More harm than good: Antiseizure prophylaxis after traumatic brain injury does not decrease seizure rates but may inhibit functional recovery

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BACKGROUND: The purposes of this study were to examine the current Brain Trauma Foundation recommendation for antiseizure prophylaxis with phenytoin during the first 7 days after traumatic brain injury (TBI) in preventing seizures and to determine if this medication affects functional recovery at discharge.

METHODS: The records of adult (age ≥ 18 years) patients with blunt severe TBI who remained in the hospital at least 7 days after injury were retrospectively reviewed from January 2008 to January 2010. Clinical seizure rates during the first 7 days after injury and functional outcome at discharge were compared for the two groups based on antiseizure prophylaxis, no prophylaxis (NP) versus phenytoin prophylaxis (PP). Statistical analysis was performed using χ^2.

RESULTS: A total of 93 adult patients who met the previously mentioned criteria were identified (43 [46%] NP group vs. 50 [54%] PP group). The two groups were well matched. Contrary to expectation, more seizures occurred in the PP group as compared with the NP group; however, this did not reach significance (PP vs. NP, 2 [4%] vs. 1 [2.3%], $p = 1$). There was no significant difference in the two groups (PP vs. NP) as far as disposition are concerned, mortality caused by head injury (4 [8%] vs. 3 [7%], $p = 1$), discharge home (16 [32%] vs. 17 [40%], $p = 0.7$), and discharge to rehabilitation (30 [60%] vs. 23 [53%], $p = 0.9$). However, with PP, there was a significantly longer hospital stay (PP vs. NP, 36 vs. 25 days, $p = 0.04$) and significantly worse functional outcome at discharge based on Glasgow Outcome Scale (GOS) score (PP vs. NP, 2.9 vs. 3.4, $p < 0.01$) and modified Rankin Scale score (2.3 ± 1.7 vs. 3.1 ± 1.5, $p = 0.02$).

CONCLUSION: PP may not decrease early posttraumatic seizure and may suppress functional outcome after blunt TBI. These results need to be verified with randomized studies before recommending changes in clinical practice and do not apply to penetrating trauma. (*J Trauma Acute Care Surg*. 2014;76: 54–61. Copyright © 2014 by Lippincott Williams & Wilkins)

LEVEL OF EVIDENCE: Therapeutic study, level IV; epidemiologic study, level III.

KEY WORDS: Phenytoin; antiseizure prophylaxis; functional outcome; traumatic brain injury.

Traumatic brain injury (TBI) is the leading cause of death and disability among children and young adults in the United States.[1] Every year, of the 1.7 million patients who sustain a TBI, approximately 230,000 are hospitalized and survive, 90,000 experience long-term disability, and 50,000 die.[1] One of the complications that may occur after TBI is posttraumatic seizures (PTSs). These seizures are traditionally classified into early, occurring within 7 days of injury, or late, occurring after 7 days of injury. Because of insufficient data, the Brain Trauma Foundation currently provides only a Level II recommendation for prophylactic antiepileptic drug (AED) use (phenytoin [PHE] or valproate) to decrease the incidence of early PTS.[2] These recommendations are heavily based on the single randomized Class II study performed over two decades ago by Temkin et al.[3] who demonstrated a significant reduction in the incidence of early PTS from 14.2% to 3.6% ($p < 0.001$) with the treatment of PHE as compared with placebo. Although there was a second randomized study performed in 1983 by Young et al.[4] who reported that PHE was not effective in preventing early PTS, this study has been largely discounted and lowered to Class III data owing to methodological flaws. Given the paucity of randomized studies with conflicting findings, compliance for AED prophylaxis among neurosurgeons has been poor. A 1996 survey of 127 neurosurgical departments in Europe demonstrated that antiseizure prophylaxis was provided after TBI as follows: always (12%), never (36%), and sometimes (52%).[5] A more recent 2007 Canadian survey evaluated 32 hospitals and 247 physicians (99 neurosurgeons and 148 critical care) regarding the management of a traumatic epidural hematoma (EDH) with midline shift. PHE prophylaxis was graded as "uncertain appropriateness."[6]

Along with its controversial protection against early seizures, PHE prophylaxis may be associated with worse functional outcomes. In 1991, Dikmen et al.[7] performed a secondary analysis of the randomized data from the trial of Temkin et al.[3] and found a significantly impaired performance on neuropsychological tests at 1 month in severe TBI patients maintained on PHE. One possible reason for this may be that PHE is not without adverse effects and has been associated with fever, somnolence, and cognitive supression.[8–18]

The purpose of this study was to compare the early seizure rate and functional outcome at discharge (as measured by Glasgow Outcome Scale [GOS] score and modified Rankin Scale [mRS] score) for patients who received no antiseizure prophylaxis with those that received PHE.

PATIENTS AND METHODS

The records of adult (age ≥ 18 years) patients with blunt severe TBI (positive computed tomography [CT] scan result of the head and admission Glasgow Coma Scale [GCS] score of 3–8) who remained in the hospital at least 7 days after injury at a Level I trauma center were retrospectively reviewed from January 2008 to January 2010 using the National Trauma Registry of the American College of Surgeons. Positive CT scan result was defined by the presence of one or more of the following: subarachnoid hemorrhage (SAH), intracerebral hemorrhage (ICH), subdural hematoma (SDH), EDH, or diffuse axonal injury (DAI). PTSs were divided into two groups: (1) early (first 7 days after injury) and (2) late (>7 days after injury). Patients excluded from the original data set included those with GCS score of 9 to 15, antiseizure prophylaxis with levetiracetam (LEV), seizure in the field or en route or upon arrival to the trauma bay before possible AED loading opportunity, and catastrophic brain injury with death within 72 hours of hospital admission. GCS score of 9 to 15 were excluded because the majority of these patients (81%) were discharged before the required study period of 7 hospital days. The LEV group was excluded because worse functional outcome with AED has primarily been reported with PHE use.

The Brain Trauma Foundation guidelines were followed for the management of the TBI.[2] However, the use of AED prophylaxis varied (none, PHE, or LEV) based on the judgment of the neurosurgeon on call after his or her review of the case. PHE seizure prophylaxis was administered with a loading dose of PHE 20 mg/kg intravenously (IV) (maximum, 2,000 mg) and then a maintenance dose (5 mg/kg/d, IV every 8 hours). PHE serum levels were checked, and dosing was adjusted by an institutional pharmacist as needed to maintain therapeutic free levels of 1 μg/mL to 2 μg/mL. Once tolerating a diet, the dosing was switched to oral administration. Patients were maintained on study medications for 7 days. If there were no clinical seizures at that time, medication was discontinued after discussion and approval of the neurosurgeon. In the event of a seizure, the antiseizure medication was individualized based on the neurosurgeon recommendations.

Data collected included demographic information, mechanism of injury, admission GCS score, Injury Severity Score (ISS), and Abbreviated Injury Scale (AIS) score for the head, operative procedures, head CT results, type of TBI (SAH, SDH, EDH, ICH, and/or DAI), AED prophylaxis (none vs. PHE vs. LEV), PHE levels, disposition, GOS score at discharge, and mRS score at discharge. Marshall scores were calculated from the initial head CT scan.[19] Hospital length of stay (LOS), intensive care unit (ICU) LOS, ventilation days, complications, clinical seizures, drug adverse events, and mortality were also recorded. Patients were divided into two groups (no prophylaxis [NP] vs. PHE prophylaxis [PP]) based on antiseizure prophylaxis provided during the period of first 7 days after TBI. The primary end point of the study was early clinical seizure rate (first 7 days after TBI). The secondary end points were functional outcome at discharge (as measured by GOS and mRS scores), LOS, mortality (mortalities caused by other causes outside TBI were excluded), and disposition (home or rehabilitation). Data are presented as the mean ± SEM. Numerical variables were analyzed by the analysis of variance, and categorical variables were analyzed by Fisher's exact test and χ^2 test. A $p < 0.05$ was considered statistically significant.

This study included only the hospital course of patients until discharge. Although all patients were provided follow-up in our outpatient clinics, there are no data as to the long-term functional recovery after hospital discharge. The University of Florida College of Medicine–Jacksonville Institutional Review Board reviewed and approved the study protocol.

RESULTS

There were 766 patients identified with a CT scan positive for blunt TBI from January 1, 2008, to December 31, 2010. A total of 144 (19%) had LEV prophylaxis, 450 (59%) had a GCS score of 9 to 15, 76 (10%) had a catastrophic brain injury with death within 72 hours of hospital admission, and 3 (0.4%) had a seizure in the field, en route, or upon arrival to the trauma bay before possible AED loading opportunity. These were all excluded from further analysis. The remaining 93 (12%) were then divided into the two study groups (NP, 43 [6%] vs. PP, 50 [6%]). There was no significant difference in the clinical seizure rate between the two groups during the period of first 7 days after TBI (NP vs. PP, 1 (2.3%) vs. 2 (4.0%), $p = 1$) (Fig. 1).

The two groups were well matched (Table 1). Comparison of the demographic and clinical characteristics of these two groups (NP vs. PP) indicated no significant differences in age (36 ± 16 years vs. 41 ± 16 years, $p = 0.53$), sex (male, 65% vs. 84%, $p = 0.63$), ISS (26 ± 10 vs. 27 ± 11, $p = 0.95$), or AIS score (3.8 ± 0.8 vs. 4.0 ± 0.8, $p = 0.42$), respectively (Table 1). There was no significant difference in the mechanism of injury for the two groups (NP vs. PP) with motor vehicle crash being the most common cause (47% vs. 28%; $p = 0.23$). With regard to the type of injuries noted, both groups (NP vs. PP) had a similar rate of skull fractures (35% vs. 30%, $p = 0.83$) with SAH (61% vs. 62%, $p = 1.0$), followed by ICH (37% vs. 52%, $p = 0.46$) being the most common injuries

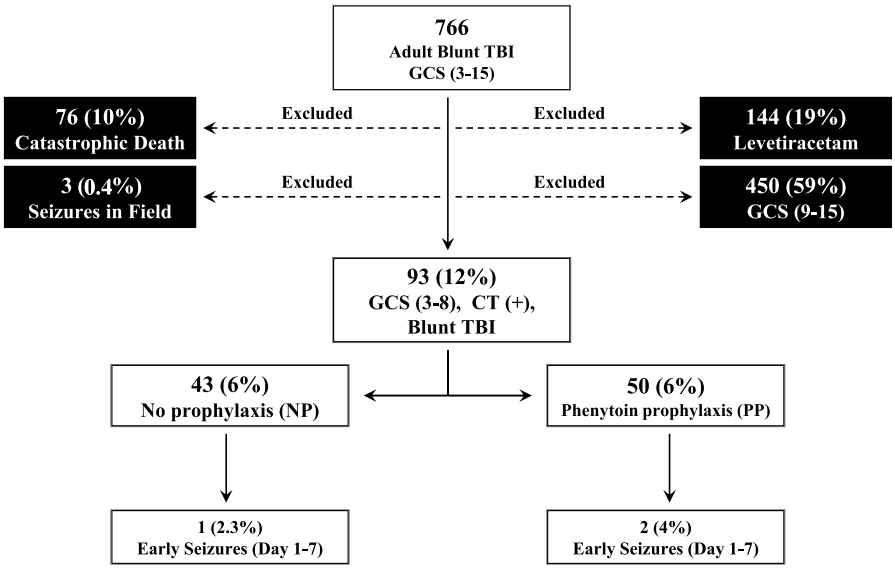

Figure 1. Flow chart of the antiseizure prophylaxis of 93 adult trauma patients with GCS score of 3 to 8 during the first 7 days after blunt TBI and the resultant clinical seizure rate (NP vs. PP, 2% vs. 4%, $p = 1$).

TABLE 1. Demographic and Clinical Variables According to Antiseizure Prophylaxis Regimen for Blunt TBI Patients

Variable	NP (n = 43)	PP (n = 50)	Statistical Significance
Male	28 (65%)	42 (84%)	NS
Female	15 (35%)	8 (16%)	NS
Age	36 ± 16	41 ± 18	NS
ISS	26 ± 10	27 ± 11	NS
AIS	3.8 ± 0.8	4.0 ± 0.8	NS
Admission SBP	129 ± 25	129 ± 24	NS
Mechanism of injury			
MVC	20 (47%)	14 (28%)	NS
MCC	7 (16%)	7 (14%)	NS
PEDS	5 (12%)	7 (14%)	NS
Fall	6 (14%)	12 (24%)	NS
Assault	2 (5%)	5 (10%)	NS
Other	3 (6%)	5 (10%)	NS
CT of head data			
Skull fracture	15 (35%)	15 (30%)	NS
SAH	26 (61%)	31 (62%)	NS
SDH	16 (37%)	26 (52%)	NS
ICH	25 (58%)	26 (52%)	NS
EDH	3 (7%)	7 (14%)	NS
DAI	11 (26%)	9 (18%)	NS
Marshall score I	0 (0%)	0 (0%)	NS
Marshall score II	34 (79%)	32 (64%)	NS
Marshall score III	8 (19%)	16 (32%)	NS
Marshall score IV	1 (2%)	2 (4%)	NS
Marshall score V	0 (0%)	0 (0%)	NS
Sedation IV infusion			
Diprivan (propofol) drip	41 (95%)	47 (94%)	NS
Midazolam (versed) drip	16 (37%)	27 (54%)	NS

MCC, motorcycle crash; MVC, motor vehicle crash; NS, no significant differences between the two groups; PEDS, pedestrian versus auto crash; SBP, systolic blood pressure.

sustained. There were no differences in the Marshall score classifications for the two groups. Sedation with continuous IV infusion of diprivan and/or midazolam was similar for the two groups (NP vs. PP), diprivan (95% vs. 94%, $p = 0.96$) and midazolam (37% vs. 54%, $p = 0.36$) (Table 1).

The free PHE levels were checked and recorded on hospital Day 3 as per protocol for the 50 patients in the PP group (Fig. 2). Therapeutic levels (1–2 μg/mL) were present in 43 patients (86%), with 3 of these being in the supratherapeutic range (>2 μg/mL). Only 7 (14%) had subtherapeutic levels, and none of these went on to have a clinical seizure. Both the patients who had PTS in the PP group had therapeutic levels on Day 3 (1.2 and 1.6 μg/mL); the seizures occurred on hospital Day 5 and Day 6 (Fig. 2).

There was no significant difference between the two groups with regard to the various interventions for the TBI management (Table 2). Although all 93 patients in the study group met the Brian Trauma Foundation guidelines for AED use and intracranial pressure (ICP) monitor placement, overall neurosurgeon compliance was only 54% (50 of 93 patients) for AED and 41% (38 of 93) for ICP. Only 1 patient underwent bifrontal decompressive craniectomy in the PP group for cerebral edema and ICP control. Most of the patients underwent craniotomy burr holes or craniectomy bone flap removals for evacuation of SDH or EDH immediately after arrival.

When outcomes were analyzed for the two groups (NP vs. PP), there were no significant differences in early seizure rates (2.3% vs. 4.0%, $p = 1$), ICU LOS (17 ± 13 vs. 21 ± 10, $p = 0.1$), or ventilator days (12 ± 12 vs. 13 ± 6, $p = 0.72$). There was no significant difference in disposition for the two groups (NP vs. PP), home (40% vs. 32%, $p = 0.69$), rehabilitation center (53% vs. 60%, $p = 0.86$), or death caused by the TBI (7% vs. 8%, $p = 1$). However, the PP group had a significantly longer hospital stay (NP vs. PP) (25 ± 16 vs. 36 ± 31, $p = 0.03$) and a significantly worse functional outcome at discharge based on GOS score (3.4 ± 1.1 vs. 2.9 ± 1.0, $p = 0.01$) and mRS score (2.3 ± 1.7 vs. 3.1 ± 1.5, $p = 0.02$) (Table 3).

DISCUSSION

The use of prophylactic AED (PHE or valproate) to decrease the incidence of early PTS has not become standard of care despite the Level II recommendations from the Brain Trauma Foundation.[2] The compliance rate by neurosurgeons at our institution was only 54% (50 of 93) for PP in qualified severe TBI patients. However, not much has changed during the last 40 years. In 1973, a National Institutes of Health survey of 1,064 board-certified neurosurgeons revealed that only 58% used some kind of antiseizure prophylaxis in patients with severe TBI.[20] Of those surveyed, 91% based their decision on clinical experience and only 9% on specific references.[20] In 1996, a survey of 127 neurosurgical departments in Europe demonstrated that antiseizure prophylaxis was provided after TBI as follows: always (12%), never (36%), and sometimes (52%).[5] More recently in 2007, a Canadian survey evaluated 32 hospitals and 247 physicians (99 neurosurgeons and 148 critical care) regarding the management of a traumatic EDH with midline shift. The need for PP was graded as "uncertain appropriateness."[6]

This poor compliance may be caused by the fact that the only two randomized studies performed to evaluate early seizure rates were completed two to three decades ago (Temkin et al.[3] [1990] vs. Young et al.[4] [1983]) and had contradictory conclusions. Our study supported the conclusions of Young et al. because we found no significant difference in the early seizure rate between the two groups (NP vs. PP, 2.3% vs. 4.0%, $p = 1$). However, we are not the first clinical retrospective study to demonstrate this. In 1973, Rish and Caveness[21] demonstrated no significant decrease in the early seizure rate between prophylaxis versus no prophylaxis (1.6% vs. 3.7%) in 1,614 Vietnam TBI patients. Of the 1,614, 1,136 (70%) received routine anticonvulsant therapy, 465 (29%) received no prophylaxis, and in 13 (1%), it was unknown. Of the prophylaxis, 93% was with diphenylhydantoin alone, 4% with phenobarbital alone, and in the remaining 3%, both were used. However, blood levels of the drugs were not assayed, placing in question the therapeutic levels achieved.[21] A decade later, in 1983, Young et al.[4] presented the first randomized study that demonstrated no benefit of PHE in preventing early seizures. They randomized 244 trauma patients with blunt and penetrating TBI to PHE or placebo group. Plasma concentrations greater

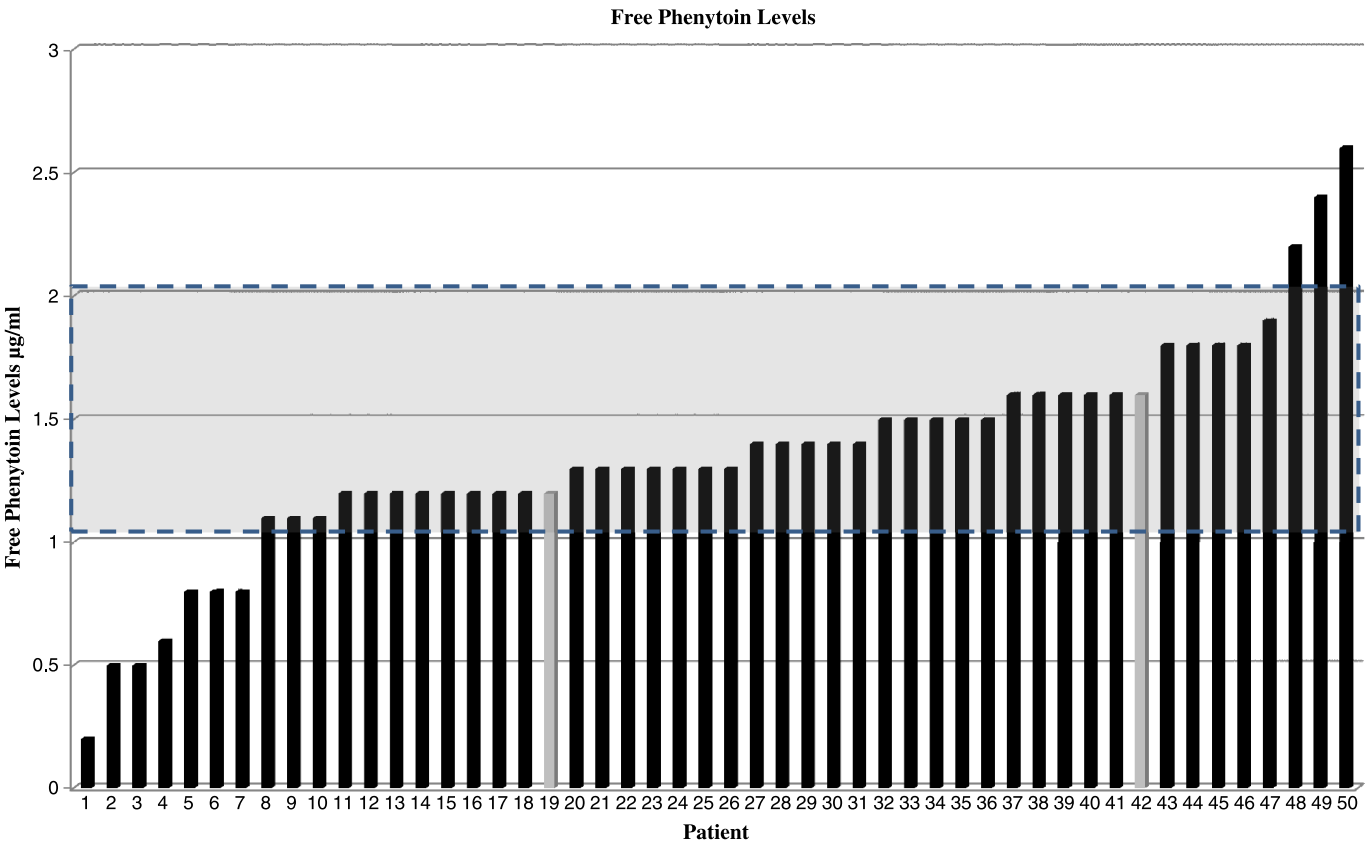

Figure 2. Free PHE levels on Day 3 after TBI. Therapeutic range (as indicated by *gray box*, 1–2 µg/mL) was achieved by 43 of the 50 patients. Of the 43, 3 had supratherapeutic levels. Patients who had seizures (n = 2) are marked in *gray*, both had therapeutic levels at the time of the seizure.

than 10 µg/mL were obtained by Days 1, 3, and 7 in 83%, 85%, 79% of the patients respectively. Ten patients had seizures in the field before arrival and were excluded. There was no significant difference in the early seizure rate between the two study groups (placebo vs. PHE, 3.7% [4 patients] vs. 3.7% [5 patients], $p = 0.75$).[4] Based on these findings, they concluded that PHE should only be used after an early seizure has occurred and not for prophylaxis. More recently, Debenham et al.[16] concluded after their retrospective analysis of 1,008 TBI patients during a 2-year period that the frequency of early PTS was very low (5.4%) and there was no significant difference between PP versus NP (2.3% vs. 3.1%, $p = 0.33$). Of the 54 (5.4%) who developed early seizure, only 19 (1.9%) had GCS score of 3 to 8.

In contrast, there is only one study that demonstrated the effectiveness of prophylactic PHE in reducing early seizures after TBI. In 1990, Temkin et al.[3] randomized 404 trauma

TABLE 2. Interventions

Intervention	NP (n = 43)	PP (n = 50)	*p*
ICP Monitor			
None	32 (82%)	23 (46%)	0.23
Surface monitor (Camino)	5 (9%)	11 (22%)	0.29
Ventriculostomy	6 (9%)	16 (32%)	0.15
Medical interventions			
Mannitol	8 (19%)	19 (38%)	0.12
Hypertonic saline 23.4%	8 (19%)	19 (38%)	0.12
Surgical interventions			
Bifrontal decompressive craniectomy for ICP control	0 (0%)	1 (2%)	1
Craniotomy burr hole for SDH/EDH	1 (2%)	6 (12%)	0.13
Craniectomy with bone flap removal for SDH/EDH	2 (5%)	9 (18%)	0.11

Significance, $p < 0.05$.

TABLE 3. Outcomes

Outcomes	NP (n = 43)	PP (n = 50)	*p*
Seizure	1 (2%)	2 (4%)	0.50
ICU LOS	17 ± 13	21 ± 10	0.10
Ventilator days	12 ± 12	13 ± 6	0.72
Hospital LOS	25 ± 16	36 ± 31	0.03
GOS score	3.4 ± 1.1	2.9 ± 1.0	0.01
mRS score	2.3 ± 1.7	3.1 ± 1.5	0.02
Disposition			NS
Mortality	3 (7%)	4 (8%)	NS
Rehabilitation center	23 (53%)	30 (60%)	NS
Home	17 (40%)	16 (32%)	NS

Significance, $p < 0.05$.

patients with blunt and penetrating severe TBI to PHE (208) or placebo (196) for one year. The groups were well matched, and PHE loading was performed within 24 hours of injury. Within 24 hours, 81% of the patients had therapeutic levels (3.0–5.9 μmol/L) and 16% had supratherapeutic levels (6.0 to >10.0 μmol/L). Although PHE significantly decreased the early seizure rate (14% vs. 4%, $p < 0.001$), it had no effect on the late seizure rate (22% vs. 16%, $p > 0.2$).

One of the criticisms of the study of Young et al. is that the early seizure rate for NP was much lower than that of Temkin et al. (3.7% vs. 14%), with a wide confidence interval (0.27–3.58) suggesting insufficient power to detect statistical difference. A review of the literature from 1940 to 2013 revealed an early seizure rate with NP in adults between 2.2% and 4.7% (Table 4).[3,4,21–27] This was much more consistent with Young et al. (3.7%) and our study (4%) than with Temkin et al. (14%). Better understanding of this key difference, which may in part be caused by patient selection, may explain the subsequent significance only achieved by Temkin et al.[3]

Most seizures occurred in the field before arrival and were excluded. We had six total seizures identified, of which three (50%) were excluded because they occurred in the field before arrival and three included (NP vs. PP, 1 [2.3%] vs. 2 [4%], $p = 1$). Similarly, of the 19 seizures in the study of Young et al., 10 (53%) were excluded because they occurred in the field before arrival and 9 were included (NP vs. PP, 4 [3.7%] vs. 5 [3.7%], $p = 0.75$).[4] If seizures in the field had been added to the NP group, PP may have been shown to be effective, our study (NP vs. PP, 4 [9.3%] vs. 2 [4%], $p = 0.05$) and Young et al. (NP vs. PP, 14 [14.8%] vs. 5 [3.7%], $p = 0.02$).

While Temkin et al. did not report the short- and long-term functional outcomes for the two groups in their study, in 1991, Dikmen et al.[7] performed a secondary analysis of the data and found significantly impaired performance on neuropsychological tests at 1 month after injury in severe TBI patients maintained on PHE. They concluded that PHE had negative cognitive effects.[7] This was also demonstrated in our study; the PP group had a significantly worse functional outcome at discharge based on GOS score (3.4 ± 1.1 vs. 2.9 ± 1.0, $p = 0.01$) (Table 3). In 2010, Szaflarski et al.[29] randomized 52 patients with severe TBI (GCS score of 3–8 with a positive CT scan finding of the brain) to either PHE (18 patients) or LEV (34 patients) for early PTS prophylaxis. The two groups were well matched and followed with continuous EEG monitoring for seizure activity for the first 72 hours. There was no difference in the early seizure rate for the two groups (PHE vs. LEV, 16.7% vs. 14.7%, $p = 1$). The PHE group did however have worsening neurologic status more often than the LEV group (50% vs. 18%, $p = 0.024$). One possible reason for this may be that PHE is not without adverse effects and has been associated with fever, somnolence, and cognitive supression.[8–18]

One of the biggest strengths of our study was that a comparable number of patients achieved therapeutic levels of PHE on Day 3 in our study (86%) as compared with previous randomized trials by Young et al. (83%) and Temkin et al. (81%). Furthermore, our data confirmed seizure rates from other retrospective and randomized studies performed decades apart. The seizure rates obtained for (NP vs. prophylaxis) in our study (2.3% vs. 4.0%) were similar to that of Young et al.[4] (3.7% vs. 3.7%), Rish and Caveness[21] (3.7% vs. 1.6%), and Debenham et al.[16] (2.3% vs. 3.1%). All four demonstrated ineffectiveness of PP to reduce early seizure rates.[28]

The weaknesses of our data derive from a retrospective analysis of a single institutional experience, in which some cohorts have small numbers, which may bring Type II errors into the results placing the conclusions into question. We also lacked long-term follow-up and only evaluated functional outcome at discharge rather than 6 months or a year out. Although the individual surgical interventions did not differ significantly between the groups (Table 2) when combined, the total surgeries were significantly higher for the PP group (NP vs. PP, 3 [7%] vs. 16 [32%], $p = 0.02$). This may have contributed to the longer stay and worse functional outcome. The bias of PHE use after surgery may be based on the randomized double-blinded study by North et al.[30] who compared PHE versus placebo for seizure prophylaxis after supratentorial neurosurgery and found significantly lower seizures in the PHE group.

TABLE 4. Comparison of Published Early (Within 7 Days After Injury) Seizure Rates With No Antiseizure Prophylaxis (NP)

References	Year	n	GCS Score	Early Seizure Rate With NP	Comment
Ascroft[22]	1941	317	3–15	4.7%	WWI
Rowbotham[23]	1942	450	3–15	2.5%	Edinburgh
Phillips[24]	1954	2,000	3–15	2.3%	WWII
Jennett and Lewin[25]	1960	1,000	3–15	4.6%	British Infirmary
Hendrick and Harris[26]	1968	4,465	3–15	6.5%*	Children (age ≤ 15 y)
Rish and Caveness[21]	1973	1,614	3–15	3.7%	Vietnam war
McQueen et al.[27]	1983	164	3–15	2.2%	Randomized study
Young et al.[4]	1983	244	3–8	3.7%	Randomized study
Temkin et al.[3]	1990	404	3–10	14.2%	Randomized study
Debenham et al.[16]	2011	1,008	3–15	3.1%	Retrospective
Zhao et al.[28]	2012	2,826	3–12	4.0%	Retrospective
Bhullar et al. (current study)	2013	93	3–8	4.0%	Retrospective

*Children 15 years and younger.
PB, Phenobarbital; WWI, World War I; WWII, World War II.

CONCLUSION

PP may not decrease early PTS and may suppress functional outcome after blunt TBI. These results need to be verified with prospective randomized studies before recommending any change in clinical practice and do not apply to penetrating trauma patients.

AUTHORSHIP

All authors contributed to the design of this study, for which I.S.B. conducted the literature search. I.S.B., J.P.P., and D.J. performed data collection. I.S.B. analyzed and interpreted the data. I.S.B., J.J.T., and

A.J.K. wrote and edited the manuscript. I.S.B. prepared the figures, tables, and manuscript for submission.

DISCLOSURE

The authors declare no conflicts of interest.

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DISCUSSION

Dr. Kenji Inaba (Los Angeles, California): I would like to congratulate the authors for their hard work and for utilizing their data to challenge the results of the randomized data that our current practices rest upon. I have five specific questions for the authors:

How were these seizures diagnosed clinically and by whom? Perhaps more importantly, how was this data abstracted for the study, by whom and from where? This is a critical issue as seizures are notoriously difficult to capture and adjudicate as to whether or not it truly was a seizure using retrospective data.

You state that the patients received identical treatments based on Brain Trauma Foundation guidelines, and yet you were able to separate your data into two distinct treatment groups. Please clarify what criteria your neurosurgeons used to decide who did or did not get prophylaxis and what potential confounders might also be unaccounted for.

You did point out some differences between groups. For example, the craniotomy rate was 7% in the no prophylaxis group and 32% in the prophylaxis group, the group that you also concluded had worse outcomes, due to the Phenytoin. How did you correct for this difference?

The manuscript contained no reference to associated injuries which could impact all of the outcome measures you compared. What were the associated non-cranial injuries, and did they differ between the two treatment groups?

Finally your sample size went from 766 patients eligible for treatment down to 93, due to a large numbers of exclusions. Why were patients treated with Keppra excluded, there were about 3 times more patient treated with Keppra than Dilantin? Why were patients with a moderately depressed GCS treated with Phenytoin excluded? Thank you again for your excellent work and thank you for the privilege of discussing this very interesting paper.

Dr. Rachael Callcut (San Francisco, California): Although the seizure numbers were small, do you have any data about the severity of the seizures? It may be that even though you decreased the number of seizures or there is no difference in them, the quality of the seizures are different.

Dr. Eileen M. Bulger (Seattle, Washington): I saw that you showed no difference in head AIS or ISS scoring between the groups, but we and others have shown that the GSC score

on admission or in the field is more predictive of long-term outcome than the AIS score.

So were there any differences between your groups in GSC score? In other words, just like the craniotomy rate differed, were neurosurgeons more likely to give the prophylaxis to more severely injured presenting patients and, therefore, they had a worse outcome?

Dr. S. Nabeel Zafar (Washington, D.C.): I know a number of neurosurgeons select patients who they treat prophylactically based on the lesion and on the head CTtemporal or frontal lesions are more likely to be treated prophylactically. Did you look at what lesion there was on the head CT? And temporal and frontal lesions also have worse outcome, GCS outcomes, as well.

Dr. Indermeet Bhullar (Jacksonville, Florida): Thank you all for the kind comments and insightful questions. In regard to Dr. Inaba's questions:

First, in regard to how were these seizures diagnosed clinically and by whom. This was a labor-extensive endeavor. The patients identified through the database search as having the diagnosis of seizures were cross checked against an independent and thorough chart review of all patients with TBI and GCS 38; the various components of each chart were reviewed in great detail, including admission history and physical, physician daily progress notes, nursing notes, medication administration records (MARS), laboratory and radiographic reports, and discharge summaries to verify the accuracy of all the information from the data base and identify the patients that had seizures. The seizure patients identified through the chart review were then cross checked with the patient list obtained from the database analysis for the final accurate list of patients that had seizures. This thorough chart review process also allowed for elimination of those patients that were identified as having catastrophic brain injuries and those that had a seizure in the field prior to arrival. Documentation of the seizure was verified in multiple areas in the chart, however, the severity of the seizure, in reference to the follow up question, was difficult to define.

Second, in regard to the criteria the neurosurgeons used to decide whether or not the patients got prophylaxis. We were unable to identify a clear correlation, except that it was neurosurgeon-dependent. Similar patients would receive antiseizure prophylaxis one night and not the next. As stated above, compliance to the Brain Trauma Foundation guidelines was 54% at our institution; in brief discussion with the neurosurgeons, choices appear to be based on personal preferences applied after review of individual patient mechanism, history and physical findings, CT head Marshall Score classification, radiographic and laboratory findings. The great disparity, per the neurosurgeons, is in part due to limited and conflicting findings in the randomized studies in the literature. To this end, one of goals of this study was to demonstrate a much higher seizure rate in matched patients that did not receive prophylaxis in order to then develop a standard protocol for our institution to eliminate the variation. As you can see, we were not successful at that. Rather, we strengthened the argument against the use of prophylaxis, since there appears to be no benefit in preventing early seizures and possibly a harm to functional recovery and length of hospital stay. This, however, needs to be further studied in a more up-to-date randomized trial that incorporates the advances made in the management of TBI in the last two to three decades since the last randomized studies.

Third, in regard to the higher anti-seizure prophylaxis use in patients that underwent craniotomy and surgical intervention. This is a great point and we acknowledge this difference in the groups. This may highlight a subgroup of patients that may benefit from seizure prophylaxis, as demonstrated by the randomized study by North et al.

Fourth, in regard to the exclusion of patients that received Keppra and GCS 915. First of all, one of the main reason why Keppra, and GCS 915 were excluded was that we were trying to replicate the patient populations described in the original randomized studies by Young et al. and Temkin et al. The controversy, at its core, lies in the significantly different early seizure rate reported by the two similar randomized studies for patients that did not receive prophylaxis (Young et al. vs. Temkin et al., 4% vs. 14%). This subsequently led the first study to find no difference in the seizure rate with the addition of phenytoin while the second did (Young et al., 4% vs. 4%; Temkin et al., 14% vs. 4%). So we wanted to know the true seizure rate of a similar patient population with no prophylaxis. As reported above, our finding of an early seizure rate of 2% in the no prophylaxis group was more consistent with Young et al.

Also, 81% of our patients with GCS 915 were discharged soon after admission. They rarely stayed in the hospital for the full seven days.

Future studies will need to look at all the various permutations of TBI including but not limited to, penetrating trauma, blunt trauma with supratentorial burr holes and craniectomies, Keppra, Dilantin, GCS 915, 315 and so forth to identify groups, if any, that may benefit from early prophylaxis.

The Brain Trauma Foundation has not provided recommendations regarding Keppra. That's another reason why we excluded this group from the study.

In regard to Dr. Calcutt's question about the severity of seizures: As I addressed above, it was difficult to define severity with accuracy given the limited data despite the extensive chart review, partly due to the inherent limitations of a retrospective approach.

In regard to Dr. Bulger's question regarding GCS in the field and on admission: Excellent point, we only looked at GCS on admission but we will address GCS in the field in future studies.

Finally, in regards to Zafra's question regarding location of the lesions and their role in neurosurgeon decision: I again apologize in saying I do not have insight into their decision process. But after discussions with them, it appears they may not as well.

Thank you, again.