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Lacosamide versus phenytoin for the prevention of early post traumatic seizures

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ABSTRACT

Purpose: To compare the efficacy and safety of lacosamide versus phenytoin for seizure prophylaxis following TBI.
Materials and methods: All TBI patients who received prophylaxis with either phenytoin or lacosamide were retrospectively identified. The incidence of seizures within the first 7 days of injury were compared along with adverse effects requiring drug discontinuation. A planned sub-group analysis was performed for patients with severe TBI (GCS < 9).
Results: There were 481 patients (phenytoin, $n = 116$; lacosamide, $n = 365$). Demographics were similar but age (50 ± 21 vs 58 ± 22 years, $P < .001$) and initial GCS (11.3 ± 4.3 vs 12.5 ± 3.8, $P = .010$) were lower in the phenytoin group. The need for mechanical ventilation was higher (53% vs 38%, $P = .004$). Seizures occurred in 0.9% of the phenytoin group and 1.4% of the lacosamide group ($P = 1.00$). ADEs were significantly higher with phenytoin (5.2% vs 0.5%, $P = .003$). This difference remained significant upon multivariate analysis [OR(95% CI) = 9.4 (1.8–48.9)]. Subgroup analysis for patients with severe TBI revealed no difference in seizures (phenytoin, 0% vs lacosamide, 1.5%; $P = 1.00$) but more ADEs with phenytoin (12.5% vs 0%, $P = .010$).
Conclusion: There was no difference between lacosamide and phenytoin in the prevention of early post traumatic seizures in patients following TBI. Lacosamide may have a more tolerable side effect profile.

1. Introduction

The development of early post traumatic seizures (PTS) in patients with severe traumatic brain injury (TBI) can be as high as 12%, causing potential detrimental consequences including secondary brain injury, longer length of stay, chronic epilepsy, and death [1]. Anti-epileptic drug (AED) use is a common practice for the prevention of PTS, and phenytoin in particular has long since been the treatment of choice. In a landmark randomized controlled trial, PTS rates were significantly lower with phenytoin use versus placebo but only during the first week after severe head injury [2]. In addition, recent evidence-based guidelines and recommendations support the use of phenytoin to decrease the incidence of early PTS. [1,3] However, phenytoin's drug profile does possess the potential for significant side effects and numerous drug interactions. Phenytoin has also been shown to produce worse functional outcomes after rehabilitation [4]. Finally, there is debate over the accuracy of formulas commonly used to interpret total phenytoin levels as one investigation revealed the agreement between total (adjusted) levels and free levels to be poor [5]. The availability of free phenytoin concentrations however, coupled with the prolonged turnaround time encountered with most laboratories presents a challenge for many institutions.

These concerns have led to investigations with alternative antiepileptic agents for the prevention of early PTS. Levetiracetam has been the most common alternative considered in practice, but lacks strong evidence to support its use over phenytoin [6-13]. Furthermore, levetiracetam dosing is not well defined and therapeutic concentrations are infrequently obtained. In fact, in one pharmacokinetic study of neurocritical care patients, daily doses of 3 to 4 g were necessary to maintain serum concentrations between 6 and 20 μg/ml [14]. This is substantially higher than the starting doses that are currently utilized for seizure prevention (i.e., 500–1000 mg twice daily). Furthermore, levetiracetam can lead to somnolence and behavioral abnormalities potentially clouding a neurologic exam. Additional studies exploring levetiracetam and other AEDs are warranted, especially with the introduction of newer drug developments.

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Lacosamide is a slow sodium channel inhibitor and neuronal membrane stabilizer. It does not bind to any other binding sites of anticonvulsants or analgesics and is available as both intravenous and oral formulations. Lacosamide has a low degree of protein binding and a favorable adverse effect profile compared to phenytoin. Collectively, these properties make it an attractive option in neurocritical care patients [15]. At our institution, lacosamide is commonly used for the prevention of early PTS in patients following TBI. Our objectives, therefore, were to compare the incidence of early PTS and adverse drug events with lacosamide versus phenytoin in patients with TBI who required seizure prophylaxis.

2. Material and methods

This retrospective cohort study was conducted at an American College of Surgeons-verified level-I trauma center. Institutional board approval (and waiver of informed consent) was obtained prior to study initiation. Consecutive patients admitted from August 2012 to September 2016 who received monotherapy with either lacosamide or phenytoin for seizure prophylaxis following TBI were identified using the institution's trauma registry and electronic medical record. Patients were included in the study if they presented within 24 h of injury, had seizure prophylaxis initiated within 24 h of admission, were ≥ 18 years old, and had a CT scan that revealed subarachnoid hemorrhage (SAH), subdural hemorrhage (SDH), epidural hemorrhage (EDH), intraparenchymal hemorrhage (IPH), or intraventricular hemorrhage (IVH) or cortical contusion. Patients were excluded if they were taking anti-epileptic medications prior to admission, had received multiple seizure prophylaxis medications, had a seizure before prophylaxis was initiated, had expected or confirmed brain death within 48 h of admission, or were transferred to another hospital within 24 h. Data collected included demographics, mechanism of injury, severity of injury (injury severity score, abbreviated injury scale, Glasgow coma scale, mechanical ventilation, systolic blood pressure), CT scan diagnoses, incidence of early PTS, adverse drug events and mortality.

Lacosamide was introduced into local practice in April 2014. There was no standardized protocol dictating a preferred AED. Lacosamide dosing was either 50 mg twice daily (if GCS was between 13 and 15) or 200 mg once, followed by 100 mg twice daily (if GCS was ≤12 or a large structural lesion was noted on brain imaging, at the discretion of the neuro-intensivist). Phenytoin was dosed at 15–20 mg/kg (load) followed by 300–400 mg daily. The duration of prophylaxis was 7 days.

The two primary outcomes of this study assessed the efficacy and safety of lacosamide versus phenytoin for seizure prophylaxis in TBI patients. Efficacy was measured by incidence of clinical seizures within first 7 days following TBI as documented by a board-certified neurointensivist. Safety was determined by incidence of adverse effects requiring drug discontinuation at the discretion of the medical team. A planned sub-group analysis was performed for patients with severe TBI defined as GCS < 9 upon admission.

Chi-square or Fisher's Exact was used to compare nominal variables. Student's *t*-test was used to compare continuous variables for normally distributed data or Mann Whitney-U if the data was skewed. Univariate analysis was performed to identify confounding variables for the two primary outcomes and covariates with a $p < .1$ were considered for inclusion in a multivariate analysis. Multivariate analysis was performed using logistic regression in a step-wise approach. Goodness-of-fit was assessed using the Hosmer-Lemeshow test. Data are expressed as either mean ± standard deviation, median (interquartile range) or n (%). A *p*-value <.05 was considered statistically significant. Statistical analyses were conducted using SPSS (Version 24, IBM, Armonk, NY).

3. Results

There were 481 patients evaluated; 116 received phenytoin and 365 received lacosamide. Baseline demographics were similar between groups, except age (50 ± 21 vs 58 ± 22 years, $p < .001$) and admission GCS (11.3 ± 4.3 vs 12.5 ± 3.8, $p = .01$) were lower in the phenytoin group, while mechanical ventilation was higher (53% vs 38%, $p = .004$). (Table 1) The most common mechanism of injury was motor vehicle collision (phenytoin, 40% vs lacosamide, 39%; $p = .116$). For phenytoin treated patients, the initial serum concentration was 14.9 ± 4.6 μg/ml ($n = 108$).

The incidence of early PTS was 0.9% (1/116) in the phenytoin group and 1.4% (5/365) in the lacosamide group ($p = 1.00$). There were no additional factors associated with early PTS thus multivariate analysis was not performed. (Table 2) Adverse drug events requiring drug discontinuation were significantly higher in the phenytoin group (5.2% [6/116] vs 0.5% [2/365], $p = .003$). Specific ADE's are displayed in Table 3. Therapeutic phenytoin concentrations were present at the time of the ADE in 5 of the 6 patients (one patient was supratherapeutic). Other factors associated with ADE's were IVH (38% vs. 9.1%, $p = .033$) and initial GCS < 9 (50% vs. 20%, $p = .058$).(Table 4) Upon controlling for these variables in a multivariate analysis, the association between phenytoin and ADE's was confirmed (OR [95% CI] = 9.4 [1.8–48.9], $p = .008$). (Table 5) There was no difference in mortality between the phenytoin and lacosamide groups, respectively (7.8% [9/116] vs. 4.1% [15/365]; $p = .116$).

In the subgroup analysis, 98 patients with severe TBI (defined by GCS < 9) were evaluated; 32 received phenytoin and 66 received lacosamide. Similar to the primary analysis, there was no difference in early PTS rates between both groups (phenytoin, 0% [0/32] vs lacosamide, 1.5% [1/66]; $p = 1.00$) but phenytoin had a higher incidence of ADEs (12.5% [4/32] vs 0% [0/66], $p = .01$).

Table 1
Demographics.

Variable	Phenytoin (N = 116)	Lacosamide (N = 365)	P-Value
Age (years)	50 ± 21	58 ± 22	<0.001
Gender (% Male)	82 (71%)	242 (66%)	0.380
Weight (kg)	81 ± 19	80 ± 22	0.572
Serum creatinine (mg/dL)	0.9 (0.8–1.0)	0.9 (0.8–1.1)	0.963
Initial systolic blood pressure (mmHg)	142 ± 28	141 ± 28	0.846
Mechanism of Injury:			0.116
Motor vehicle collision	49 (42%)	147 (40%)	
Fall	41 (35%)	134 (37%)	
Motor vehicle collision vs Pedestrian	9 (7.8%)	41 (11%)	
Assault	7 (6%)	26 (7.1%)	
Gunshot wound	1 (0.9%)	3 (0.8%)	
Miscellaneous	9 (7.8%)	14 (3.8%)	
Diagnosis CT Scan:			
Subarachnoid hemorrhage	79 (68%)	235 (64%)	0.438
Subdural hematoma	55 (47%)	186 (51%)	0.464
Epidural hematoma	15 (13%)	38 (10%)	0.506
Intraparenchymal hemorrhage	9 (7.8%)	11 (3%)	0.450
Intraventricular hemorrhage	11 (9.5%)	35 (9.6%)	0.026
Cortical Contusion	43 (37%)	121 (33%)	0.973
GCS:			
Initial GCS	11.3 ± 4.3	12.5 ± 3.8	0.010
Initial GCS < 9	32 (28%)	66 (18%)	0.027
Injury severity score	17 (13–29)	18 (16–25)	0.655
Head AIS	3.7 ± 0.9	3.6 ± 0.9	0.437
Admit blood alcohol concentration:			
>80 mg/dL	26 (22%)	72 (20%)	0.531
>150 mg/dL	23 (20%)	59 (16%)	0.361
>250 mg/dL	12 (10%)	25 (6.8%)	0.218
Mechanical Ventilation	62 (53%)	140 (38%)	0.004
Continuous infusion sedation (propofol or midazolam)	52 (45%)	127 (35%)	0.051

GCS, Glasgow coma scale; AIS, abbreviated injury scale.

Table 2
Univariate analysis of factors associated with early post traumatic seizures.

Variable	Seizure ($n = 6$)	No Seizure ($n = 475$)	P-Value
Age	67 ± 25	56 ± 22	0.226
Diagnosis CT Scan:			
Subarachnoid hemorrhage	3 (50%)	311 (66%)	0.423
Subdural hematoma	5 (83%)	236 (50%)	0.216
Epidural hematoma	0 (0%)	53 (11%)	1.00
Intraparenchymal hemorrhage	0 (0%)	20 (4.2%)	1.00
Intraventricular hemorrhage	0 (0%)	46 (9.7%)	1.00
Cortical Contusion	1 (16.7%)	163 (34%)	0.669
GCS:			
Initial GCS	11.3 ± 4.5	12.2 ± 4	0.811
Initial GCS < 9	1 (17%)	97 (20%)	1.00
Injury severity score	16 (16–22.3)	17 (14–26)	0.638
Head AIS	3.8 ± 0.4	3.7 ± 0.9	0.624
Mechanical Ventilation	3 (50%)	199 (42%)	0.699
Continuous infusion sedation (propofol or midazolam)	2 (33%)	177 (37%)	1.00
Lacosamide ppx	5 (83%)	360 (76%)	1.00
Admit blood alcohol concentration:			
>80 mg/dL	1 (17%)	97 (20%)	1.00
>150 mg/dL	1 (17%)	81 (17%)	1.00
>250 mg/dL	0 (0%)	37 (7.8%)	1.00

GCS, Glasgow coma scale; AIS, abbreviated injury scale

Table 4
Univariate analysis of factors associated with adverse drug events.

Variable	ADE ($n = 8$)	No ADE ($n = 473$)	P-Value
Age	62 ± 29	56 ± 22	0.430
Diagnosis CT Scan:			
Subarachnoid hemorrhage	3 (38%)	311 (66%)	0.133
Subdural hematoma	5 (38%)	238 (50%)	0.504
Epidural hematoma	1 (13%)	52 (11%)	1.00
Intraparenchymal hemorrhage	0 (0%)	20 (4.2%)	1.00
Intraventricular hemorrhage	3 (38%)	43 (9.1%)	0.033
Cortical Contusion	1 (13%)	163 (35%)	0.275
GCS:			
Initial GCS	10.3 ± 4.7	12.3 ± 4	0.156
Initial GCS < 9	4 (50%)	94 (20%)	0.058
Injury severity score	16.5 (16–29)	17 (14–26)	0.861
Head AIS	4 ± 0.5	3.6 ± 0.9	0.280
Mechanical Ventilation	4 (50%)	198 (42%)	0.726
Continuous infusion sedation (propofol or midazolam)	4 (50%)	175 (37%)	0.478
Lacosamide	2 (25%)	363 (77%)	0.003
Admit blood alcohol concentration:			
>80 mg/dL	1 (13%)	97 (21%)	1.00
>150 mg/dL	1 (13%)	81 (17%)	1.00
>250 mg/dL	1 (13%)	36 (7.6%)	0.475

GCS, Glasgow coma scale; AIS, abbreviated injury scale

4. Discussion

Antiepileptic drug administration is associated with a reduction in early, but not late, post-traumatic seizures [16,17]. Phenytoin has historically been the drug of choice for seizure prophylaxis following a TBI and the current recommended agent according to practice guidelines [1,3]. Although studies and guidelines support phenytoin's efficacy, its drug profile can lead to complications in practice [1,2]. Phenytoin pharmacokinetics are highly variable in the critically ill due to its high degree of protein binding and nonlinear elimination. Furthermore, phenytoin has been notoriously known for side effects, drug interactions, and adverse effects on cognitive function, all of which can be significant in critically ill patients. Finally, the accuracy of formulas commonly used to adjust total phenytoin concentrations for hypoalbuminemia has been questioned. In one study, the disagreement in the interpretation of the free level and the adjusted total level (e.g., therapeutic, subtherapeutic or supratherapeutic) was 23% [5]. This was largely due to the adjusted level overestimating the free level. Given these barriers and newer drug developments, the need for evidence supporting other AEDs for this indication is growing and apparent.

This is the first study (to our knowledge) evaluating lacosamide for the prevention of early PTS following TBI. The results highlight that the incidence of clinically witnessed, early PTS in patients receiving prophylaxis is low but ADE's with phenytoin are common. This was evident upon controlling for potential confounders as well as those with severe TBI. Research evaluating the safety and efficacy of lacosamide, specific to the ICU, is beginning to emerge particularly for patients with refractory status epilepticus [15,18-21]. Overall, lacosamide appears to be well tolerated. Notable ADE's in these reports included hypotension, transaminitis and angioedema. In our cohort, the 2 ADE's with lacosamide (necessitating discontinuation) were bradycardia and hallucinations.

There are no data specifically evaluating the pharmacokinetics of lacosamide in critically ill patients but its generalized pharmacokinetic/phamacodynamic profile make it an attractive option in the ICU. Lacosamide has a predictable dose-response curve largely due to its low inter-individual variability for both volume of distribution and elimination [22]. Dosing adjustments are not necessary based on age, gender or body weight but serum concentrations can accumulate in patients with severe renal impairment or hepatic disease. The potential for pharmacokinetic drug-drug interactions is low.

The most widely studied alternative to phenytoin for prevention of early PTS is levetiracetam [6-13]. Data supporting levetiracetam for this indication however are inconsistent. In one randomized comparative trial, no difference was noted in early seizure occurrence between phenytoin and levetiracetam (17% vs 15%; $p = 1.00$) but levetiracetam was associated with a lower frequency of worsened neurological status ($p = .024$) and gastrointestinal problems ($p = .043$) [11]. A second, prospective trial included 813 patients and reported no difference in seizure rate (1.5% vs. 1.5%, $p = .997$) or adverse drug events (7.9% vs. 10.3%, $p = .227$) between levetiracetam and phenytoin [7]. In contrast, a third study reported seizure activity recorded by electroencephalography in patients with severe TBI treated with either levetiracetam or phenytoin [8]. There was no difference in seizure activity between the two groups (6.7% vs. 0%, $p = .556$) but levetiracetam was associated with an increased frequency of abnormal EEG findings (53% vs. 0%, $p = .003$) and seizure tendency (47% vs. 0%, $p = .007$). Similarly, another study

Table 3
Adverse drug events necessitating antiepileptic drug discontinuation.

Adverse drug event	Phenytoin	Lacosamide
Drug fever*	3	0
Drowsiness	1	0
Nystagmus	1	0
Pruritis	1	0
Bradycardia	0	1
Hallucinations	0	1

* Defined as temperature > 38 °C with no other explanation.

Table 5
Multivariate analysis for adverse drug events.

Step	Variable	OR (95% CI)	p
1	Phenytoin	8.8 (1.7–44.6)	0.009
	Initial GCS < 9	3.2 (0.8–13.3)	0.113
2	Phenytoin	9.4 (1.8–48.9)	0.008
	Initial GCS < 9	2.9 (0.7–12.4)	0.154
	Intraventricular hemorrhage	6.1 (1.3–28.4)	0.022

Hosmer-Lemeshow test for step 2, $p = .312$
Variables included in the model: phenytoin, initial GCS < 9, intraventricular hemorrhage.

found no difference in clinical and electrographic seizures between levetiracetam and phenytoin but in patients with a midline shift >0 mm, levetiracetam was associated with an increased risk of electrographic seizures (OR = 1.34, $p = .028$) [13]. Last, in one retrospective, propensity score-matched analysis, the incidence of seizures with levetiracetam was similar to the cohort of patients who receive no prophylaxis (1.9% vs. 3.4%, $p = .50$) [12]. The inconsistencies in these studies along with the unpredictable dose-response curve with levetiracetam raises questions as to its standing as the "preferred" alternative to phenytoin for this indication. Additional studies are needed with not only levetiracetam, but other potential alternatives such as valproic acid.

Continuous infusions of sedative medications used to facilitate mechanical ventilation such as propofol and midazolam also have anticonvulsant properties thus can contribute to seizure prophylaxis. In our cohort, propofol and midazolam infusions were more prevalent in phenytoin treated patients but they were not associated with the incidence of seizures or prophylaxis-related ADE's. The doses of sedatives used in the setting of status epilepticus however are typically larger than that used to facilitate mechanical ventilation, particularly when treatment goals are consistent with light levels of sedation. Nevertheless, the potential for drug interactions with anti-epileptics and sedatives do exist [23,24]. One study revealed cytochrome-P450-mediated antiepileptics (e.g., phenytoin) decrease the clearance of propofol leading to a longer time to emerge from anesthesia [23]. Conversely, phenytoin has been shown to increase the clearance of midazolam, likely through induction of the cytochrome P-450 system [24]. Lacosamide does not induce or inhibit cytochrome P-450 enzymes therefore these drug interactions are not expected to be observed.

There are several limitations to our study which must be considered. First it was a single-center, retrospective study thus the limitations that accompany such a design are apparent. This includes the perceptions among the clinicians (at the time prescribing decisions were made) pertaining to the adverse effect profile for each agent (e.g., phenytoin > lacosamide). Allocation to the phenytoin or lacosamide groups were not randomized but more so based on the introduction of lacosamide into local practice and lacosamide dosing was not standardized. There was no practitioner-based bias or bias secondary to severity of injury but time-dependence bias does exist. Additionally, there were inherent differences between the 2 groups and while we attempted to account for those differences via multivariate analysis, randomization via a prospective trial would be necessary. Another limitation pertains to the fact that continuous EEG monitoring is only used at our institution after a clinical seizure occurs; thus we were unable to capture and categorize clinical seizures or detect the initial PTS or subclinical seizures. As subclinical seizures are more common than clinically evident seizures (and associated with worse outcomes), continuous EEG monitoring should be included in future clinical trials. Next, only 20% of our cohort had severe TBI therefore the generalizability in this population could be questioned. Finally, our study did not have an adequate sample size to detect a significant difference in seizure rate. While we did evaluate 481 patients, >2000 patients would be needed to achieve 80% power, assuming a baseline seizure incidence of 4% and a relative reduction of 50%.

5. Conclusion

There was no difference in the incidence of early post traumatic seizures following traumatic brain injury in patients who received lacosamide versus phenytoin. Lacosamide however, had a more tolerable side effect profile which was associated with less treatment discontinuation due to ADE's. These data support the need for a randomized controlled trial to better ascertain the role of a 7-day course of lacosamide for this indication. Additional studies describing lacosamide pharmacokinetics and pharmacodynamics, specifically in the critically ill are necessary along with long term clinical outcomes such as neurologic function and quality of life.

Declarations of interest

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