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LEVETIRACETAM VERSUS PHENYTOIN FOR SEIZURE PROPHYLAXIS IN SEVERE TRAUMATIC BRAIN INJURY

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ABSTRACT

INTRODUCTION: *Seizure following traumatic brain injury (TBI) is a common complication that needs effective prevention to improve the outcome of TBI. For seizure prophylaxis, Phenytoin has been the only recommended antiepileptic drug (AED); however, several shortcomings have affected its use. Current standard of care for patients with severe traumatic brain injury (TBI) is prophylactic 7 days treatment with phenytoin to decrease the risk of early posttraumatic seizures. Phenytoin alters drug metabolism, induces fever, and requires therapeutic-level monitoring. Whereas, levetiracetam does not require serum monitoring or have significant pharmacokinetic interactions. In the current study, the authors compare the EEG findings in patients receiving phenytoin with those receiving levetiracetam monotherapy for seizure prophylaxis following severe TBI.*

MATERIALS AND METHODS: *The present study is conducted in Mamata medical college, Khammam, Telangana. Data were prospectively collected in 30 cases in which patients were treated with levetiracetam for the first 7 days after severe TBI and is compared with data from a historical cohort of 40 cases in which patients received phenytoin monotherapy. If patients displayed persistent coma, decreased mental status, or clinical signs of seizures they received 3-hour electroencephalographic (EEG) monitoring.*

RESULTS: *The EEG results were grouped into normal and abnormal findings. 15 of 30 patients in the levetiracetam group warranted EEG monitoring. In 7 of these 15 cases the results were normal and in 8 abnormal; 1 of the patients had seizure activity. 12 of 40 patients in the phenytoin group underwent EEG monitoring, with all results being normal.*

CONCLUSION: *Patients treated with levetiracetam and phenytoin had equivalent incidence of seizure activity whereas patients receiving levetiracetam had a higher incidence of abnormal EEG findings.*

KEYWORDS :

1. INTRODUCTION

Post-traumatic seizure (PTS) is a frequent complication following TBI. Based on the occurrence time of the seizure following TBI, Post traumatic seizure has been divided into early seizure, which occurs within the first 7 days, and late seizure, which occurs after the first 7 days following TBI.

Current standard practice for patients with severe TBI is prophylactic treatment with phenytoin for 7 days after injury to decrease the risk of early posttraumatic seizures.[3,13] Phenytoin therapy after the initial 7-day period has not been shown to reduce the development of late seizures nor has prophylaxis against early seizures been shown to minimize morbidity or mortality rates associated with severe TBI[1,14]. Phenytoin has a side-effect profile that includes severe cutaneous hypersensitivity reactions and induction of the hepatic cytochrome P450 system, causing significant drug-drug interactions[5,10]. Also, phenytoin usage requires close monitoring to maintain a narrow therapeutic window and has been described as causing fever and decreased levels of consciousness, particularly concerning in patients with TBI. For these reasons, alternative AED therapy has been sought. Valproate and carbamazepine have been investigated for usage in TBI but even they have similar side-effect profiles and require serum monitoring[4,14].

Levetiracetam is a non–enzyme-inducing AED which does not require serum level monitoring or induce fever or cutaneous hypersensitivity reactions and is not known to have significant pharmacokinetic interactions[7]. In November 2006, FDA approval of the intravenous form of levetiracetam created an attractive option for antiseizure prophylaxis. Szaflarski et al.[12] retrospectively analyzed levetiracetam use in a neuroscience ICU population, and concluded that levetiracetam monotherapy was associated with lower complication rates and shorter ICU stays than treatment with other AEDs.

To date, there are no published data investigating the efficacy of seizure prevention with levetiracetam compared with standard treatment with phenytoin in patients with severe TBI. In the current study, we evaluated the occurrence of early posttraumatic seizure activity recorded by electroencephalography in patients with severe TBI treated with phenytoin versus levetiracetam as seizure prophylaxis

2. METHODS

After taking proper consent from patient and attendants we initiated a protocol of intravenous levetiracetam monotherapy for early seizure prophylaxis in patients with severe TBI, defined by a post-resuscitation GCS score of 3–8. Levetiracetam therapy was started within 24 hours of injury. From May 2018 to June 2019, 30 consecutive patients with severe TBI were admitted and received levetiracetam 500 mg IV every 12 hours for the first 7 days after traumatic injury. We compared this prospective cohort to a historical cohort of patients from our severe TBI database in which patients received phenytoin for 7 days after trauma. From June 2017 to June 2018, 40 patients with severe TBI received IV phenytoin therapy within 24 hours of traumatic injury. Patients underwent EEG examination if there is a suspicion of a seizure. In the current study, only patients who received an EEG examination were included in the analysis. 15 (50%) of the 30 patients in the levetiracetam cohort warranted EEG testing to assess for seizures given persistent coma, change in mental status, or clinical seizure activity. 10 (25%) of the 40 patients in the phenytoin cohort required an EEG examination to investigate for seizures. Individual EEG recordings were reviewed by an attending neurologist specializing in electroencephalography in order to assess the efficacy of seizure prevention in the 2 cohorts. The EEG findings for each patient were then divided into normal or abnormal based on the presence of focal abnormal waveforms. Abnormal EEG findings were further classified into the following 3 categories: status epilepticus, seizure activity, or seizure tendency. The electroencephalograms categorized as demonstrating seizure tendency exhibited epileptiform activity of intermittent sharp waves or periodic lateralized epileptiform discharges without capturing electrographic seizures.

The CT-based classification of head injury of Marshall et al.[6] was used to define intracranial pathology on admission head CTs for each patient undergoing EEG monitoring. Glasgow Outcome Scale scores were obtained at 3- and 6-months post-trauma. Differences between the 2 cohorts with respect to abnormal EEG findings, seizure activity, and seizure tendency with epileptiform activity was determined using Fisher exact test. Statistical analysis of GOS scores obtained at 3 and 6 months postinjury was performed to monitor functional TBI outcomes

3. RESULTS

Analysis was performed on possible confounders to test whether the differences seen between the drugs could be attributed to other factors. There were no significant differences in age, sex, or admission GCS scores between the cohorts. The median Marshall CT scores were the same in the 2 cohorts, and there was no statistically significant between groups. Four of the patients in the levetiracetam cohort underwent 2 EEG studies, for a total of 19 EEG examinations performed in the 15 patients treated with levetiracetam. Seven (46.7%) of these 15 had normal EEG findings while 8 (53.3%) had abnormal EEGs. The abnormal EEG findings has shown no status epilepticus, although 1 (12.5%) of the 8 patients with abnormal EEG findings had seizure activity, and 7 (87.5%) had seizure tendency with abnormal waveforms. Four of the patients in the phenytoin cohort underwent 2 EEG studies and 1 underwent 3; thus, a total of 19 EEG examinations were performed in the 12 patients treated with phenytoin. All 12 patients had normal findings. The Fisher exact test showed a significant difference between the occurrence of abnormal EEG findings (seizure or seizure tendency with epileptiform activity) in the levetiracetam versus phenytoin cohorts, but there was no significant difference between the finding of seizures on electroencephalograms between the 12 phenytoin and 15 levetiracetam patients who underwent EEG monitoring. GOS scores were collected at 3 and 6 months post injury. With respect to GOS scores at 3 and 6 months, there were no significant differences between patients treated with levetiracetam and those treated with phenytoin. No patients were lost to follow-up at 3 months; one patient from a group was lost to follow-up at 6 months.

4. DISCUSSION

The present study would indicate that levetiracetam monotherapy in the first 7 days following severe TBI is associated with an increased seizure tendency and increased epileptiform activity on electroe ncep halograms when compared to phenytoin. The rates of seizure activity were equivalent in patients treated with levetiracetam and those treated with phenytoin. The implications of increased seizure tendency and epileptiform activity require further study. One important complication of TBI is seizure. Seizure risk after TBI is related to injury severity. In one study[1], seizures developed during the first year postinjury in < 1% of patients with mild TBI and in 6% of patients with severe TBI. Temkin et al.[14] found a 2-year seizure rate of 21% in patients with severe TBI. Early seizures(defined as occurring within the first 7 days posttraum) have been shown to increase intracranial pressure episodically, thereby increasing the risk for cerebral ischemia[15]. Late seizures, developing after the initial 7-day period, are associated with a worse functional outcome measured by the GOS[2]. Early seizure prophylaxis, however, does not influence occurrence of late seizures. Ronne-Engstrom and Winkler[2], in study of a series of cases involving continuous EEG recordings in patients with unspecified severity of TBI, reported high-frequency bursts of epileptiform activity that developed into electrographic seizures in 12 (66.7%) of 18 patients[8]. Patients in our study treated with levetiracetam whose EEG studies showed seizure tendency may have had uncaptured waveform deterioration into electrographic seizures. The current study is limited 3hr EEG monitoring and by a small sample size and by the retrospective, historical cohort design. The strength of the current findings lies in the use of actual EEG data to evaluate brain and seizure activity in relation to the use of AEDs as seizure prophylaxis following severe TBI. We restricted the analysis to patients in whom EEG monitoring was performed because overtclinical seizures themselves are relatively rare events and subject to observer bias. The current study highlights the fact that clinical seizures are difficult to identify through observation or physical examination in the early stages after severe TBI. Both the TBI itself and sedative and neuromuscular blockade agents used in intensive care management of severe TBI may mask seizure activity. Therefore, any prospective study intended to test the utility of levetiracetam versus phenytoin for seizure prophylaxis after severe TBI should include routine use of EEG monitoring. Since levetiracetam does not require loading doses or monitoring of drug levels and lacks significant drug-drug interaction, it is an appealing alternative therapy in the prevention of early posttraumatic seizures. On the basis of the results of the current study, we urge caution against widespread practice changes in converting to levetiracetam as monotherapy for seizure prophylaxis following severe TBI.

5. CONCLUSION

Our data indicate that levetiracetam is as effective as phenytoin in preventing early posttraumatic seizures. But, levetiracetam monot herapy was associated with increased frequency of abnormal EEG findings. Further study is necessary to determine the clinical impli ca tion of this finding as well as to determine whether these patients exhibit a higher incidence of late posttraumatic seizures. Prospective studies comparing levetiracetam and phenytoin among patients with mild, moderate, and severe TBI are indicated. Because prophylaxis against early seizures has not been shown either to reduce the incidence of late posttraumatic seizures or influence outcome, future prospective studies should also include a placebo group to assess the possibility that early seizure prophylaxis following TBI exposes patients to unnecessary morbidities of AEDs without benefits of enhancing neurological recovery.

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