



Research Article

COMPARING THE EFFICACY OF PHENYTOIN, LEVETIRACETAM AND SODIUM VALPROATE IN PREVENTION OF POST-TRAUMATIC SEIZURES IN BRAIN INJURY

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ABSTRACT

Background: Traumatic brain injury is said to be a variation of brain function or other corroboration of brain pathology, which are caused by the outward jolts, penetration or expeditious brain movements within the skull which results in mental state alteration. There is evidence that use of anti-epileptics as a prophylaxis have been found to be variable efficacy against post-traumatic seizures. In patients who are diagnosed with moderate to severe traumatic brain injury (TBI) the efficacy of Phenytoin, Levetiracetam and Sodium valproate regarding the post-traumatic seizures were compared to appraise their effectiveness's. **Material and methods:** Males and females of 17-80 years diagnosed with moderate to severe traumatic brain injury were included in our study. **Results:** There was a significant reduction in early and late post-traumatic seizures in patients treated with Phenytoin and Levetiracetam than those treated with Sodium valproate. **Conclusion:** From this study we concluded that the efficacy of Levetiracetam was relatively similar to Phenytoin in preventing early and late post-traumatic seizures, whereas Sodium valproate showed poor efficacy.

Key words: Post-traumatic seizures (PTS), Traumatic brain injury (TBI), early post-traumatic seizures (ePTS), Phenytoin, Levetiracetam, Sodium valproate.

INTRODUCTION

Traumatic brain injury is contemplated to be a utmost health problem, particularly in urban trauma centres with a generic difficulty in emergency properties.^{1,2} Its consequential complications such as changes affecting the language, thinking, emotions or sensation, which may not be easily evident and lack of knowledge among the public, therefore it is cited as 'silent epidemic'.³ A seizure is the 'physical response to abnormal electrical activity in the brain'.⁴ Post traumatic seizures have been used to describe the seizure occurrence after head trauma and they are believed to be incidentally related to the trauma itself.⁵ They arise from the traumatic brain injury and brain harm caused by physical trauma.⁶ Generally post-traumatic seizures are classified into three categories based on the seizure occurrence after the brain injury as-'immediate seizures', 'early seizures', and 'late seizures'. Immediate seizures refers to those which occurs at or minute after the thwack; early seizures are those that occurs within a week of the brain injury whereas as those that occurs after the week of the brain injury are called as late seizures.^{7,8,9} The actual therapy for TBI patients depends on the particular injuries that the patient has succoured, well timed diagnosis, imaging results and clinical data.^{1,10} In a study performed for identifying the brain injury associated with development of seizures in particular species; it has shown that the enhanced risk of seizures after TBI generally depends on the injury severity and time from its occurrence.¹¹ An age of 65 or older, a skull fracture, brain bruise with subdural hematoma, and consciousness deficient or amnesia (more than one day) are considered to be a vital risk factors for the later seizures.^{11,12,13}

The time course of the risk and the risk factors are considered to be a notable factors for designing the seizure prophylaxis studies.¹⁴ The outcomes of patients with TBI varies according to the age; in a study conducted by Aisekainen et al expressed that children are more susceptible to early seizures, whereas adolescents and adults are more prone to late seizures.^{15,16} Antiepileptic's have been used for many years to prevent the development of posttraumatic seizures. The prophylactical use of the phenytoin was effective, which was proposed by early retrospective studies.^{17,18,19} Nevertheless, succeeding prospective, double blind trials of treatment with phenytoin and lower doses other antiepileptic's like phenobarbital failed to show that such treatment had more benefit than placebo.^{20,21,22,23} Levetiracetam has shown to have similar efficacy in preventing the seizures after the traumatic brain injury which was proposed by a study conducted by Syed Nabeel Zafar et al. However there is a limited evidence regarding this statement, further studies need to be conducted.²⁴ Sodium valproate has less side effects and it has been recommended to the traumatic brain injury patients. There is evidence from the clinical trials that it has no effect on reduction of late posttraumatic seizures. It has been suggested that the early posttraumatic seizures progression can be prevented by the Sodium valproate administration.²⁵

MATERIAL AND METHODS

It is a prospective, comparative and observational study conducted in patients from Mahatma Gandhi Memorial hospital, Warangal. Patients were explained about the study and informed consent forms were obtained by explaining them in their local

language. Institutional Human Ethical Committee Endorsement was obtained after submission of protocol and IHEC No. is MGM/VCOP/PHARMD/V/08/2018.

Inclusion criteria:

Patients are included into the study based on the following criteria for severe brain injury: A bruise on the cortical region which is visible on CT scanning. Hematoma of the epidural, subdural or intra cerebral regions. The skull fracture which is of depressed type. The wound which is deeply pierced into the head. A seizure within 24 hours of injury or a score of 10 or less on the Glasgow Coma Scale on admission.

Exclusion criteria:

Exclusion criteria for the study subjects includes: Patients with age less than 16 years. The meantime between brain injury to administration of the study drug is greater than the 24 hours, Female patients who are either in pregnancy or lactation condition. Patients with history of chronic alcoholism. The previous history of head injury. The occurrence of seizures before injury or the administration of anti-seizure medication before study-drug loading. Previous neurosurgery involving penetration of Dura or another previous neurologic condition that might predispose the patient to seizures.

Study design:

It is a prospective observational, comparative study design and the patients who were taking Phenytoin 100 mg, Levetiracetam 500 mg and Sodium valproate 100 mg were included.

Clinical response assessment:

The efficacy of drugs in preventing the seizure control was assessed by considering the seizure onset. Our research outcomes were assessed based on the occurrence of seizures, which were categorised as: Immediate onset- The incident of seizures within 24 hours of drug administration, early onset- The event of seizures within a week of drug administration and Late onset- The seizures which develop either on day 8 or later.

RESULTS

Demographics and baseline characteristics of study population:

This is presented in table 1

Distribution of patients according to gender:

A total of 79 patients included in the study of which maximum numbers of subjects were males 54(70%) than females 23(30%). This is presented in figure 1.

Distribution of patients according to age:

Distribution of patients according to their age group was overall 79 patients were included in the study of which age group between 18-20 were 7 (9%), age group between 21-30 were 23 (29%), age group between 31-40 were 22(28%), age group between 41-50 were 19(24%), age group between 51-60 were 5(6%) and age group above 60 were 3 (4%). From all these groups maximum number of subjects were in between age of 21-50 years. This is presented in figure 2.

Distribution of patients according to their type of injury:

From the selected population most of the patients having Epidural hematoma (EDH) were 36(45%), followed by subarachnoid hematoma (SAH) were 16(20%), Sub Dural hematoma (SDH) were 21(18%) and intra cerebral hematoma (ICH) were 6(8%). This is presented in figure 3.

Distribution of patients on phenytoin according to occurrence of seizures:

Out of 30 patients who were on with phenytoin, early onset was seen in 2 patients, late onset was seen in 9 patients and no seizure onset was seen in 19 patients. This is presented in figure 4.

Distribution of patients on levetiracetam according to occurrence of seizures:

Out of 24 patients who were on with levetiracetam, early onset was seen in 4 patients, late onset was seen in 6 patients and no seizure onset was seen in 14 patients. This is presented in figure 5

Distribution of patients on sodium valproate according to occurrence of seizures:

Out of 25 patients who were on with sodium valproate, immediate onset was seen in 5 patients, early onset was seen in 7 patients, late onset was seen in 9 patients and no seizure onset was seen in 4 patients. This is presented in figure 6.

Comparison of phenytoin, levetiracetam, and sodium valproate based on seizure occurrence:

From a total of 79 patients who were divided into three groups of phenytoin, levetiracetam and sodium valproate. Immediate onset type of seizures was observed only in patients treated with Sodium valproate. Early onset type of seizures was observed in a maximum number in patients treated with Sodium valproate Sodium valproate 5 followed by patients with Levetiracetam 4 and Phenytoin 2. Late onset type of seizures were occurred maximum in patients treated with Sodium valproate and Phenytoin 9 followed by Levetiracetam 6. The absence of seizures were found to be maximum in patients who were treated with Phenytoin which was 19 followed by Levetiracetam and Sodium valproate as 14 and 4 respectively. This is presented in figure 7.

DISCUSSION

Early post traumatic seizures are thought result from direct effect of brain damage caused by physical trauma to brain. The probability of development of seizures based on the type of injury and severity of the person. For example those with penetrating injuries and bleeding within the brain confer a high risk.²⁶

According to the guidelines of the Brain Trauma Foundation and American Association of Neurosurgery (AAN) which are according to the current available literature, the prophylactical use of anti-epileptical drugs should be administered only during the first week after a moderate or severe traumatic brain injury. Earlier prophylaxis for post-traumatic seizures in patients who are encountered with the risk factors will going to be advantageous.^{27, 28}

In our study we observed that efficacy of levetiracetam was relatively similar to phenytoin in preventing early post traumatic seizures. Our results were similar to research conducted by Jones KE et al. in 2008.²⁹

In present study the efficacy of sodium valproate in preventing early post traumatic seizures was low compared to phenytoin. Our results were similar to research conducted by Gail D. Anderson et.al in 1999.³⁰

In our study we noticed that patients of age group of 18-50 were found to be dominant which is in comparison to other age groups and it is in contrast with a clinical research done by Ch. Jyothi in 2017.³¹ but in smaller number of population.

Table-1: demographics and baseline characteristics of study population

Characteristics	Phenytoin	Levetiracetam	Sodium valproate
Gender			
Males	13	24	17
Females	16	1	6
Age(years)			
18-20	1	3	1
21-30	6	9	8
31-40	9	6	7
41-50	8	4	7
51-60	3	2	0
>60	2	0	0
Post traumatic seizures			
Yes	11	10	21
No	19	14	4

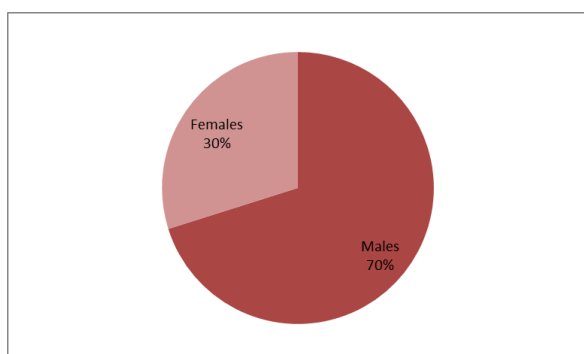


Figure 1: Distribution of patients according to gender

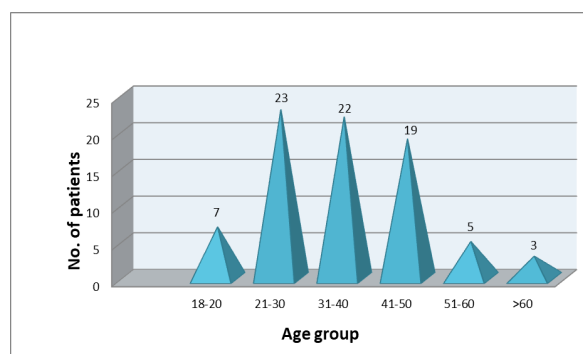


Figure 2: Distribution of patients according to age

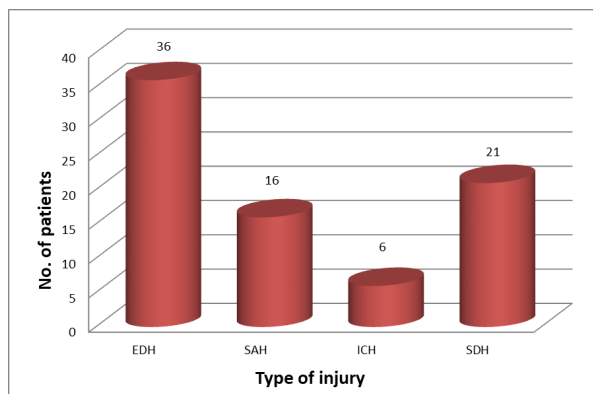


Figure 3: Distribution of patients according to type of injury

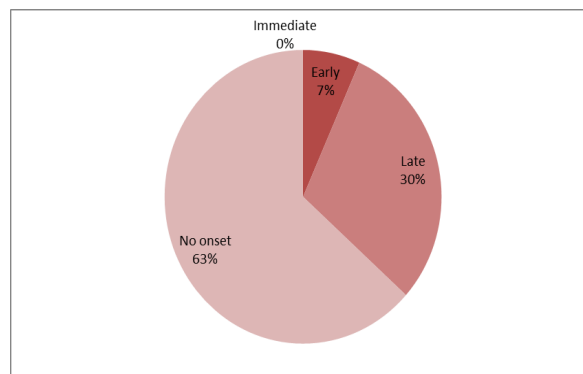


Figure 4: Distribution of patients on phenytoin according to occurrence of seizures

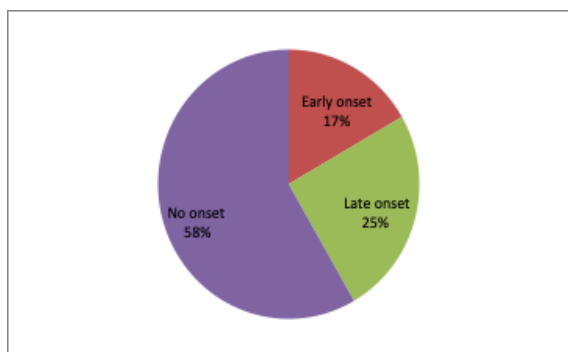


Figure 5: Distribution of patients on levetiracetam according to occurrence of seizures

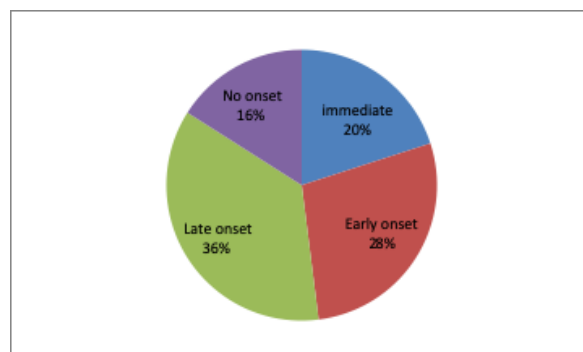


Figure 6: Distribution of patients on sodium valproate according to occurrence of seizures

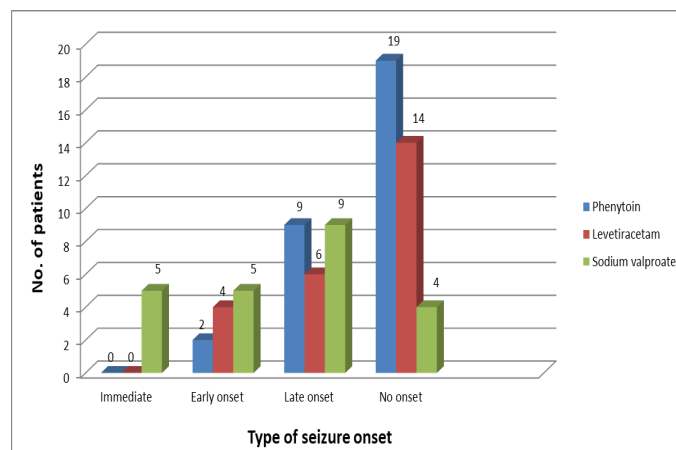


Figure 7: Comparison of phenytoin, levetiracetam, and sodium valproate based on seizure occurrence

In our study 42(53%) of the study population showed early post traumatic seizures whereas a study conducted by Rajashekar reballi et al.³² have found that 40% of study population with traumatic brain injury developed seizures and found that there was significance decrease in incidence of epilepsy.

CONCLUSION

From our research we culminate that the phenytoin and levetiracetam have shown relative efficacy regarding the prevention of early post traumatic seizures whereas sodium valproate had showed poor efficacy. Further studies can be performed by adding a new drug to sodium valproate as add on therapy to enhance its efficacy in prevention post traumatic seizures.

REFERENCES

- Barkley JM, Morales D, Hayman LA, Diaz-Marchan PJ. Static neuroimaging in the evaluation of TBI. *Brain injury medicine: Principles and practice*. 2007; 2007:129-48.
- Shukla D, Devi BI, Agrawal A. Outcome measures for traumatic brain injury. *Clinical neurology and neurosurgery*. 2011 Jul 1; 113(6):435-41.
- Faul M, Wald MM, Xu L, Coronado VG. Traumatic brain injury in the United States; emergency department visits, hospitalizations, and deaths, 2002-2006.
- Acharya UR, Sree SV, Swapna G, Martis RJ, Suri JS. Automated EEG analysis of epilepsy: a review. *Knowledge-Based Systems*. 2013 Jun 1; 45:147-65.
- Labate D, Inuso G, Occhiuto G, La Foresta F, Morabito FC. Measures of brain connectivity through permutation entropy in epileptic disorders. In *Neural Nets and Surroundings 2013* (pp. 59-67). Springer, Berlin, Heidelberg.
- Wagner AK, Miller MA, Scanlon J, Ren D, Kochanek PM, Conley YP. Adenosine A1 receptor gene variants associated with post-traumatic seizures after severe TBI. *Epilepsy research*. 2010 Aug 1; 90(3):259-72.
- Frey LC. Epidemiology of posttraumatic epilepsy: a critical review. *Epilepsia*. 2003 Oct; 44:11-7.
- Jennett B. *Epilepsy after non-missile head injuries*. London, UK: Heinemann Medical; 1975.
- Annegers JF, Grabow JD, Groover RV, Laws ER, Elveback LR, Kurland LT. Seizures after head trauma: a population study. *Neurology*. 1980 Jul 1; 30(7):683.
- Najafi MR, Abrishamkar S, Sonbolstan SA, Hamrah H. The effects of gabapentin on improvement of consciousness level in patients with traumatic brain injury: A randomized clinical trial. *Journal of research in medical sciences*. 2012 Mar 1; 17:S24-7.
- Annegers JF, Hauser WA, Coan SP, Rocca WA. A population-based study of seizures after traumatic brain injuries. *New England Journal of Medicine*. 1998 Jan 1; 338(1):20-4.
- Annegers JF, Grabow JD, Kurland LT, Laws ER. The incidence, causes, and secular trends of head trauma in Olmsted County, Minnesota, 1935-1974. *Neurology*. 1980 Sep 1; 30(9):912-.
- Annegers JF, Coan SP. The risks of epilepsy after traumatic brain injury. *Seizure*. 2000 Oct 1; 9(7):453-7.
- Temkin NR. Risk factors for posttraumatic seizures in adults. *Epilepsia*. 2003 Oct; 44:18-20.
- Asikainen I, Kaste M, Sarna S. Early and late posttraumatic seizures in traumatic brain injury rehabilitation patients: brain injury factors causing late seizures and influence of seizures on long-term outcome. *Epilepsia*. 1999 May; 40(5):584-9.
- Najafi MR, Tabesh H, Hosseini H, Akbari M, Najafi MA. Early and late posttraumatic seizures following traumatic brain injury: a five-year follow-up survival study. *Advanced biomedical research*. 2015; 4.
- Servit Z, Musil F. Prophylactic Treatment of Posttraumatic Epilepsy: Results of a Long-Term Follow-Up in Czechoslovakia. *Epilepsia*. 1981 Jun; 22(3):315-20.
- Wohns RN, Wyler AR. Prophylactic phenytoin in severe head injuries. *Journal of neurosurgery*. 1979 Oct 1; 51(4):507-9.
- Young B, Rapp R, Brooks WH, Madauss W, Norton JA. Posttraumatic epilepsy prophylaxis. *Epilepsia*. 1979 Dec; 20(6):671-81.
- Young B, Rapp RP, Norton JA, Haack D, Tibbs PA, Bean JR. Failure of prophylactically administered phenytoin to prevent late posttraumatic seizures. *Journal of neurosurgery*. 1983 Feb 1; 58(2):236-41.
- Penry JK. A controlled prospective study of the pharmacologic prophylaxis of posttraumatic epilepsy. *Neurology*. 1979; 29:600-1.
- Blackwood D, McQueen JK, Harris P. A clinical trial of phenytoin in the prophylaxis of epilepsy following head injury: preliminary report. *Advances in Epileptology*. 1981:521-5.
- McQUEEN JK, Blackwood DH, Harris P, Kalbag RM, Johnson AL. Low risk of late post-traumatic seizures following severe head injury: implications for clinical trials of prophylaxis. *Journal of Neurology, Neurosurgery & Psychiatry*. 1983 Oct 1; 46(10):899-904.
- Zafar SN, Khan AA, Ghauri AA, Shamim MS. Phenytoin versus levetiracetam for seizure prophylaxis after brain injury—a meta-analysis. *BMC neurology*. 2012 Dec; 12(1):30.
- Beghi E. Overview of studies to prevent posttraumatic epilepsy. *Epilepsia*. 2003 Oct; 44:21-6.

26. Xue YJ, Ming LI, Zhang Y, LI GZ. Sodium valproate for prevention of early posttraumatic seizures. *Chinese Journal of Traumatology (English Edition)*. 2010 Oct 1; 13(5):293-6.
27. Bratton SL, Chestnut RM, Ghajar J, McConnell Hammond FF, Harris OA, Hartl R, Manley GT, Nemecek A, Newell DW, Rosenthal G, Schouten J. Brain Trauma Foundation; American Association of Neurological Surgeons; Congress of Neurological Surgeons; Joint Section on Neurotrauma and Critical Care, AANS/CNS. Guidelines for the management of severe traumatic brain injury. *J Neurotrauma*. 2007; 24(Suppl 1):S59-64.
28. Chang BS, Lowenstein DH. Practice parameter: antiepileptic drug prophylaxis in severe traumatic brain injury: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2003 Jan 14;60(1):10-6.
29. Jones KE, Puccio AM, Harshman KJ, Falcione B, Benedict N, Jankowitz BT, Stippler M, Fischer M, Sauber-Schatz EK, Fabio A, Darby JM. Levetiracetam versus phenytoin for seizure prophylaxis in severe traumatic brain injury. *Neurosurgical focus*. 2008 Oct 1; 25(4):E3.
30. Temkin NR, Dikmen SS, Anderson GD, Wilensky AJ, Holmes MD, Cohen W, Newell DW, Nelson P, Awan A, Winn HR. Valproate therapy for prevention of posttraumatic seizures: a randomized trial. *Journal of neurosurgery*. 1999 Oct 1; 91(4):593-600.
31. Ch. Jyothi, Dr.P. Kishore, Dr.T. Sanjay, Dr.D. Sudheer kumar, R.Deepthi. Prophylactic effect of sodium valproate in traumatic brain injury in patients with early posttraumatic seizures. *IOSR Journal of Pharmacy*. www.iosrphr.org (e)-ISSN: 2250-3013,(P)-ISSN:2319-4219,Vol-9,Issue 9 Version.II(September 2017), PP.35-41.
32. Reballi R, Kasimahanti SP. Incidence of epilepsy and cognitive impairment following traumatic brain injury: a hospital based cross-sectional study. *Archives of Mental Health*. 2014 Jul 1; 15(2):240.

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