

Should Levetiracetam or Phenytoin Be Used for Posttraumatic Seizure Prophylaxis? A Systematic Review of the Literature and Meta-analysis

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BACKGROUND: Posttraumatic seizure (PTS) is a significant complication of traumatic brain injury (TBI).

OBJECTIVE: To perform a systematic review and meta-analysis to compare levetiracetam with phenytoin for seizure prophylaxis in patients diagnosed with severe TBI.

METHODS: An inclusive search of several electronic databases and bibliographies was conducted to identify scientific studies that compared the effect of levetiracetam and phenytoin on PTS. Independent reviewers obtained data and classified the quality of each article that met inclusion criteria. A random effects meta-analysis was then completed.

RESULTS: During June and July 2015, a systematic literature search was performed that identified 6097 articles. Of these, 7 met inclusion criteria. A random-effects meta-analysis was performed. A total of 1186 patients were included. The rate of seizure was 35 of 654 (5.4%) in the levetiracetam cohort and 18 of 532 (3.4%) in the phenytoin cohort. Our meta-analysis revealed no change in the rate of early PTS with levetiracetam compared with phenytoin (relative risk, 1.02; 95% confidence interval, 0.53-1.95; $P = .96$).

CONCLUSION: The lack of evidence on which antiepileptic drug to use in PTS is surprising given the number of patients prescribed an antiepileptic drug therapy for TBI. On the basis of currently available Level III evidence, patients treated with either levetiracetam or phenytoin have similar incidences of early seizures after TBI.

KEY WORDS: Dilantin, Keppra, Levetiracetam, Meta-analysis, Phenytoin, Seizures, Trauma

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Posttraumatic seizure (PTS) is a well-known sequelae of traumatic brain injury (TBI), with reported prevalence rates between 4% and 25%.¹⁻³ A landmark randomized, double-blind, controlled trial of 404 patients by Temkin et al⁴ in 1990 demonstrated that seizure prophylaxis with phenytoin in patients with TBI decreased the amount of early (ie, within 7 days) PTS from 14.2% to 3.6% ($P < .001$). This study, however, showed no difference in late PTS or overall outcome.⁴ A Cochrane review in 2010 found no evidence that the use of an anticonvulsant in patients with TBI decreased the rate of early seizures, and it did not decrease neurological disability or mortality.⁵ Currently, brain trauma

guidelines recommend the use of an antiepileptic for 7 days after severe TBI (Level II evidence).⁶ The use of levetiracetam has recently become popularized because there is no need to monitor serum levels and the side-effect profile is more favorable compared with phenytoin. Phenytoin has been associated with hepatic cytochrome-P450 induction, leading to drug-drug interactions, cutaneous hypersensitivity, and rare serious side effects such as hypotension, cardiovascular collapse, toxic epidermal necrolysis, and Steven Johnson syndrome.⁷⁻⁹

As a result of the side-effect profile and narrow therapeutic window of phenytoin, several reports have compared phenytoin with levetiracetam. A recent systematic review and meta-analysis in 2012 by Zafar et al¹⁰ evaluated patients with brain injury, including subarachnoid hemorrhage, intraparenchymal hemorrhage, and supratentorial glioma surgery, and found no difference in seizure rates with levetiracetam or phenytoin. The use of levetiracetam or phenytoin in TBI

ABBREVIATIONS: ADE, adverse drug event; AED, antiepileptic drug; CI, confidence interval; OR, odds ratio; PTS, posttraumatic seizure; TBI, traumatic brain injury

varies widely at different centers and is highly dependent on the prescriber's preference rather than supporting evidence. The purpose of this study was to perform a systematic review and meta-analysis comparing levetiracetam with phenytoin for seizure prophylaxis exclusively in patients with severe TBI.

METHODS

This study protocol was performed with the Assessment of Multiple Systematic Reviews measurement tool¹¹ and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.¹²

Research Question

The study question for this project was the following: Is the rate of post-TBI seizure different when levetiracetam is used compared with phenytoin?

Search Strategy

The systematic search strategy involved a search through multiple electronic databases, bibliographies of relevant articles, and consultation with the senior author. We electronically searched PubMed/MEDLINE, ClinicalTrials.gov, EMBASE, Google Scholar, The Cochrane Library, Web of Knowledge, and Scopus to find English-language articles (excluding gray literature) with no time-frame restrictions in June 2015.

The following terms in various combinations were used: phenytoin, levetiracetam, seizure, traumatic brain injury, and prophylaxis. Two independent researchers (coauthors on this study), along with librarians at our academic institution, performed separate literature searches. Any discrepancies among reviewers were solved through consensus and discussion with the senior author.

Inclusion Criteria, Data Extraction, End Points, Definitions

The goals of the search were to find articles that met the following inclusion criteria: described a group of adult (>18 years of age) patients with severe TBI treated with phenytoin, described another group treated with levetiracetam, had the use of antiepileptic drugs (AEDs) as the main treatment difference between the 2 groups, and reported the number of patients and number of seizures for each group. Thus, noncomparison studies, case reports, and pediatric reports were excluded.

Two coauthors of this study screened all potential articles and extracted data independently. The data extracted from each article included dose of medication, the complete number of patients per group, the rate of early (<7 days) and late (>7 days) seizures (both clinical and electrographic), the authors' definition of a seizure, and any complications related to the use of antiepileptic medications. Each study was graded with the use of the Oxford Centre for Evidence Based Medicine guidelines.¹³ Study quality was determined with the Newcastle-Ottawa Quality Assessment Scale¹⁴ for controlled observational cohort studies and Jadad¹⁵ scale for randomized controlled trials. Differences among any of the above data points were resolved through consensus among the authors.

Meta-analysis

For each study, the numbers of seizures in patients treated with phenytoin and levetiracetam were identified, and a relative risk was calculated. The overall risk ratio was computed with methods we have previously described.¹⁶

A random-effects meta-analysis was performed on the selected studies. Heterogeneity was assessed by the Q and I^2 statistics. Heterogeneity was considered significant when the P value derived from Cochran Q was $<.1$. I^2 values of at least 50% are usually considered to represent moderate heterogeneity, whereas values of at least 75% indicate severe heterogeneity according to the Cochrane handbook.¹⁷ Publication bias (ie, assessment of bias across studies) was graphically evaluated with a funnel plot.¹⁸⁻²⁰

RESULTS

The initial search identified 6097 articles (Figure 1). After the exclusion of articles not directly related to our hypothesis and duplicates, a total of 10 articles remained. Of these 10 articles, 3 were excluded because 2 studies were cost analyses^{21,22} and the study by Ramakrishnan et al²³ did not provide sufficient information for a comparison to be made between levetiracetam and phenytoin. Thus, 7 studies were eligible for analysis. Only 30 of the 287 patients in the study by Radic et al²⁴ with depressed Glasgow Coma Scale scores were included in the analysis because the remainder did not have what the authors considered significant TBI.

Characteristics of Eligible Studies

There was 1 prospective randomized controlled trial, 3 retrospective cohort studies, 2 prospective cohort studies, and 1 combined

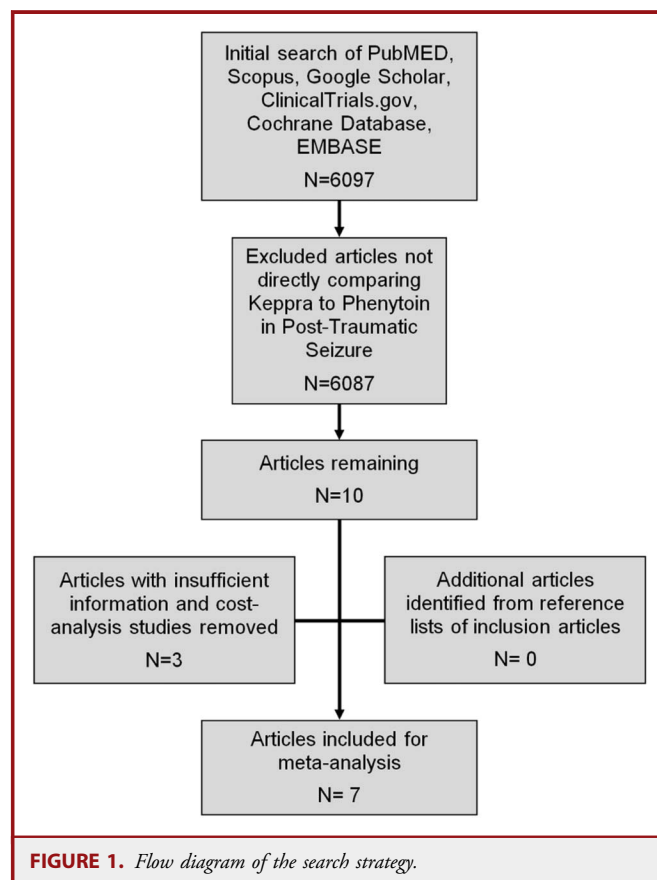


FIGURE 1. Flow diagram of the search strategy.

TABLE 1. Results of Studies Comparing Levetiracetam vs Phenytoin^a

Author/Year	Study Type	Patients, n	Inclusion Criteria	Exclusion Criteria	Dosage	Length of Treatment, d
Jones et al, ²⁵ 2008	Prospective cohort with retrospective control	73	GCS score 3-8, had to have had EEG monitoring	Patient not receiving EEG	PHT: N/A; LEV: 500 mg twice daily	7
Szaflarski et al, ²⁶ 2010	Randomized, blinded, controlled trial	52 (88.5% severe TBI)	Severe TBI or SAH, GCS 3-8, CT scan showing intracranial pathology, SBP >90 mm Hg, >17 y/o, 1 reactive pupil	No venous access, spinal cord injury, h/o prior brain injury, hemodynamic instability, anoxic event, trauma resulting in liver failure, <17 y/o, known allergy to AEDs, contraindication to LEV/PHT, inability to obtain consent	PHT: 20 mg/kg loading dose, 5 mg·kg ⁻¹ ·d ⁻¹ maintenance dose; LEV: 20 mg/kg loading dose, 1000 mg twice daily	7
Inaba et al, ²⁷ 2012	Prospective cohort	813	>18 y/o with severe TBI, GCS ≤8 or GCS >8 with abnormal CTH	Pregnancy, prehospital use of AED, devastating brain injury, development of seizures before enrollment	PHT: 20 mg/kg loading dose, 5 mg·kg ⁻¹ ·d ⁻¹ maintenance dose; LEV: 1000 mg twice daily	7
Kruer et al, ²⁸ 2013	Retrospective cohort	109	AIS of 3, GCS ≤ 8	Patients < 18 y/o, had a seizure before prophylactic AED, had a history of seizure disorder, continuous infusion of paralytic agent, received >1 AED, no evidence of TBI on CTH	N/A	Varies
Caballero et al, ²⁹ 2013	Retrospective cohort	90	>18 y/o with ICU admission, >48 h of either LEV or PHT for seizure prophylaxis, at least 1 d of EEG monitoring	Pregnancy, history of epilepsy, previous TBI, hypersensitivity to study medication, receiving nonstudy AEDs	PHT: 13 mg/kg loading dose; 4 mg·kg ⁻¹ ·d ⁻¹ ; LEV: 1 g loading dose, 500 mg twice daily maintenance dose	9-14
Gabriel and Rowe, ³⁰ 2014	Prospective cohort	19	Patients who received LEV or PHT for >48 h and had a TBI ICD-9 code	Patients <18 y/o, pregnant, patients who had a documented history of seizures or a seizure in the prior 6 mo	PHT: 14.6 ± 1.93 mg/kg loading dose, 4.4 ± 0.5 mg·kg ⁻¹ ·d ⁻¹ maintenance dose; LEV: 500 mg twice daily	4-11
Radic et al, ²⁴ 2014 ^b	Retrospective cohort	30	Subdural and TBI, admitted in 2002, 2003, 2011	SDH not primary pathology, other AEDs given	PHT: 15-20 mg/kg loading dose, 15-20 mg/kg 3 times daily; LEV: 1 g loading dose, 500 mg twice daily	Until DC

Author/Year	Early Seizures (≤7 days)	Late Seizures (>7 days)	Definition of Seizure	ADEs	Length of Follow-up	Authors' Conclusions	NOS/Jadad
Jones et al, ²⁵ 2008	PHT: 0/41; LEV: 1/32	N/A	Electrographic and clinical	N/A	PHT: 7 d; LEV: 7 d	No difference in seizures, increased EEG tendency toward seizures in LEV	8 of 9
Szaflarski et al, ²⁶ 2010	PHT: 3/18; LEV: 5/34	PHT: 0/18; LEV: 1/34	Clinical and electrographic	Significantly worse neurological status and gastrointestinal complications with PHT	6 mo	Improved outcomes in LEV patients, no difference in seizures compared with PHT	Jadad 2/5

(Continues)

TABLE 1. Continued

Author/Year	Early Seizures (≤7 days)	Late Seizures (>7 days)	Definition of Seizure	ADEs	Length of Follow-up	Authors' Conclusions	NOS/Jadad
Inaba et al, ²⁷ 2012	PHT: 6/407; LEV: 6/406	N/A	Clinical	PHT: 42/407; LEV: 32/406	PHT: 7.5 d; LEV: 11.8 d	No difference in seizure rate, mortality, or complications between LEV and PHT	8 of 9
Kruer et al, ²⁸ 2013	PHT: 1/89; LEV: 1/20	N/A	Clinical and/or electrographic	N/A	PHT: 11 d; LEV: 16.5 d	Low incidence of PTS with a shift toward the use of LEV compared with PHT	8 of 9
Caballero et al, ²⁹ 2013	PHT: 21/72; LEV: 5/18	N/A	Electrographic	N/A	Hospital DC	No difference in seizure activity between LEV and PHT	7 of 9
Gabriel and Rowe, ³⁰ 2014	PHT: 3/14; LEV: 0/5	PHT: 2/14; LEV: 0/5	Not described	PHT: 3/14; LEV: 1/5	PHT: 27 mo; LEV: 16.1 mo	Long-term functional outcome not affected by use of PHT or LEV	7 of 9
Radic et al, ²⁴ 2014 ^b	PHT: 1/13; LEV: 0/17	PHT: 1/13; LEV: 2/17	Clinical and electrographic	PHT: 26/122; LEV: 6/164	Hospital DC	No difference in early seizures	9 of 9

^aADE, adverse drug event; AED, antiepileptic drugs; AIS, Abbreviated Injury Scale; CT, computed tomography; CTH, computed tomography of the head; DC, discharge; EEG, electroencephalogram; GCS, Glasgow Coma Scale; ICD-9, *International Classification of Diseases, Ninth Revision*; ICU, intensive care unit; LEV, levetiracetam (Keppra, Levetiracetam); N/A, not available; NOS, Newcastle Ottawa Scale; PHT, phenytoin (Dilantin, Phenytek); PTS, posttraumatic seizures; SAH, subarachnoid hemorrhage; SBP, systolic blood pressure; SDH, subdural hemorrhage; TBI, traumatic brain injury; y/o, years old. ^bThe study by Radic et al²⁴ had a total of 287 patients; however, all but 30 patients were excluded because they did not have a severe TBI, defined by the authors as having a traumatic cause and GCS score ≤8.

retrospective and prospective study²⁵ (Level III; Table 1). The average number of stars with the Newcastle-Ottawa Quality Assessment Scale was 7.8 ± 0.8 of a maximum of 9, indicating good quality of included studies. The study by Radic et al²⁴ controlled for differences among comparison groups by adjusting odds ratios (ORs). The 1 randomized controlled trial in this analysis did not mention the method of randomization and was inappropriately blinded; therefore, it received only 2 of 5 points when the Jadad criteria were used for grading randomized controlled trials.²⁶ There were no reported conflicts of interest in the included study.

Meta-Analysis

A total of 1186 patients were included. The rate of early (≤7 days) PTS was 35 of 654 (5.4%) in the levetiracetam cohort and 18 of 532 (3.4%) in the phenytoin cohort. A meta-analysis comparing levetiracetam with phenytoin in the prevention of early PTS showed no difference (OR, 1.02; 95% confidence interval [CI] 0.53-1.95; P = .96; Figure 2). There were insufficient data to perform a meta-analysis on the rate of late seizures (>7 days).

A sensitivity analysis was performed that included only the prospective cohort studies and the randomized controlled study. It showed no difference when levetiracetam was compared with phenytoin in the prevention of early PTS (OR, 1.15; 95% CI, 0.48-2.79; P = .75).

Adverse Drug Events

A total of 3 studies directly reported adverse drug events (ADEs).^{25,27,30} The study by Szaflarski et al²⁶ reported the incidence of complications in both treatment arms but did not directly attribute this to use of the AED. The incidence of ADEs by study is shown in Table 2. A total of 71 ADEs occurred in 543 patients (13%) in the phenytoin group and 42 in 575 patients (7%) in the levetiracetam group.

Publication Bias

The funnel plot suggests an absence of publication bias given its symmetrical distribution (Figure 3).

DISCUSSION

Literature Review

The current Brain Trauma Foundation guidelines support the use of prophylactic AED therapy during the first 7 days after TBI (Level II evidence).⁶ The decision on which AED to use is still controversial and not well supported by evidence. Our review of the literature and meta-analysis found only 7 studies that met our inclusion criteria, 6 of which showed no difference in seizure rates. The study by Jones et al²⁵ reported an increase in electrographic seizure activity in the levetiracetam group compared with the phenytoin group (P = .003). All but 2 studies^{27,30} described the use of electroencephalography as part of their

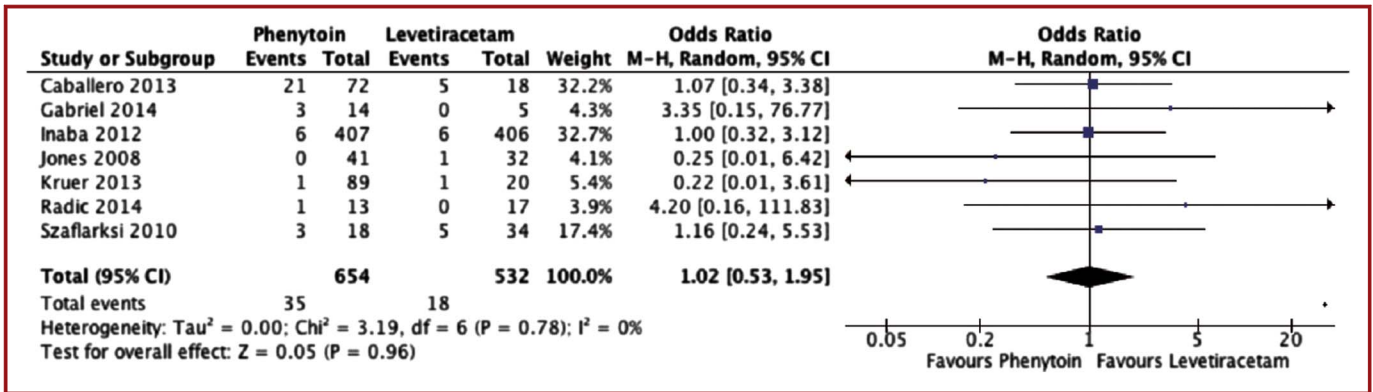


FIGURE 2. Forest plot of all studies with their respective relative risk and 95% confidence interval (CI), events (early seizures), and overall Newcastle-Ottawa Quality Assessment Scale. M-H, Mantel-Haenszel. Color version available online only.

TABLE 2. Adverse Drug Events by Study^a

	Phenytoin-Associated ADEs (n)	Levetiracetam-Associated ADEs (n)
Gabriel and Rowe ³⁰ (n = 19)	Slurred speech (1) ^b Neutropenia (1) Fever (1) Total = 3	Delirium (1) Total = 1
Radic et al ²⁴ (n = 126)	Decreased level of consciousness (5) Liver dysfunction (4) Rash (4) Persistent fever (3) Neutropenia (1) Vertigo (2) Drug switch (7) Total = 26	Liver dysfunction (1) Drug switch (1) Fatigue (1) Vomiting (1) Decreased appetite (1) Death (1) Total = 6
Inaba et al ²⁷ (n = 813) ^c	Rash (1) Leukocytosis (39) Hypotension (4) Drug discontinuation (12) Total = 42	Rash (1) Leukocytosis (5) Hypotension (1) Drug discontinuation (0) Total = 32
Szafarski et al ²⁶ (n = 52) ^d	Fever (10) Increased intracranial pressure (8) Stroke (3) Worse neurological status (9) Hypotension (2) Cardiac arrhythmia (6) Anemia (4) Thrombocytopenia (3) Coagulation deficits (1) Dermatological (0) Liver function tests (0) Renal (1) Gastrointestinal (2) Total = 49	Fever (18) Increased intracranial pressure (13) Stroke (7) Worse neurological status (6) Hypotension (7) Cardiac arrhythmia (14) Anemia (17) Thrombocytopenia (5) Coagulation deficits (2) Dermatological (0) Liver function tests (2) Renal (2) Gastrointestinal (4) Total = 97
Total ADEs (excluding Szafarski et al ²⁶)	71	39

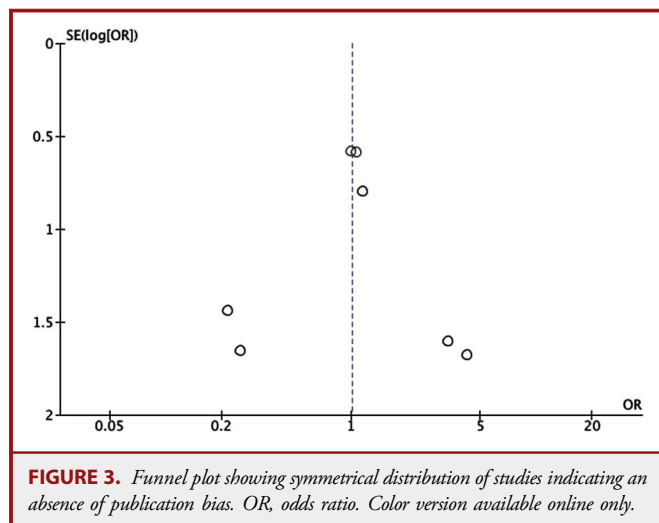
^aADE, adverse drug event.

^bNumber in parentheses indicates number of patients who experienced the specified ADE.

^cThe article by Inaba et al²⁷ did not provide a comprehensive list of all ADEs, only the most common ADEs.

^dThe article by Szafarski et al²⁶ did not specifically look at known ADEs related to both phenytoin and levetiracetam. Instead, it looked at the occurrence of a multitude of conditions in both treatment arms.

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definition of what constituted a seizure. One study did not describe its definition of a seizure.³⁰ Four of the studies reported ADEs associated with drug therapy.^{24,27,30} The dosing among the included studies was heterogeneous (Table 1), which could have resulted in different rates of seizures between populations. The majority of studies had at least 7 days of follow-up, allowing analysis of early seizures but not the occurrence of late seizures.

In our meta-analysis, we found that there was no statistically significant difference between using phenytoin or levetiracetam in preventing early (ie, ≤ 7 days) PTS ($P = .96$; Figure 2). The I^2 statistic of 0% indicates minimal heterogeneity among our findings. The funnel plot performed was symmetrical, indicating a decreased likelihood of publication bias (Figure 3); however, given the small number of inclusion articles ($n = 7$), this effect may be due to chance alone. The Cochrane Review manual does not recommend higher-level testing when the number of inclusion articles is < 10 .¹⁷ The rate of seizures in this study was 5% when the phenytoin and levetiracetam groups were combined.

ADEs were reported in only 3 of the studies and were more frequent in the phenytoin group (13%) compared with the levetiracetam group (7%). This finding is consistent with previously reported rates of higher ADEs with phenytoin compared with levetiracetam.³¹ The rate of ADEs should be a topic of future research and could help to guide the clinician in deciding which agent to use. The incidence of late seizure was reported in only 3 of the inclusion studies; therefore, higher-order analysis was not performed on this secondary outcome. The overall rate of late seizures in the phenytoin group (6.6%) was similar compared with the levetiracetam group (5.3%).

Study Implications

The fact that only 6 small cohort studies and 1 low-quality randomized controlled trial are available on this topic limits the number of conclusions that can be drawn from these data.

However, it is unlikely that there is a true statistical, or even clinical, difference in seizure rates with phenytoin or levetiracetam. The lack of evidence on this topic is surprising, considering the amount of patients receiving AEDs after TBI. Browning et al³² recently published preliminary data that suggest a neuroprotective benefit to levetiracetam in certain brain trauma mechanisms induced in rats.²⁸ Early single intravenous levetiracetam (5-minute postinjury dose of 54 or 170 mg/kg) produced multiple benefits in controlled cortical impact and fluid percussion brain injury and reduced glial fibrillary acidic protein levels in penetrating ballistic-like brain injury. Another consideration is the cost of AED therapy to the hospital, patients, and the overall healthcare system. A recent study by Kazerooni et al²¹ showed a potential cost-effectiveness benefit with levetiracetam over Dilantin. Another study from the pharmacy literature by Caballero et al²⁹ in 2013 also showed a benefit in cost for levetiracetam compared with phenytoin. However, they stated that their practice utilized phenytoin levels often, which directly affected cost. The cost analysis of AED therapy can be complex. A combination of drug monitoring, sequelae of side effects, and drug cost contributes to the actual cost of AED therapy. A detailed cost comparison was outside the scope of this review because details were not sufficiently reported in the original studies.

Furthermore, the evidence on actual clinical outcomes (ie, morbidity, mortality) with the use of AEDs compared with placebo still needs to be investigated to clarify whether AED therapy after trauma actually makes a long-term difference in patient outcome.

Limitations

The strength of a meta-analysis is only as robust as the quality of articles from which it is derived. The eligible articles for this analysis were nearly all Level III studies with the exception of a single Level II prospective randomized controlled trial. The included studies are heterogeneous. There were different durations of treatment, ages of patients, methods of drug administration (intravenous or oral), dosages of drugs, severities of TBI, and methods for determining seizure activity (Table 1). The quality of all the studies was acceptable. Despite the study by Inaba et al²⁷ that included a majority (90%) of patients with TBI, there was a minority of patients (10%) with a diagnosis other than TBI in the comparison and control groups. The authors of that study were contacted but did not reply with additional information that would allow us to separate these 2 subpopulations. Therefore, this study could have introduced a small element of heterogeneity into our analysis.

CONCLUSIONS

The lack of evidence on the choice of a prophylactic AED for PTS is surprising given the large number of patients with TBI treated each year in this country and around the world. On the basis of currently available Level III evidence, patients treated with

either levetiracetam or phenytoin have similar incidences of seizure after TBI. Further high-quality, well-populated studies are necessary to make definitive recommendation(s) on this topic.

Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENT

The authors performed a systematic review and meta-analysis to compare phenytoin and levetiracetam for seizure prophylaxis in patients diagnosed with severe traumatic brain injury. The incidence of seizure in the levetiracetam group was 35 of 654 (5.4%) and in the phenytoin group was 18 of 532 (3.4%), with no statistically significant difference between the groups. Currently, the Brain Trauma Foundation guidelines recommend as Level II evidence the use of anticonvulsants to decrease the incidence of early posttraumatic seizure.

The strength of the recommendations from a meta-analysis and the conclusions drawn are only as strong as the quality of articles from which the meta-analysis is derived. The studies included in the meta-analysis fail to be homogeneous for several reasons. Within the studies, there were differences in the severity of TBI, duration of treatment, mode of drug administration (intravenous vs oral), dosage (initial and maintenance), and age of patients. Some studies mentioned monitoring of phenytoin levels, whereas others failed to mention it at all. Most important, there was no uniformity in the method to determine seizure activity. Some studies used both electroencephalography monitoring and clinical examination;

others used one or the other; and some studies made no mention of how they monitored for seizure activity.

The authors conclude, "On the basis of currently available Level III evidence, patients treated with either levetiracetam or phenytoin have similar incidences of seizure after TBI." The neurosurgical community has more or less embraced levetiracetam as its anticonvulsant medication

of choice because of the relative paucity of side effects from that medication. Studies such as these help justify that decision.

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