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Original Article

Comparison of Effectiveness of Brivaracetam and Levetiracetam for Prophylaxis of Early Post-Traumatic Seizures: A Prospective Comparative Interventional Study

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Abstract

Introduction Early posttraumatic seizures (EPTS) are a major complication after a head injury, defined as seizures developing within the first 7 days of trauma. Levetiracetam has become a popular drug for the prevention of posttraumatic seizures in institutions worldwide. However, it has been reportedly associated with adverse effects like behavioral changes and somnolence. This study aimed to compare the efficacy of a newer drug, brivaracetam, which is reported to have a better pharmacokinetic profile. These findings may be significant in providing a safer yet efficacious alternative to levetiracetam.

Objective The aim of this study was to evaluate the efficacy of brivaracetam for prophylaxis of EPTS and to compare it with levetiracetam.

Materials and Methods A prospective, single-blind, parallel-group (alternate allocation) controlled trial over 100 patients admitted with traumatic brain injury in the Department of Neurosurgery, Goa Medical College, Panaji, Goa, India. The data was analyzed using IBM SPSS Statistics 29.0.

Results Twenty patients developed EPTS in the study group: 8 from the group receiving brivaracetam and 12 from the group receiving levetiracetam. Although the brivaracetam group had a lower incidence of EPTS, the difference was not statistically significant. Eleven patients from the levetiracetam group developed side effects, while six patients from the brivaracetam group had side effects. There was no significant difference in the incidence of side effects.

Conclusion Brivaracetam has efficacy equal to that of levetiracetam for prophylaxis of EPTS.

Keywords
- early posttraumatic seizure
- traumatic brain injury
- seizure prophylaxis
- brivaracetam
- levetiracetam

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Introduction

Traumatic brain injury (TBI) is a major cause of mortality and disability among young individuals.[1] One of the most disabling and significant sequelae of TBI is posttraumatic seizures (PTS), which are characterized by one or more seizure events following a TBI.[2] Early PTS (EPTS) is specifically defined as a seizure occurring within 7 days of the initial TBI.[3]

Studies have demonstrated that experiencing early seizures after a TBI is associated with prolonged stays in the intensive care unit, extended overall hospitalization, and an increased probability of being discharged to a nursing facility.[4] The estimated incidence of EPTS falls within the range of 2.1 to 16.9%.[5] The occurrence of EPTS serves as a predictive factor for late PTSs (LPTS), which are defined as seizures occurring more than 7 days after the TBI, and posttraumatic epilepsy (PTE). PTE, characterized by recurring seizure episodes following a TBI, may account for as much as 20% of all epilepsy cases.[6]

Risk factors for PTS include severe TBI, chronic alcohol use, extended amnesia, skull fractures, younger age, and immediate seizure onset.[7] The pathophysiology of PTE involves excitotoxicity, neuroinflammation, oxidative stress, and neurodegeneration, with oxidative stress and mitochondrial dysfunction playing crucial roles in epileptogenesis.[8] Further research is needed to fully understand PTE, given the diverse injury mechanisms in TBI. Considering the link between EPTS and both LPTS and PTE, as well as the extended hospital stays and intensive care unit durations associated with early seizures, it is crucial to enhance our comprehension of EPTS and its management.

In the acute setting, it is essential to use an antiepileptic drug (AED), which is available both, a parenterally administrable form for immediate use and an orally administered form that can be continued after discharge.

Numerous medications have been employed in the attempt to prevent PTS, with older retrospective investigations highlighting the effectiveness of phenytoin (PHT).[9] In a randomized, double-blind trial, Temkin et al[10] examined PHT's role in preventing PTS and concluded that PHT diminishes the occurrence of EPTS but does not have the same impact on LPTS. This suggests that PHT may primarily suppress early seizures rather than serving as a comprehensive prophylactic measure. Reducing the occurrence of early seizures is of paramount importance. Further, nearly a quarter of individuals experiencing EPTS are at risk of developing LPTS.[11] PHT suffers from serious consequences when administered parenterally, such as arrhythmia and hypotension.

Due to its enhanced safety profile and comparable effectiveness to PHT, levetiracetam (LEV) has emerged as the preferred treatment for PTS prophylaxis at numerous institutions. A systematic review by Xu et al[12] comparing the safety and efficacy of LEV and PHT for PTS prevention concluded that both drugs exhibit similar efficacy, but LEV offers a more favorable safety profile. A systematic review by Bakr and Belli[13] revealed comparable incidences of late seizures between LEV and PHT, with LEV demonstrating superior long-term outcomes. These studies support a shift from PHT to LEV for seizure prophylaxis, owing to LEV's improved adverse effect profile and equivalent effectiveness.

With widespread adoption of LEV, adverse effects associated with LEV were identified, and the side effect profile of LEV have been divided into: asthenia/somnolence, coordination difficulties, and psychiatric/behavioral abnormalities.[14] Apart from these, LEV administration is associated with headaches and thrombocytopenia.[15] Brivaracetam's (BRV) exceptional selectivity in its mechanism of action and higher affinity for receptor synaptic vesicle protein 2A (SV2A) suggests that it might exhibit superior clinical tolerability in comparison to LEV.[16]

The increased possibility of behavioral abnormalities like aggression, coordination difficulties, somnolence, and headaches can complicate the acute management of TBI, as TBI itself may lead to such reactions in various combinations. Switching LEV to BRV in patients developing behavioral adverse effects results in the resolution of behavioral side effects.[17] Given the better safety profile of BRV, particularly with respect to psychiatric adverse effects, we investigated its role as a probable agent of choice for prophylaxis of EPTS.

Materials and Methods

After getting clearance from the Institutional Review Board and Ethics Committee, along with successful registration of the study under the Clinical Trials Registry - India (CTRI), we conducted a prospective, single-blinded, parallel-group (alternate allocation) control trial over 100 consecutive patients admitted to the Department of Neurosurgery, Goa Medical College, Panaji, Goa, India meeting inclusion criteria without exclusion criteria as described below.

All patients coming to our trauma center with suspected head trauma were evaluated and initially managed as per 10th edition Advanced Trauma Life Support guidelines[18] and patients requiring computed tomography (CT) brain within 1 hour as per the latest National Institute for Health and Care Excellence guidelines[19] were subjected to CT brain. Patients were treated as per the Brain Trauma Foundation guidelines, 4th edition.[20]

Patients were divided into two groups, the allocation method used was "alternate allocation," wherein each patient was allocated alternatively into treatment groups A (receiving BRV) and B (receiving LEV) in the predetermined order of A-B-A-B-A-B and so on, on the basis of the order of admission. Both group A (BRV) and B (LEV) had 50 patients each.

For the purpose of this study injectable formulation of BRV, available as vials in strength of 10 mg/mL containing total 50 mg/5 mL of BRV, manufactured by "LINUX Laboratories," commercially available in India under trade name "BRITAM" was used. Oral formulation of BRV manufactured by the same manufacturer, marketed under trade name "BRITAM 50" as tablet containing 50 mg of BRV was used for group A (BRV). Whereas injectable formulation of LEV, available as vials in the strength of 100 mg/mL containing total 500 mg/5 mL of LEV, manufactured by "CIPLA Ltd.," commercially available in India under trade name "LEVEPSY" was used. Oral formulation of LEV manufactured by the same

manufacturer, marketed under trade name "LEVEPSY 500" as tablet containing 500 mg of LEV was used for group B (LEV). These formulations were chosen as they were available as routine supply at central drug supply of our institute.

Patients in group A were given an initial injection BRV intravenous loading dose of 2 mg/kg diluted in 100 mL of 0.9% NaCl over 15 minutes within the first hour of evaluation or as soon as possible in the trauma center, followed by 2 mg/kg/day in two divided doses.

Patients in group B were given an initial injection LEV intravenous loading dose of 20 mg/kg diluted in 100 mL of 0.9% NaCl over 15 minutes within the first hour of evaluation or as soon as possible in the trauma center, followed by 20 mg/kg/day in two divided doses.

In both groups, drugs were switched to oral doses equal to the total daily parenteral dosage divided into two doses, 12 hours apart, once enteral feeding was resumed.

Patients with history of trauma having the following findings on a plain CT brain with Glasgow Coma Scale (GCS) equal to or more than 5 were included:

1. Acute subdural hematoma
2. Compound-depressed fracture with underlying contusions
3. Intracerebral hematoma
4. Diffuse axonal injury
5. Cerebral contusion
6. Traumatic subarachnoid hemorrhage

Patients with the following were excluded:

1. Normal plain CT brain
2. Preexisting seizure disorder
3. Any other preexisting pathological brain condition
4. GCS less than 5
5. Absence of brain stem reflexes
6. Previous history of psychiatric illness or medication
7. Patients with polytrauma requiring surgical intervention for injury apart from brain injury
8. Seizure before administration of LEV or BRV

Patients were followed for 7 days for the study period from admission, and the following details were collected for the study:

1. Age/sex
2. Mode of injury
3. Comorbidities
4. GCS on admission
5. Duration of loss of consciousness
6. Convulsions or seizure events
7. Neurological deficits
8. CT scan findings
9. Type of treatment: medical or surgical
10. Antiepileptic dose
11. Adverse reactions

Statistical Analysis

Group-wise data was collected and statistically analyzed with appropriate statistical tests like chi-squared test, Fisher's exact test, *t*-test, and Wilcoxon-Mann-Whitney *U* test as applicable using IBM SPSS Statistics 29.0.

Results

During the study period of 3 months, 100 patients with TBI, meeting the inclusion criteria were alternately assigned to the two groups: group A receiving BRV and group B receiving LEV. The collected data for both the groups were analyzed and compared. The patients in the two groups were well matched in age (45.32 vs. 41.78 years, $p = 0.316$) and sex (male, 72 vs. 80%, $p = 0.349$) and other clinical parameters. Causes of head injuries were statistically similar in the two groups ($p = 0.100$) and motor vehicle accident was the most common cause in both groups; 74% in group A (BRV) and 72% in group B (LEV). Prevalence of comorbidities (diabetes, hypertension, ischemic heart disease, alcohol abuse) was similar ($p = 1.000$). There was no significant difference between the groups in terms of GCS categories at admission. Majority of patients had GCS 14 to 15 in both groups ($n = 22$; 44% vs. $n = 27$; 72%: group BRV vs. LEV, respectively). Second highest number of patients had GCS between 9 and 13 ($n = 21$; 42% vs. 15; 30%: group BRV vs. group LEV). Medical management alone was sufficient in 78% patients ($n = 39$) of group BRV and 76% patients of group LEV ($n = 38$). The remaining required surgical intervention.

Clinical and radiological risk factors for seizures in both groups have been shown in ►**Table 1**. There was no significant difference between the various groups in terms of distribution of number of posttraumatic convulsion (chi-square = 1.563, $p = 0.492$). In group BRV, 84.0% ($n = 42$) of the participants had no seizure, 4.0% ($n = 2$) of the participants had single seizure, and 12.0% ($n = 6$) of the participants had multiple episodes of seizure. In group LEV, 76.0% ($n = 38$) of the participants in the group had no seizure, 10.0% ($n = 5$) of the participants had single episode of seizure, and 14.0% ($n = 7$) of the participants had multiple episodes of seizure. There was no significant difference between both groups in terms of distribution of side effects, that is, 12.0% ($n = 6$) on BRV reported adverse reaction while 22.0% ($n = 11$) of the participants in group LEV reported adverse reaction. Neither of the group reported any severe adverse drug reaction necessitating change of drug. Headache was the most reported complaint in group BRV (14%; $n = 7$) while asthenia/somnolence was the most reported adverse effect in group LEV (14%; $n = 7$).

Patients in both groups who underwent surgical intervention received general anesthesia; general anesthetic drugs like propofol, which themselves reduce the risk of seizure, may act as an effect modifier. To negate this effect, patients were analyzed independently on the basis of type of treatment as a variable as described in ►**Table 2**. There was no statistically significant difference in the frequency of seizure in patients undergoing surgery under general anesthetics in both groups, viz. BRV and LEV.

Discussion

The presence of EPTS has been documented to complicate clinical care and the trajectory of hospitalization.[21] Seizures lead to increased occurrences of aspiration; an increase in

Table 1 Summary table for demographic data and various associations of parameters in both groups

Parameters	Group		*p*-Value
	Brivaracetam ($n = 50$)	Levetiracetam ($n = 50$)	
Age (y)	45.32 ± 16.77	41.78 ± 18.29	0.316[a]
Gender			0.349[b]
Male	36 (72.0%)	40 (80.0%)	
Female	14 (28.0%)	10 (20.0%)	
Mode of injury			1.000[c]
MVA	37 (74.0%)	36 (72.0%)	
Fall	12 (24.0%)	13 (26.0%)	
Assault	1 (2.0%)	1 (2.0%)	
GCS category			0.455[b]
14-15	22 (44.0%)	27 (54.0%)	
9–13	21 (42.0%)	15 (30.0%)	
≤ 8	7 (14.0%)	8 (16.0%)	
Posttraumatic convulsion (yes)	8 (16.0%)	12 (24.0%)	0.317[b]
Type of posttraumatic convulsion			0.085[c]
None	42 (84.0%)	38 (76.0%)	
Generalized	8 (16.0%)	7 (14.0%)	
Focal	0 (0.0%)	5 (10.0%)	
Number of posttraumatic convulsion			0.492[c]
None	42 (84.0%)	38 (76.0%)	
Single	2 (4.0%)	5 (10.0%)	
Multiple	6 (12.0%)	7 (14.0%)	
Loss of consciousness (yes)	36 (72.0%)	29 (58.0%)	0.142[b]
Any comorbidity (yes)	15 (30.0%)	15 (30.0%)	1.000[b]
Comorbidity: None (yes)	35 (70.0%)	35 (70.0%)	1.000[b]
Comorbidity: Hypertension (yes)	10 (20.0%)	7 (14.0%)	0.424[b]
Comorbidity: Diabetes mellitus (yes)	5 (10.0%)	7 (14.0%)	0.538[b]
Comorbidity: Others (yes)	5 (10.0%)	3 (6.0%)	0.715[c]
Comorbidity: Chronic alcoholism (yes)	2 (4.0%)	5 (10.0%)	0.436[c]
Past convulsions (yes)	0 (0.0%)	0 (0.0%)	1.000[b]
CT scan findings: Acute SDH (yes)[d]	19 (38.0%)	32 (64.0%)	0.009[b]
CT scan findings: Contusion (yes)	20 (40.0%)	20 (40.0%)	1.000[b]
CT scan findings: Extradural hematoma (yes)	14 (28.0%)	7 (14.0%)	0.086[b]
CT scan findings: SAH (yes)	8 (16.0%)	5 (10.0%)	0.372[b]
CT scan findings: None (yes)	0 (0.0%)	0 (0.0%)	1.000[b]
Type of treatment			0.812[b]
Conservative	39 (78.0%)	38 (76.0%)	
Surgery	11 (22.0%)	12 (24.0%)	
Advice on discharge[d]			< 0.001[b]
Brivaracetam	50 (100.0%)	0 (0.0%)	
Levetiracetam	0 (0.0%)	50 (100.0%)	
Any side effect (yes)	6 (12.0%)	11 (22.0%)	0.287[b]
Side effects: None (yes)	44 (88.0%)	39 (78.0%)	0.287[b]

Table 1 (*Continued*)

Parameters	Group		*p*-Value
	Brivaracetam ($n = 50$)	Levetiracetam ($n = 50$)	
Side effects: Asthenia/Somnolence (yes)	5 (10.0%)	7 (14.0%)	0.538[b]
Side effects: Behavior changes (Yes)	1 (2.0%)	4 (8.0%)	0.362[c]
Complaint of headache (yes)	7 (14.0%)	6 (12.0%)	0.766[b]

Abbreviations: CT, computed tomography; GCS, Glasgow Coma Scale; MVA, motor vehicle accident; SAH, subarachnoid hemorrhage; SDH, subdural hematoma.
[a]*t*-Test.
[b]Chi-squared test.
[c]Fisher's exact test.
[d]Significant at $p < 0.05$.

cerebral edema could contribute to brain herniation in the presence of raised intracranial pressure and a worsening of the sensorium postictally which can confound neurological monitoring for an existing posttraumatic intracranial space-occupying hematoma. To the best of our knowledge, there are no direct studies comparing the efficacy of LEV and BRV in acute TBI for EPTS. We found no significant difference in the occurrence of EPTS in patients receiving BRV and LEV for prophylaxis, 16 and 24%, respectively.

Seizure prophylaxis for PTS involves the administration of anticonvulsants to individuals after TBI to forestall the occurrence of seizures. The rationale behind routine seizure prophylaxis stems from the relatively high incidence of PTS in severe TBI cases, with potential advantages in averting seizures after TBI, such as limiting disruptions in acute physiology, preventing the onset of chronic epilepsy, and averting herniation and mortality. Nonetheless, it is essential to balance these potential benefits with the desire to minimize neurobehavioral and other side effects, especially if the medications prove ineffective in seizure prevention. Therefore, a critical assessment of the efficacy, overall benefits, and potential risks associated with anticonvulsants used for PTS prevention is crucial.

Owing to its favorable characteristics, including ease of use, minimal interactions, and impressive effectiveness and tolerability, LEV has gained worldwide recognition as one of the prominent AEDs. BRV, which demonstrates increased selectivity at the SV2A binding site and generally provides improved tolerability in terms of psychiatric adverse events, can prove to be a much safer option for use in TBI patients.

LEV ([S]. alpha-ethyl-2-oxo-1-pyrrolidineacetamide) (C8H14N2O2)[22] and BRV ([2S]-2-[(4R)-2-oxo-4-propylpyrrolidin-1-yl] butanamide) (C11H20N2O2)[23] are part of a class of pyrrolidone compounds derived from piracetam and are the results of a development program initiated by the Belgian pharmaceutical company UCB.[24]

Piracetam was first synthesized in 1964 as a gamma-aminobutyric acid (GABA)[25] analog intended to induce sleep. However, it did not exhibit GABA-ergic effects but instead demonstrated atypical psychotropic effects. These findings suggested a selective and direct action on the telencephalon, making piracetam the first nootropic agent. Further research led to the development of etiracetam, an ethyl analog of piracetam. LEV ((S)-α-ethyl-2-oxo-1-pyrrolidineacetamide), the S-enantiomer of etiracetam,[26] failed to show cognitive benefits in humans but was investigated in epilepsy models. With further studies,[27] LEV was identified as a potent anticonvulsant drug, and further development of a drug with much higher affinity for the presynaptic SV2A receptor site, which is the main and unique mode of action of LEV, lead to the development of BRV.

LEV binds to SV2A[28] in a saturable, reversible, and stereoselective manner.[29] LEV displays only modest affinity for SV2A and exerts its effects through multiple other

Table 2 Distribution of patients developing seizure in conservative and surgical management in both groups

	Group		*p*-Value
	Brivaracetam	Levetiracetam	
Patients managed conservatively[a]	($n = 39$)	($n = 38$)	1
Not developing seizure	34 (87.17%)	33 (86.84%)	
Conservatively managed developing seizure	5 (12.82%)	5 (13.15%)	
Patients managed surgically[a]	($n = 11$)	($n = 12$)	0.214
Not developing seizure	8 (72.72%)	5 (41.66%)	
Surgically managed developing seizure	3 (27.27%)	7 (58.33%)	

[a]Fisher's exact test.

mechanisms of action, including the inhibition of N-type calcium channels and acting as an antagonist for AMPA receptors.[30] However, the SV2A binding mechanism is the main mechanism of LEV activity as an anticonvulsant.[31] BRV exhibits a 15- to 30-fold greater affinity for SV2A when compared to LEV. Moreover, at doses exceeding 100 times higher, BRV demonstrated no binding, activation, or inhibition of a comprehensive panel comprising 55 other receptors, channels, and enzymes[32] suggesting better tolerability, fewer adverse effects, and lesser interaction with other drugs.

Current recommendations endorse the administration of prophylactic AEDs within the initial 7 days following TBI to reduce the occurrence of EPTS.[33] However, as per the Brain Trauma Foundation guidelines[32] for the management of severe TBI, evidences are insufficient to support a level 1 recommendation for the use of AED for prophylaxis, as well as to endorse LEV over PHT concerning its effectiveness in preventing EPTS and minimizing toxicity.

Our study demonstrated that about 20% of the patients admitted with TBI suffered EPTS, which is comparable to the documented range of 2[34] to 14 to 30%.[35] The most common adverse effect associated with LEV was asthenia or somnolence in 14% (7 cases) of patients, comparable to 14.8% in the controlled trial by De Smedt et al.[36]

A total of 4 (8%) patients in the LEV group developed behavioral change in our study, comparable to 7.6% patients in a study conducted by Mula et al.[37]

Headache was reported to occur in 9 to 10.5% of patients in randomized control studies by Ryvlin et al[38]and Brandt et al,[39] in patients on treatment for seizure, all these patients had no history of trauma. In our patients with trauma, the injury itself could have contributed to the headache, therefore, the occurrence of headache as an adverse effect cannot be commented.

Limitations

Our sample is small with 100 patients; further studies with a larger sample size will help establish BRV as a safe alternative for early posttraumatic prophylaxis. Further, in the current study, we aimed to study the efficacy of BRV for EPTS only, longer duration studies are needed to confirm the efficacy for LPTS.

Conclusion

Our study shows that BRV has efficacy equal to that of LEV for prophylaxis of EPTS and is one of the first studies, to the best of our knowledge, comparing LEV and BRV in TBI for EPTS.

Note

Clinical Trial Registry – India (ICMR-NIMS) Reg. no. CTRI/2023/11/073013. Registered with Clinical Trial Registry-India (ICMR-NIMS) CTRI/2023/11/059371.

Ethical Approval

Ethical clearance obtained from Goa Medical College Institutional ethics committee with reference number GMCIEC/2023/07.

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None.

Conflict of Interest

P.K.S. S.S.B. reported all work done at Government run Goa Medical College and drugs were available in hospital supply.

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