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Original Investigation

Use of Levetiracetam in Prophylaxis of Early Post-Traumatic Seizures

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ABSTRACT

AIM: Traumatic brain injury is one of the leading causes of mortality and morbidity worldwide. The role of prophylactic anti-epileptic drugs has been established. Phenytoin used traditionally for this purpose carries a burden of adverse reactions and cumbersome need of monitoring and maintaining levels in serum. Therefore, as the evidence on levetiracetam, emerged part of neurosurgery section started using this drug for seizure prophylaxis after early loading with phenytoin. So we decided to assess the use of enteral levetiracetam in prophylaxis of early post-traumatic seizures.

MATERIAL and METHODS: This was a retrospective cohort study done at the department of neurosurgery of Aga Khan University in Karachi from July 2010 to March 2011. Charts of patients who were started on levetiracetam enterally were reviewed and followed for occurrence of clinical seizures within one week of trauma. The results were then compared to the group of patients treated prophylactically with phenytoin alone over the same time period.

RESULTS: The study included 50 patients in each group. Both groups were comparable in terms of demographics and baseline characteristics. However, 2 patients in each group suffered from clinical seizures with a non-significant p value.

CONCLUSION: Enteral levetiracetam after initial phenytoin loading is a viable option in the armamentarium of anti-epileptic drugs. Further larger prospective studies are required to improve the evidence.

KEYWORDS: Early post-traumatic seizure, Levetiracetam, Phenytoin, Head injury, Prophylaxis

INTRODUCTION

Traumatic brain injury is one of the leading causes of mortality and morbidity worldwide (18). 1.5 million patients die and several millions receive emergency treatment for traumatic brain injury every year (12). According to the World Health Organization (WHO) report titled "The Global Burden of Disease," traffic injuries are expected to become the third highest disease burden by the year 2020 (21). Seizures are a known complication of traumatic brain injury and have been classified on the basis of time of onset into early (occurring within 7 days of head injury) and late post-traumatic seizures (after 7 days of injury) (3,7). Incidence of post-traumatic early seizures in case of civilian head injuries varies from 4 to 25% in blunt head trauma while the incidence of late post-traumatic seizures has been reported to vary from 9 to 50% (19).

Post-traumatic seizures may be associated with acute worsening of neurological status and poor clinical outcomes. Prevention of early post-traumatic seizures is thought to prevent post-traumatic epilepsy (19,22). Some experimental studies have reported generation of a permanent focus of abnormal activity leading to post-traumatic epilepsy syndrome (2). Brain trauma foundation guidelines recommend the use of anticonvulsants for prevention of early post-traumatic seizures (2). However, a similar role has not been suggested for late post-traumatic seizures.

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Several drugs have been studied for this purpose including carbamazepine, valproic acid and phenytoin. Brain trauma foundation guidelines (7) recommend the use of phenytoin (level II evidence).

The drug, however, is associated with several disadvantages. It has a narrow therapeutic window with a side effect profile that has been well established and includes intravenous (IV) site reactions (1,15), exfoliative dermatitis (15), granulocytopenia (5), transient hemiparesis (20), permanent B-cell immunodeficiency (6), and fatal phenytoin hypersensitivity syndrome (16). Phenytoin-associated hypotension is a box warning in the United States and an important factor in polytrauma patients with an element of shock. There have also been some Class II data to suggest that both phenytoin and carbamazepine have negative effects on cognition, particularly involving tasks with significant motor and speed components (8). Phenytoin is metabolized through the P450 system and thus can cause numerous drug interactions. Failure to maintain therapeutic serum levels may lead to breakthrough seizures due to inadequate levels. Therefore frequent monitoring of serum levels is required. In countries like Pakistan, biochemical tests for phenytoin level are not freely available, making it inconvenient and expensive to frequently monitor and maintain its serum levels, especially in large populations. Phenytoin has also been found to interact with feeding and it has therefore been recommended to pause nasogastric (NG) feeding one to two hours before and after the administration of phenytoin.

These disadvantages have led to a search for new anticonvulsants. Levetiracetam is one the drugs that has rapidly gained in popularity in recent times. Its efficacy has been demonstrated in a wide variety of seizure types and status epilepticus (10). It does not induce fever, cutaneous hypersensitivity reactions or have drug interactions (13). Recently, the effectiveness of levetiracetam has been studied in the prophylaxis of post-traumatic seizures (9) and seizures following trauma and subarachnoid hemorrhage (17). Jones et al. (9) have compared the drugs in severe traumatic brain injury and did not find a statistically significant difference between the two drugs. The drug has more than 95% bioavailability and is not affected by co-ingestion (9,11). In an experimental study on healthy subjects, single doses of levetiracetam 1,500 mg administered as a 15-minute IV infusion and as oral tablets were shown to be bioequivalent (14). Similar results have been supported by experimental studies on normal cats (4).

However IV forms of levetiracetam are not commercially available worldwide. Oral levetiracetam became available in Pakistan in 2008. We therefore decided to use enteral levetiracetam and observe its effectiveness in prophylaxis of early post-traumatic seizures.

MATERIAL and METHODS

This was a cohort study conducted at the Aga Khan University Hospital in Karachi from 1st July 2010 to 31st March 2011. This is a tertiary care hospital located at the heart of the city and has level 1 trauma center facilities. As standard practice, anti-seizure prophylaxis is given to patients according to the brain trauma foundation recommendations in patients who have one or more of the following: Glasgow Coma Scale (GCS) score <10, cortical contusions, depressed skull fracture, subdural hematoma, epidural hematoma, penetrating head wound and seizures within 24 hours of injury. A new practice of starting patients on enteral levetiracetam on the third day of head injury was started by one of the faculties (Group: 1). The patients were loaded with IV phenytoin and were switched to enteral Levetiracetam at the dose of 35 mg/kg per dose, three doses daily as enteral feed was established (by 72 hours). Such consecutive 50 adult patients were registered from 1st September 2010 to 31st March 2011. The brain injury severity was graded according to the post-resuscitation GCS score and Marshall Classification of computed tomography (CT) scan findings. Oral, NG routes were used in the initial phase. Patients were followed for occurrence of seizures over a total of 7 days. Patients younger than 16 years, with a history of epilepsy, those not requiring seizure prophylaxis or who had intolerance to enteral feed, or with a known history or hypersensitivity to the drug were excluded from the study. Patients presenting after 24 hours of injury, or the patients who expired or were shifted out to other facilities before completion of 7 days after the traumatic brain injury were also excluded from the study. Observations of this group were then compared to a cohort of patients in our database who were kept on phenytoin during the same time period (Group: 2). As an institutional practice, all patients with clinical seizure, mental state change or deep coma underwent electroencephalography (EEG). EEG was further interpreted by an attending neurologist. All findings were recorded and analyzed on SPSS 19 for windows (SPSS Inc.). The rate of EEG evidence of seizures was compared in the two groups. Descriptive statistics, chi square test, and Mann-Whitney U test were used to compare the groups for demographic characteristics, post-resuscitation GCS score, and frequency of seizures before presentation. Fischer's exact test was used to compare the effectiveness of seizure control in the two groups. A p value of 0.05 was considered statistically significant.

RESULTS

The study included 50 patients for each group. The mean age in the study group (group 1) was 31.16 +/- 17.39 years. The mean age of our historical cohort (Group 2) was 34.96 +/- 18.26 years (p=1.06). Univariate analysis showed no significant statistical difference in terms of gender, age, and severity of injury. Five patients in group 1 had post-traumatic seizures before presenting at the emergency room (ER) compared to 2 in group 2 (p=0.24).

Seven patients in group 1 underwent EEG according to the previously mentioned criteria compared to 5 in group 2 (p=0.76). Two patients from each group had an EEG positive for seizure activity (p=1.00). Marshall Class of patients undergoing EEG in both groups was comparable (p=0.29).

There was therefore no statistically significant difference in the incidence of early post-traumatic seizures in patients who received oral levetiracetam after the initial use of phenytoin.

DISCUSSION

Our study showed that relative risk of early post-traumatic seizures in patients managed with enteral levetiracetam after initial phenytoin use is equal to the risk of early post-traumatic seizures in patients who receive phenytoin alone. There is no similar study in the literature. However several studies have compared the two drugs. In 2008, Jones et al. compared the two drugs in a cohort of severe traumatic brain injury (9). Statistically, no significant difference was found between the two drugs in terms of seizure control but the incidence of abnormal EEG was higher in the levetiracetam group in their study (9). A randomized controlled trial by Szaflarski et al. compared the two drugs in patients with subarachnoid hemorrhage and traumatic brain injury (17). This study also showed better long-term outcomes in patients that received levetiracetam.

Being a relatively newer drug, levetiracetam is still not available in all parts of world and in countries like Pakistan. The cost of this drug remains an important issue. Levetiracetam costs much more than phenytoin. However, when we factor in the cost of monitoring serum levels, and chances of breakthrough seizures with sub-therapeutic levels, the economics start to balance out. Also the lack of electricity and load shedding or refrigeration facilities in far-flung areas of underdeveloped countries makes the enteral form a better choice.

EEG remains an important component of seizure work-up. In the current study, the number of patients with abnormal EEG was higher in the levetiracetam group, but the number of patients with severe injury was also higher although the difference was insignificant.

This is the first study to specifically assess the enteral form of the drug in prophylaxis of early post-traumatic seizures. The study design is not ideal for comparison of drugs. However it shows encouraging results with the use of enteral levetiracetam. As the IV form of levetiracetam becomes available, it is possible to start patients on IV levetiracetam and then switch to the oral form at an appropriate time period. A randomized controlled trial should be conducted and efforts are being made to conduct a clinical trial at our institute.

CONCLUSION

Enteral levetiracetam after initial phenytoin loading is a viable option in the armamentarium of anti-epileptic drugs. It has fewer long-term side effects and seldom requires need of drug-level monitoring. The chance of breakthrough seizures due to inadequate level is also less common. However, further larger prospective studies are required to verify the results.

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