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Original Research

A comparative study of levetiracetam and fosphenytoin in the treatment of benzodiazepine- refractory status epilepticus in pediatric patients

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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 levetiracetam and fosphenytoin in the treatment of benzodiazepine refractory status epilepticus (BRSE) in pediatric patients. **Materials & Methods:** The present study was conducted on 84 pediatric cases of status epilepticus who were divided into 2 groups of 42 each. Group I patients received fosphenytoin at 20 mg/kg phenytoin equivalents (PE) dose and group II patients received levetiracetam at 40 mg/kg over 10 min. Time to terminate seizure (response latency) was measured. Primary and secondary outcome measures were recorded in all cases. **Results:** Type of seizures was GTCS 30 in group I and 32 in group II, focal seizure 7 in group I and 5 in group II, generalized tonic seizures 4 in group I and 3 in group II and myoclonic seizure 1 in group I and 2 in group II. Neuro-developmental status was normal seen in 34 in group I and 35 in group II, development delay 4 in group I and 2 in group II, static encephalopathy 3 in group I and 4 in group II, progressive encephalopathy 1 in group I. The need of additional anti-seizure medication was seen in 11 in group I and 5 in group II, time to termination of clinical seizure was 15.2 hours in group I and 13.4 hours in group II, duration of primary illness was 2.8 days in group I and 1.7 days in group II, number needing mechanical ventilation was 4 in group I and 3 in group II. **Conclusion:** Authors found that levetiracetam is an effective alternative to fosphenytoin in management of BRSE in pediatric population.
Key words: fosphenytoin, levetiracetam, Status epilepticus

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INTRODUCTION

Status epilepticus (SE) is one of the most important neurological emergencies of children which account for 4 to 38 episodes/100,000 children per year.[1] It has higher prevalence in developing countries because of infections of central nervous system and is more common in children < 5 years of age. International league against epilepsy (ILAE) defined convulsive status epilepticus as a non-terminating seizure for > 5 minutes and an ongoing seizure for > 30 minutes that causes long term consequences.[2]

Refractory SE is defined as SE which is refractory to two intravenous antiepileptic drug (AEDs), one of which is a benzodiazepine. It has been also defined based on duration of seizure for 1 or 2 hours. It is seen in 23–43% of the patients with SE. The short-term mortality of RSE is approximately 3 times higher compared to non refractory SE. In general, RSE is associated with acute, severe, and potentially fatal underlying etiologies such as encephalitis, massive stroke, or rapidly progressive primary brain tumors, and

may be accompanied by severe impairment of consciousness.[3]

The primary treatment of phenytoin is the first-line drug is benzodiazepine. The second-line therapy include fosphenytoin, valproic acid and levetiracetam. Levetiracetam has an edge over fosphenytoin in its safety profile due to lack of adverse events like cardiopulmonary depression and absence of any end organ damage.

There are many studies endorsing the choice of levetiracetam for status epilepticus management in pediatric and adult population, though very few studies exist with comparator arm especially in pediatric age group.[5] The present study was conducted to compare levetiracetam and fosphenytoin in the treatment of benzodiazepine refractory status epilepticus (BRSE) in pediatric patients.

MATERIALS & METHODS

The present study was conducted in the department of Pediatrics. It comprised of 84 pediatric cases of Status epilepticus of both genders. The study was approved from institutional ethical committee. All parents were informed regarding the study and their written consent was obtained. Ethical approval for the study was obtained before starting the study.

Patient's information such as name, age, gender etc. was recorded. A thorough clinical examination was performed in all. They were divided into 2 groups of 42 each. Group I patients received fosphenytoin at 20 mg/kg phenytoin equivalents (PE) dose and group II patients received levetiracetam at 40 mg/kg over 10 min. Time to terminate seizure (response latency) was measured. Primary and secondary outcome measures were recorded in all cases. Results thus obtained were subjected to statistical analysis. P value less than 0.05 was considered significant.

RESULTS

Table I Distribution of patients

Groups	Group I	Group II
Drug	Fosphenytoin at 20 mg/kg	Levetiracetam at 40 mg/kg
Number	42	42

Table I shows that group I patients received fosphenytoin at 20 mg/kg phenytoin equivalents (PE) dose and group II patients received levetiracetam at 40 mg/kg over 10 min. Each group had 42 patients.

Table II Assessment of parameters in both groups

	Group I	Group II	P value
Type of seizures			
GTCS	30	32	0.01
Focal seizure	7	5	
Generalized tonic seizures	4	3	
Myoclonic seizure	1	2	
Neuro-developmental status			
Normal	34	35	0.01
Development delay	4	2	
Static encephalopathy	3	4	
Progressive encephalopathy	1	0	

Table II shows that type of seizures was GTCS 30 in group I and 32 in group II, focal seizure 7 in group I and 5 in group II, generalized tonic seizures 4 in group I and 3 in group II and myoclonic seizure 1 in group I and 2 in group II.

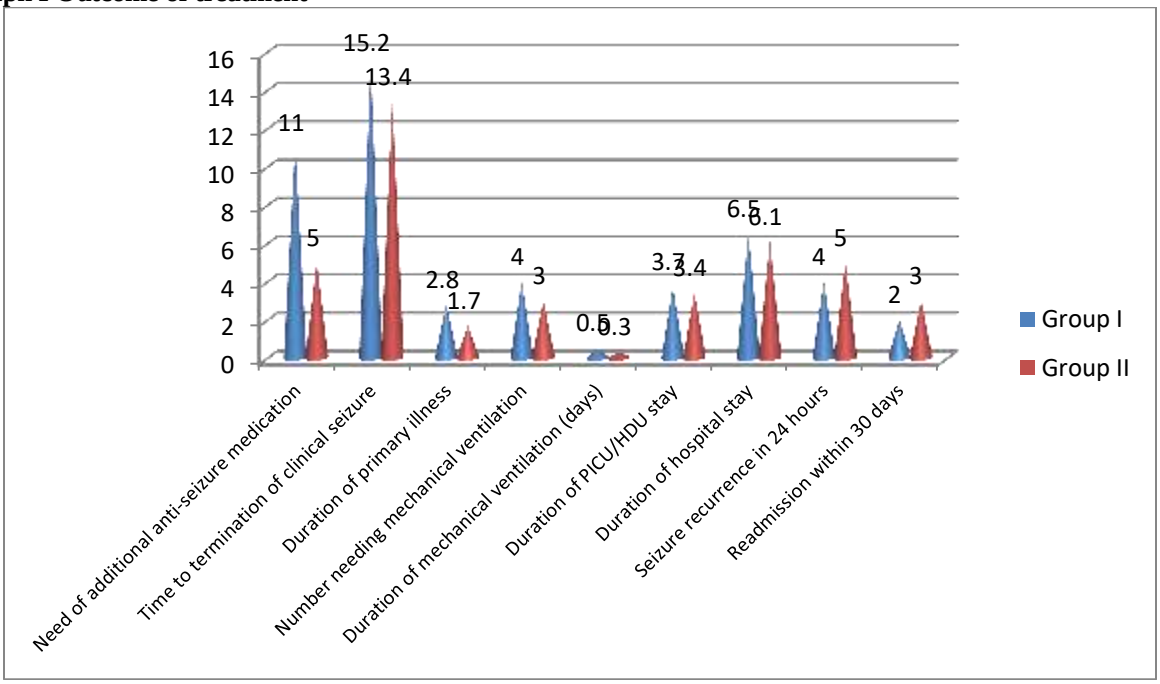
Neuro-developmental status was normal seen in 34 in group I and 35 in group II, development delay 4 in group I and 2 in group II, static encephalopathy 3 in group I and 4 in group II, progressive encephalopathy 1 in group I. The difference was significant (P< 0.05).

Table III Outcome of treatment

Parameters	Group I	Group II	P value
Need of additional anti-seizure medication	11	5	0.01
Time to termination of clinical seizure	15.2	13.4	0.05
Duration of primary illness	2.8	1.7	0.02
Number needing mechanical ventilation	4	3	0.91
Duration of mechanical ventilation (days)	0.5	0.3	0.84
Duration of PICU/HDU stay	3.7	3.4	0.93
Duration of hospital stay	6.5	6.1	0.95
Seizure recurrence in 24 hours	4	5	0.84
Readmission within 30 days	2	3	0.91

Table III, graph I shows that need of additional anti-seizure medication was seen in 11 in group I and 5 in group II, time to termination of clinical seizure was 15.2 hours in group I and 13.4 hours in group II, duration of primary illness was 2.8 days in group I and 1.7 days in group II, number needing mechanical ventilation was 4 in group I and 3 in group II, duration of mechanical ventilation was 0.5 days in group I and 0.3 days in group II, duration of PICU/HDU stay was 3.7 days and 3.4 days respectively, duration of hospital stay was 6.5 and 6.1 days, seizure recurrence in 24 hours was in 4 and in 5 respectively and readmission within 30 days was seen in 2 and 3 respectively.

Graph I Outcome of treatment



DISCUSSION

Status epilepticus (SE) is emergency seen in children especially below 5 years of age. Its prevalence in developing countries is higher compared to the developed countries because of higher prevalence of central nervous system (CNS) infections, whereas stroke and drug withdrawal are the common causes of SE in the developed countries. In the developed countries, SE is managed in the intensive care unit (ICU), whereas in the developing countries, SE is managed in the general ward because of paucity of ICU beds.[7]

Benzodiazepines are widely used as first-line anti-epileptics for effective control of seizures. BRSE is a relatively common emergency condition seen in pediatric patients.[8] Consensus guidelines recommends 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. Few studies labelled

levetiracetam as a preferred agent for BRSE.[9] The present study was conducted to compare levetiracetam and fosphenytoin in the treatment of benzodiazepine refractory status epilepticus (BRSE) in pediatric patients.

In present study, group I patients received fosphenytoin at 20 mg/kg phenytoin equivalents (PE) dose and group II patients received levetiracetam at 40 mg/kg over 10 min. Each group had 42 patients. The type of seizures was GTCS 30 in group I and 32 in group II, focal seizure 7 in group I and 5 in group II, generalized tonic seizures 4 in group I and 3 in group II and myoclonic seizure 1 in group I and 2 in group II. Nalisetty et al[10] determined 61 children admitted with BRSE who received fosphenytoin at 20 mg/kg phenytoin equivalents (PE) dose and group B who received levetiracetam at 40 mg/kg over 10 min. It was found that 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 neuro-developmental status was normal seen in 34 in group I and 35 in group II, development delay 4 in group I and 2 in group II, static encephalopathy 3 in group I and 4 in group II, progressive encephalopathy 1 in group I. Lyttle et al[11] screened 1432 children and randomized 286 children in levetiracetam (N-152) and phenytoin (N-134) groups. They concluded in favor of levetiracetam with respect to seizure termination [Levetiracetam – 106/152 (70%); Phenytoin – 86/134 (64%)] which is similar to present study results. Dalziel et al[12] screened 639 children and randomized 233 children in levetiracetam (N-119) and phenytoin groups (N-114). They concluded phenytoin as therapeutically superior with respect to seizure termination which is contradictory to present study results. Despite these contradictory results, additional anti-epileptic usage was more with children receiving levetiracetam in both these studies. In contrast, additional antiepileptic usage was more in fosphenytoin group than levetiracetam group [Fosphenytoin – 9/29 (31%); Levetiracetam – 2/32 (6.25%); P value 0.0001] with the observation being statistically significant in present study.

We found that need of additional anti-seizure medication was seen in 11 in group I and 5 in group II, time to termination of clinical seizure was 15.2 hours in group I and 13.4 hours in group II, duration of primary illness was 2.8 days in group I and 1.7 days in group II, number needing mechanical ventilation was 4 in group I and 3 in group II, duration of mechanical ventilation was 0.5 days in group I and 0.3 days in group II, duration of PICU/HDU stay was 3.7 days and 3.4 days respectively, duration of hospital stay was 6.5 6.1 days, seizure recurrence in 24 hours was in 4 and in 5 respectively and readmission within 30 days was seen in 2 and 3 respectively. The shortcoming of the study is small sample size and short follow up.

CONCLUSION

Authors found that levetiracetam is an effective alternative to fosphenytoin in management of BRSE in pediatric population.

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