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Levetiracetam vs Fosphenytoin in Benzodiazepines Refractory Convulsive Status Epilepticus

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ABSTRACT

Background: Status epilepticus (SE) is one of the most important neurological emergencies of pediatric age group. The present study was conducted to compare fosphenytoin and levetiracetam in benzodiazepines refractory convulsive status epilepticus. **Methods:** This study was conducted on 65 children age ranged 2 months to 18 year with SE refractory to second dose of benzodiazepine. Patients were divided into 2 groups. Group I was fosphenytoin (n = 30) group who received intravenous fosphenytoin at 20 mg/kg Phenytoin Equivalent (PE) dose over 10 min duration using infusion pump and group II was levetiracetam (35) group who received 40 mg/kg of intravenous levetiracetam over 10 min duration. Parameters such as weight, duration of seizure, etiology, duration of LOC, past history of seizure and type of seizures were recorded. Outcome of treatment was also recorded. **Results:** The mean age in group I patients was age was 32.4 years and in group II was 28.2 years, there were 16 males and 14 females in group I and 20 males and 15 females in group II. Mean weight in group I was 11.5 Kgs and in group II was 12.4 Kgs. Etiology was febrile seizure seen 23 in group I and 24 in group II, encephalitis 4 in group I and 6 in group II, camphor poisoning 1 in group I and 3 in group II and encephalitis 2 in group I and 2 in group II. The difference was significant (P< 0.05). The mean duration of PICU was 3.7 days in group I and 3.2 days in group II, duration of hospital stay was 6.5 days in group I and 6.1 days in group II, duration of primary illness was 2.8 days in group I and 2.1 days in group II, duration of mechanical ventilation was 0.3 days in group I and 0.4 days in group II, seizure recurrence in 24 hour was 3 in group I and 4 in group II and time to termination of clinical seizure was 16.5 hours in group I and13.2 hours in group II. The difference was non- significant (P> 0.05). **Conclusion:** Authors found that Levetiracetam may be an effective alternative to fosphenytoin in management of BRSE in children.

Keywords: Fosphenytoin, Levetiracetam, Status epilepticus.

INTRODUCTION

Status epilepticus (SE) is one of the most important neurological emergencies of pediatric age group. Among children, the incidence of SE varies from 4 to 38 episodes/100,000 children per year.[1] The incidence is somewhat higher in developing countries due to infections of central nervous system and is more common in children less than 5 years of age.[2]

As an initial treatment for status epilepticus, potent gamma aminobutyric acid agonists, such as benzodiazepines and barbiturates, must be administered quickly to stop the patient's convulsions.[3] Lorazepam and diazepam are recommended as first-line drugs, based on their efficacy in clinical studies, and hence, are commonly used. Lorazepam and diazepam are short-acting drugs that can produce immediate effects. However, treatment with another long-acting anticonvulsant drug is necessary to prevent recurrent convulsions.[4] For this purpose, phenytoin (PHT) has previously been used to treat patients with status epilepticus.

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Since fosphenytoin (FPHT) was developed, it has been associated with a lower incidence rate of adverse reactions than PHT and has been recommended as a second-line therapy for use after benzodiazepine treatment.[5]

Levetiracetam (LEV) is primarily binds to the synaptic vesicle protein 2A SV2A and regulates the release of neurotransmitters, is effective against convulsions.[6] It has also been demonstrated to be effective against status epilepticus and such treatment is associated with a low incidence of adverse reactions. Thus, both LEV and FPHT have been recommended as second-line therapies for status epilepticus in some international guidelines.[7] The present study was conducted to compare fosphenytoin and levetiracetam in benzodiazepines refractory convulsive status epilepticus.

MATERIALS AND METHODS

This study was conducted in the department of Pediatrics. It comprised of 65 children age ranged 2 months to 18 year with SE refractory to second dose of benzodiazepine. Parents were informed regarding the study and their consent was obtained. Ethical clearance was obtained before starting the study.

Demographic profile such as name, age, gender etc. was recorded. Patients were divided into 2 groups. Group I was fosphenytoin (n = 30) group who

received intravenous fosphenytoin at 20 mg/kg Phenytoin Equivalent (PE) dose over 10 min duration using infusion pump and group II was levetiracetam (35) group who received 40 mg/kg of intravenous levetiracetam over 10 min duration. Patients were observed for clinical termination of seizure activity and response latency was recorded in minutes. Parameters such as weight, duration of seizure, etiology, duration of LOC, past history of seizure and type of seizures were recorded. Outcome of treatment was also recorded. Results were subjected to statistics. P value < 0.05 was regarded significant.

RESULTS

Table 1: Comparison of variables

Variables	Group I	Group II	P value
Age	32.4	28.2	0.14
Gender	M: F- 16: 14	M: F- 20: 15	0.32
Weight	11.5	12.4	0.07
Etiology			
Febrile seizure	23	24	0.01
Encephalitis	4	6	
Camphor poisoning	1	3	
Encephalitis	2	2	
Duration of LOC (min)	26.4	22.5	0.05
Past history of seizure	12	15	0.90
Type			
GTCS	23	26	0.01
Focal seizure	4	6	
Myoclonic seizure	1	2	
Generalized tonic seizures	2	1	

[Table 1] shows that mean age in group I patients was age was 32.4 years and in group II was 28.2 years, there were 16 males and 14 females in group I and 20 males and 15 females in group II. Mean weight in group I was 11.5 Kgs and in group II was 12.4 Kgs. Etiology was febrile seizure seen 23 in group I and 24 in group II, encephalitis 4 in group I and 6 in group II, camphor poisoning 1 in group I and 3 in group II and encephalitis 2 in group I and 2 in group II. The difference was significant (P< 0.05).

Table 2: Outcome variables

Variables	Group I	Group II	P-value
Duration of PICU (days)	3.7	3.2	0.81
Duration of hospital stay (days)	6.5	6.1	0.92
Duration of primary illness	2.8	2.1	0.13
Duration of mechanical ventilation (days)	0.3	0.4	0.91
Seizure recurrence in 24 hour	3	4	0.95
Time to termination of clinical seizure	16.5	13.2	0.05

[Table 2 & Figure 1] shows that mean duration of PICU was 3.7 days in group I and 3.2 days in group II, duration of hospital stay was 6.5 days in group I and 6.1 days in group II, duration of primary illness was 2.8 days in group I and 2.1 days in group II, duration of mechanical ventilation was 0.3 days in group I and 0.4 days in group II, seizure recurrence in 24 hour was 3 in group I and 4 in group II and time to termination of clinical seizure was 16.5 hours in group I and13.2 hours in group II. The difference was non- significant (P> 0.05).

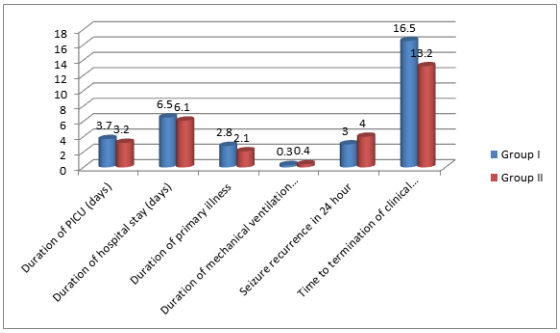

Figure 1: Outcome variables

DISCUSSION

Benzodiazepines are widely used as first-line anti-epileptics for effective control of seizures.[8] BRSE is a relatively common emergency condition and there are a small number of randomized controlled trials with inconsistent conclusions to compare the efficacy of currently available treatment options i.e., fosphenytoin, phenytoin and levetiracetam.[9] Consensus guidelines recommend phenytoin as a preferred second-line anticonvulsant, but fosphenytoin is preferred in view of better bioavailability and lesser side-effects like hemodynamic compromise and local reactions. With respect to these side-effect profiles, some studies favor levetiracetam as a preferred agent for BRSE.[10] The present study was conducted to compare fosphenytoin and levetiracetam in benzodiazepines refractory convulsive status epilepticus.

In this study, we found that mean age in group I patients was age was 32.4 years and in group II was 28.2 years, there were 16 males and 14 females in group I and 20 males and 15 females in group II. Mean weight in group I was 11.5 Kgs and in group II was 12.4 Kgs. Etiology was febrile seizure seen 23 in group I and 24 in group II, encephalitis 4 in group I and 6 in group II, camphor poisoning 1 in group I and 3 in group II and encephalitis 2 in group I and 2 in group II.

Nallisetty et al,[11] in their study children admitted with BRSE were randomized to group A, who received fosphenytoin at 20 mg/kg phenytoin equivalents (PE) dose and group B who received levetiracetam at 40 mg/kg over 10 min. Of 61 children enrolled over 18 mo period, 29 (47.5%) were randomized to group A and 32 (52.5%) were randomized to Group B. Baseline characteristics

were comparable between the two groups. Among 61 children, 58(98%) required Pediatric Intensive Care Unit (PICU) admission and among those 5(8.2%) children required mechanical ventilation. Duration of PICU stay, hospital stay, the response latency and seizure recurrence were compared between both groups. Significant number of children received additional anti-epileptic drugs (AEDs) in fosphenytoin group [9/29(31%)] compared to levetiracetam group [2/32(7%)] to control seizure.

We found that mean duration of PICU was 3.7 days in group I and 3.2 days in group II, duration of hospital stay was 6.5 days in group I and 6.1 days in group II, duration of primary illness was 2.8 days in group I and 2.1 days in group II, duration of mechanical ventilation was 0.3 days in group I and 0.4 days in group II, seizure recurrence in 24 hour was 3 in group I and 4 in group II and time to termination of clinical seizure was 16.5 hours in group I and13.2 hours in group II.

Nakamura et al,[12] in their study 21 patients who were intravenously injected with LEV as a second-line therapy and 42 matched patients (historical controls) who were treated with FPHT (1:2) were selected. The subjects had a mean age of 64.0±2.2 years, and included 48 males and 15 females. The status epilepticus control rates of the FPHT and LEV groups did not differ significantly (81.0% [34/42] vs 85.1% [18/21], respectively; P=.69). As for serious adverse events, a reduction in blood pressure was observed in the FPHT group, but not in the LEV group. The oral anticonvulsant switching rates of the 2 groups were similar, but the same-drug switching rates of the FPHT and LEV groups were 8.1% and 77.8%, respectively. The efficacy of intravenous LEV injections after status epilepticus was equivalent to that of FPHT, and the incidence of adverse events was lower in the LEV group. LEV is effective and safe at preventing recurrent seizures after status epilepticus following benzodiazepine treatment.

The shortcoming of the study is small sample size.

CONCLUSION

Authors found that Levetiracetam may be an effective alternative to fosphenytoin in management of BRSE in children.

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