 mm	9.3m m	0.009
Initial GCS	11.67	6.76	<0.001
Final GCS	13.74	8.24	<0.001
Antiepileptics			
Dilantin	78.8%	84.8%	0.49
Keppra	9.6%	15.2%	0.44
Outcome at day 30			
Seizure	3	21.2%	0.35
Lost to follow-up	5	15.2%	0.79
Death	3.8%	33.3%	<0.001

MLS: Midline shift, GCS: Glasgow coma scale

The craniectomy group had significantly less EDH ($P = 0.021$), and significantly more SDH ($P = 0.016$), without any difference in IPH. The craniotomy group versus the craniectomy group did not demonstrate a significant difference in the incidence of penetrating trauma (7.7% vs. 6.1%, respectively). Most craniotomies and craniectomies were left-sided (44.2% vs. 42.2%).

Of the clinical variables analyzed, the mean initial GCS of craniotomy patients (11.67) was significantly higher than the GCS in the craniectomy patients (6.76; $P < 0.001$). Mean final GCS on discharge from hospital was 13.74 in craniotomy patients and 8.24 in craniectomy patients ($P < 0.001$). Of the seven seizures observed in the craniotomy group, five were grand mal, one was complex partial, and one was simple partial. Out of the seven seizures in the craniectomy group, six were grand mal and one was partial seizure.

At our institution, Dilantin is the first line agent and Keppra is the second line agent for AED prophylaxis in patients with head trauma. If Keppra is not satisfactory and the patient continues to have breakthrough seizures on EEG, the Department of Neurology is

consulted to determine whether to start the patient on Depakote (Divalproex Sodium), Topamax, or Phenobarbital. In the mentioned cases, based on patient's medical history and EEG, it was determined by Neurology that Topamax would be the AED of choice. All AEDs started from when the patient presented, Day 1 (trauma).

In the caraniotomy group, 17 patients were treated with AEDs for 7 days, 23 patients between 8 and 14 days, 8 patients between 15 and 30 days, 3 patients were treated with AEDs longer than 1 month, and 1 patients was for an unknown duration. In the craniectomy group, 17 patients were treated with AEDs for 7 days, 3 patients between 8 and 14 days, 9 patients between 15 and 30 days, and 4 patients were treated with AEDs longer than 1 month. There was no significant difference in the frequency of AEDs used in the two groups. The craniotomy group used phenytoin (Dilantin) 78.8% of the time, levetiracetam (Keppra) 9.6%, a combination of both 5.8%, and topiramate (Topamax) 3.8% of the time. In contrast, the craniectomy group used phenytoin 84.8% of the time and levetiracetam 15.2% of the time.

Seizure rates did not significantly differ between craniotomy patients (13.5% 30-day seizure rate) and craniectomy patients (30-day seizure rate 21.2%; $P = 0.35$). Of the craniotomy and craniectomy groups 17.3% and 15.2%, respectively, were lost to follow up. A significantly fewer proportion of craniotomy patients (3.8%) died by30 days as opposed to craniectomy patients (33.3%; $P < 0.001$). Seizure onset did not differ significantly by postoperative day between the two groups; 5.86 days in the craniotomy cohort and 8.14 days in the craniectomy cohort ($P = 0.642$) [Figure 1]. The mean hospital duration was also not statistically significantly. Craniotomy patients were discharged on postoperative day 14.52 (mean) and craniectomy patients were discharged on postoperative day 15.73 ($P = 0.702$).

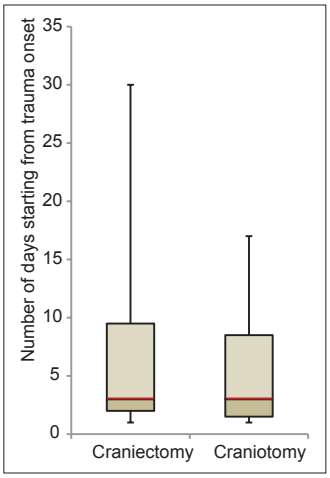

Figure 1: Box plot showing the distribution of day of onset of seizures in postcraniotomy and postcraniectomy patients starting from the day of trauma onset. The center red line represents the median day of seizure onset (i.e. day 3) with adjacent box representing first and third quartiles of data. Wiskers represent the minimum and maximum values of collected data

DISCUSSION

Our primary objective in this study is to examine the association between seizure rates and seizure prophylaxis in TBI patients undergoing decompressive craniectomy versus those undergoing a standard craniotomy. We questioned whether the usual 7- day course of antiepileptic prophylaxis established by Temkins *et al.*, and now widely used within the neurosurgical community for the TBI population, could be applied to this specific subset of patients.[3] Our goal was to examine if patients with large portions of their skull removed would be at a higher risk of seizures than patients with their bone flap left in place, even when placed on AEDs. We also wanted to explore whether the Temkins '7 day rule' could apply to craniectomy patients just as well as it does with other types of brain trauma patients.

In our study, we found that patients who underwent decompressive craniectomy for TBI had a statistically higher morbidity and mortality than their counterparts who had a retained bone flap. This may be attributable to the extent of brain injury in the craniectomy cohort even prior to neurosurgical intervention evidenced by the lower GCS score on presentation.

In light of the fact that the craniectomy group involved a much more critical subset of patients, we sought to find similarities and differences between both groups in terms of seizure rate. Although the craniectomy group of patients did have a higher rate of partial and generalized seizures compared with the craniotomy group while on AEDs, the difference was not statistically significant. Furthermore, our primary objective was to study whether or not the number of days of seizure prophylaxis differed for the craniectomy group versus the craniotomy group. We found that seizure onset by postoperative day did not differ significantly between the craniectomy group and the craniotomy group. We suggest that craniectomy patients should be treated the same as craniotomy patients in terms of antiepileptic prophylaxis timeframes.

Temkins' study in 1990 underscores the brain trauma guidelines practiced today in the United States and worldwide, where head trauma patients with no prior history of seizure are given AED for up to 7 days posttrauma, as this is seen as the highest riskperiod of having a posttraumatic seizure.[2] However, Haltiner's study in 1999, which underscored a 2- week period of maximum benefit (specifically using Dilantin), shows that there is some variability in the timeframe of

prophylaxis.[5] Therefore, it is difficult to say whether one can focus on a specific timeframe when it comes to antiepileptic prophylaxis and most likely, this treatment regimen is highly patient-specific. In our examination of the medical records from the past several years, we noticed wide variability in the time frame of AEDs for craniectomy patients. Some practitioners preferred 7 days, others 2 weeks, and still others preferred 1 month of prophylaxis. Some of these patients who were placed on AEDs for longer periods of time did not even have a past history of seizures, and did not seize during the above time-frame.

Up to this point we have been unable to find a study detailing antiepileptic prophylaxis timeframes in patients who underwent decompressive craniectomy for TBI. Although our study shows no significant difference between the craniotomy and craniectomy groups for number of days of prophylaxis, some important considerations need to be made. First and foremost, this study could benefit from a higher power with a larger cohort. In the future we may be able to recruit patient information from other large hospitals in order to find out if these results are magnified or differ with a higher power study. Second, these two groups were not matched in terms of the clinical condition of the patient, co-morbidities, and risk factors for other medical conditions including seizure. The craniectomy group involved a much more critical subset of patients, which impacted the outcomes of that group. Third, although we can draw associations between data points, we cannot prove causality in this retrospective review. Although we attempted to keep the groups as equal as possible by introducing exclusion criteria, fundamental differences continue to remain.

CONCLUSION

Antiepileptic prophylaxis for trauma patients represents a routine but nevertheless important area in trauma neurosurgery. With this study, we sought to examine a subset of patients with TBI and to determine whether the standard 7-day course of antiseizure prophylaxis could be extrapolated to craniectomy patients, or whether these patients were at higher risk for seizures posttrauma and required a longer course of treatment. Our study shows a trend toward increased seizure incidence in craniectomy group that does not reach significance, but suggests they are at higher risk. Whether this higher risk translates into a benefit on being on AEDs for a longer duration than the current standard of 7 days cannot be concluded as there is no significant difference or trend on the onset date for seizures in either group. Moreover, a prospective study will be necessary to more profoundly evaluate the duration of AED prophylaxis for each one of the stated groups.

REFERENCES

1. Annegers JF, Grabow JD, Groover RV, Laws ER Jr, Elveback LR, Kurland LT. Seizures after head trauma: A population study. Neurology 1980;30:683-9.
2. The role of antiseizure prophylaxis following head injury. Brain Trauma Foundation: Antiseizure prophylaxis. J Neurotrauma 2007;24:S83-6.
3. Dikmen SS, Temkin NR, Miller B, Machamer J, Winn HR. Neurobehavioral effects of phenytoin prophylaxis of posttraumatic seizures. JAMA 1991;265:1271-7.
4. Ecker RD, Mulligan LP, Dirks M, Bell RS, Severson MA, Howard RS, *et al*. Outcome of 33 patients from the wars in Iraq and Afghanistan undergoing bilateral or bicompartmental craniectomy. J Neurosurg 2011;115:124-9.
5. Haltiner AM, Newell DW, Temkin NR, Dikmen SS, Winn HR. Side effects and mortality associated with use of phenytoin for early posttraumatic seizure prophylaxis. J Neurosurg 1999;91:588-92.
6. North JB, Penhall RK, Hanieh A, Frewin DB, Taylor WB. Phenytoin and postoperative epilepsy: A doubleblind study. J Neurosurg 1983;58:672-7.
7. Ransohoff J, Benjamin V. Hemicraniectomy in the treatment of acute subdural hematoma. J Neurol Neurosurg Psychiatry 1971;34:106.