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Original Research Article

Levetiracetam versus phenytoin for treatment of convulsive status epilepticus in pediatric population: a randomized controlled trial

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ABSTRACT

Background: Status epilepticus is a major medical and neurological emergency. Despite advances in treatment, it is still associated with significant morbidity and mortality. The objective of the study was to compare the efficacy of levetiracetam versus phenytoin in treatment of convulsive status epilepticus.
Methods: A Randomized control trial, was conducted at tertiary care hospital, Udaipur, Rajasthan, over a period of March 2017 to September 2018. Total 250 patients (age group 6 months to 18 years) who were presented with status epilepticus in PICU, were enrolled. These patients were divided into two groups by simple randomization. Levetiracetam was given to one group, while phenytoin was given to another group. Efficacy was decided by cessation of clinical seizure activity within 30 minutes of starting of drug infusion and patient was observed for recurrence of seizure within 24 hours.
Results: A total of 250 patients were enrolled in this study. Seizure terminated in 107 patients in phenytoin group (85.6%) and in 114 patients in levetiracetam group (91.2%). The difference was significant. Recurrence of seizure (with in 24 hour) was high in phenytoin group (14.4%) in comparison with levetiracetam group (8.8%). Most common adverse effect in both the groups on treatment was hypotension, though in phenytoin group it was significantly higher than patients on levetiracetam group (7.2% v/v 2.4%).
Conclusions: Levetiracetam may be an effective alternative to phenytoin as a second line drug in the management of benzodiazepine resistant convulsive status epilepticus in children.

Keywords: Levetiracetam, Phenytoin, Seizure, Status epilepticus

INTRODUCTION

Status epilepticus is a major medical and neurological emergency. Despite advances in treatment, it is still associated with significant morbidity and mortality.[1] Status epilepticus is defined as "continuous seizures activity or recurrent seizure activity without regaining of consciousness lasting for more than 5 minutes".[2]

Overall, status epilepticus is most common below 5 year of age with incidence of > 100/1,00,000 children.[2] Immediate treatment of status epilepticus is essential to prevent neurological sequelae which occurs in up to 39% of children and mortality which is reported at 3-5%.[3] In surveys of pediatric emergency providers and neurologists, phenytoin or fosphenytoin remain the most commonly used anti-seizure medication, if status epilepticus persists after administration of benzodiazepines.[4,5]

Over last fifty years, intravenous phenytoin has been the treatment of choice for patients with benzodiazepine resistant convulsive status epilepticus. Intravenous phenytoin loading dose is a complex and time consuming

procedure which may expose patients to several side effects such as severe hypotension, cardiac arrhythmias, local cutaneous reactions (purple glove syndrome), liver toxicity, hyperglycemia, ataxia, slurred speech, nystagmus, mental confusion, paresthesia, drowsiness, gingival hyperplasia, hirsutism, aplastic anemia, megaloblastic anemia, osteomalacia, hypocalcaemia, headache, thrombophlebitis, strong enzymatic inducer and hypersensitivity reactions like morbilliform rash, Stevens-Johnson syndrome and toxic epidermal necrolysis etc.[6,7]

Levetiracetam is a new 2nd generation antiepileptic drug and this anticonvulsant is effective in management of status epilepticus.[8,9] Levetiracetam has been increasingly used to treat seizures in neonates and children.[10-12]

Levetiracetam has potential advantages when compared to phenytoin for use in convulsive status epilepticus. Levetiracetam is easy to administer and can be given as a five-minute infusion into a peripheral IV cannula without the increased risk of serious adverse events (including hypotension, cardiac arrhythmias, extravasation injury-purple glove syndrome).[13]

Though, there are some case series and small trials on the use of levetiracetam in children, but there is no randomized controlled trial in children.[8] Therefore authors conducted a randomized control trial with the objective of comparing the efficacy of levetiracetam and phenytoin in the treatment of convulsive status epilepticus in pediatric population.

METHODS

This was a randomized control trial, conducted in pediatric intensive care unit (PICU), at tertiary care hospital, Udaipur, Rajasthan, over a period of March 2017 to September 2018, after obtaining permission from ethical committee of institute.

All included patients were divided into two groups by simple randomization. Randomization was done using small square slips with computer generated numbers from 1 to 250. Odd numbers were assigned to levetiracetam group (125 patients), while even numbers were assigned to phenytoin group (125 patients). They were folded and shuffled. They were put in a serially numbered opaque envelop and sealed. Each envelop was opened to the assigned participant of the particular group. The study was single blinded. Investigator and statistician were aware of the drug, being given to patient.

Patients were treated in one group with intravenous levetiracetam (20mg/kg) and in another group with intravenous phenytoin (20mg/kg). If seizures were controlled, maintenance dose of levetiracetam (10-20mg/kg/day q 12 hours) or phenytoin (5-8mg/kg/day q 12 hours) was continued in respective groups. If seizures persisted after the loading dose of each drug, patient was treated as per standard guideline of status epilepticus (Figure 1).

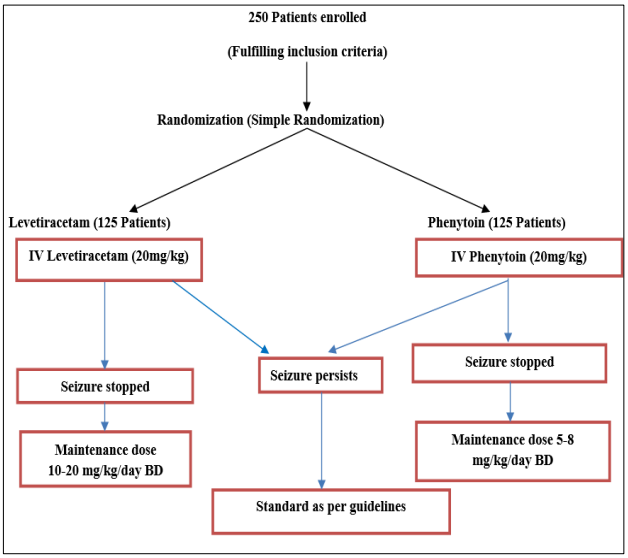

Figure 1: Study flow chart.

Efficacy was decided by cessation of clinical seizure activity within 30 minutes of starting of drug infusion. Patient was observed for recurrence of seizure within 24 hours.

Complete blood count, liver function test and kidney function tests were done at admission and when indicated. Daily monitoring, clinical assessment and follow up of the patient was done till discharge.

Inclusion criteria

- All patients (age group 6 months to 18 years) who were presented with status epilepticus in pediatric intensive care unit (PICU) over a period of March 2017 to September 2018.

Exclusion criteria

- Patients with H/O of anticonvulsant medication prior to admission, chronic kidney disease, chronic liver disease, major congenital malformations and H/O cardiac disorder, were excluded.

Statistical analysis

The collected data were transformed into variables, coded and entered in Microsoft Excel. Data were analysed and statistically evaluated using SPSS-PC-17 version. Quantitative data was expressed in mean, standard deviation and difference between two comparable groups were tested by student's t-test (unpaired) or Mann Whitney 'U' test. Three or more group's mean was analysed using one-way ANOVA, while qualitative data were expressed in percentage. Statistical differences between the proportions were tested by chi square test or

Fisher's exact test. 'P' value less than 0.05 was considered statistically significant.

RESULTS

A total of 250 patients, were enrolled in this study. The demographic and anthropometric data in both groups were shown. Both groups were comparable in term of mean age, weight, height and gender. No significant difference was observed between both groups (Table 1).

Table 1: Comparison of demographic and anthropometric data in both groups.

	Phenytoin group (n=125)		Levetiracetam group (n=125)		p value
	Mean	**SD**	**Mean**	**SD**	
Age (in years)	8.03	2.76	8.45	2.19	0.51
Weight (in kg)	24.45	19.22	22.78	16.17	0.61
Height (cm)	117.86	14.51	118.52	13.91	0.26
	No.	**%**	**No.**	**%**	
Male	80	64.0	90	72.0	0.17
Female	45	36.0	35	28.0	

Termination of seizure following levetiracetam administration was higher [114 patients (91.2%)] compared to phenytoin administration [107 patients (85.6%)] and this difference was found to be statistically significant (p=0.04) (Table 2). Seizures were re-occurred (within 24 hours) more in phenytoin group [18 patients (14.4%)] compared to levetiracetam group [11 patients (8.8%)] but this difference was not statistically significant (p=0.57) (Table 2).

Table 2: Primary outcome variable of the study groups.

	Phenytoin group (n=125)		Levetiracetam group (n=125)		p value
	No.	**%**	**No.**	**%**	
Seizure termination	107	85.6	114	91.2	0.04
Recurrence of seizure (within 24 hours)	18	14.4	11	8.8	0.57

In phenytoin group time taken to terminate seizure was 2.6±1.5 minutes and in levetiracetam group 3.4±1.2 minutes and this difference was found to be statistically significant (p=0.02) (Table 3). Seizure free interval in case of recurrence of seizure (within 24 hours) was lesser in phenytoin group (1.7±1.2 hours) compare to levetiracetam group (3.7±5.6 hours) but this difference was not statistically significant (p=0.08) (Table 3).

Table 3: Secondary outcome variable of the study groups.

	Phenytoin group (n=125)		Levetiracetam group (n=125)		p value
	Mean	**SD**	**Mean**	**SD**	
Time taken to terminate seizures (minutes)	2.6	1.5	3.4	1.2	0.02
Seizure free interval in case of seizure recurrence (hours)	1.7	1.2	3.7	5.6	0.08

PICU stay was lesser in levetiracetam group (44.4±10.7 hours) in comparison to phenytoin group (45.4±15.1 hours). Hospital stay was also lesser in levetiracetam group (5.9±4.7 days) in comparison to phenytoin group (6.7±3.8 days) but no significant difference was observed between both groups (Table 4).

Table 4: PICU and hospital stay in study subjects.

	Phenytoin group (n=125)		Levetiracetam group (n=125)		P value
	Mean	**SD**	**Mean**	**SD**	
PICU stay (hours)	45.4	15.1	44.4	10.7	0.11
Hospital stay (days)	6.7	3.8	5.9	4.7	0.24

Most common adverse effect in both the groups on treatment was hypotension, though in phenytoin group it was significantly higher than patients on levetiracetam group (7.2% v/v 2.4%).

Table 5: Adverse drug effects in both groups.

Adverse drug effects	Phenytoin group (n=125)		Levetiracetam group (n=125)	
	No.	**%**	**No.**	**%**
Hypotension	9	7.2	3	2.4
Ataxia	7	5.6	2	1.6
Worsen neurological condition	6	4.8	3	2.4
Headache	7	5.6	2	1.6
Behavioral problems	7	5.6	2	1.6
Drowsiness	6	4.8	1	0.8
Fever	7	5.6	2	1.6
Cardiac arrhythmia	3	2.4	0	00
Coagulation defects	1	0.8	0	00
Abnormal liver functional test	1	0.8	0	00
Dermatological complications	1	0.8	0	00

Other adverse effects as Ataxia (5.6%), headache (5.6%), behavioral problems (5.6%), fever (5.6%) worsening neurological condition (4.8%), drowsiness (4.8%) and cardiac arrhythmia, (2.4 %) are comparably high in phenytoin group.

Coagulation defects, abnormal liver function test and dermatological complications are present in less than 1% of patients treated with phenytoin while these adverse effects were not seen in patients on levetiracetam group (Table 5).

DISCUSSION

In present study mean age, weight, height and gender were comparable in both groups (p=0.51, 0.61, 0.26, 0.17) (Table 1). In present study levetiracetam was found to be more effective for termination of seizure in patients with status epilepticus, as compare to phenytoin. Seizures were terminated in 91.2% patients following levetiracetam administration while in 85.6% patients following phenytoin administration and this difference was statistically significant (p=0.04) (Table 2).

In a study SenthilKumar CS et al, also reported seizure termination rate of 84% in phenytoin group while it was 92% in levetiracetam group in their study.[15] Kirmani BF et al, in their study revealed that the efficacy of IV levetiracetam was 75% in terminating status epilepticus and 59% in patients with acute repetitive seizures.[16] In a retrospective study done in Indian children aged 3 weeks to 19 years Goraya Js et al, revealed that IV levetiracetam, showed seizure cessation with 90% efficacy.[17] In a meta-analysis of published studies on relative effectiveness of antiepileptic drugs in treatment of benzodiazepine resistant convulsive status epilepticus by Yasiry Z and Shorvon et al, SD et al also reveals similar results, but the efficacy of levetiracetam was 68.5% whereas the mean efficacy of phenytoin was 50.2%.[18] Singh K et al, reported overall success rate of therapy in terms of termination of seizure was 96% in phenytoin group and 94% in levetiracetam group which was not statistically significant.[14]

In present study, recurrence of seizure (within 24 hours) was observed more in phenytoin group (14.4%) as compared to levetiracetam group (8.8%) but this difference was not statistically significant (p=0.57) (Table 2). In a study conducted by Singh K et al, recurrence of seizure activity within 24 hours was seen in 3 (6%) children in levetiracetam group and 2 (4%) children in phenytoin group.[14] SenthilKumar CS et al, reported lesser recurrence (9.5%) in phenytoin group and higher (17.5%) in the LEV group.[15] Though as a secondary outcome of present study, cessation of seizure was found earlier in patients received phenytoin than patients received levetiracetam. The mean time to halt the seizures was 2.6±1.5 minutes in phenytoin group whereas in levetiracetam group it was 3.4± 1.2 minutes, which was statistically significant (p=0.02) (Table 3). Senthilkumar CS et al, also observed in their study that the mean time to halt the seizures was 2.5±1.4 minutes in phenytoin group whereas in levetiracetam group it was 3.3±1.16 minutes.[15]

In present study, there was no statistically significant difference (p=0.08) in seizure free duration following study medication between both groups but it was lesser in phenytoin group (1.7±1.2hours) compared to levetiracetam group (3.7±5.6hours) (Table 3). In a study by Senthilkumar CS et al, no significant difference was observed in seizure free duration following study medication between both groups.[15]

In this study, patients on treatment with either on phenytoin or levetiracetam, there was no statistically significant difference between the two groups in PICU stay (45.4 hours vs 44.4 hours: p value 0.11) and hospital stay (6.7 days vs 5.9 days: p=0.24) (Table 4). Mean hospital stays in Senthilkumar CS et al, study was more in levetiracetam group (6.3 days) compare to phenytoin group (5.8 days) but difference was not statistically significant.[15] In present study, the common adverse effects observed in phenytoin group were hypotension (7.2%), ataxia (5.6%), headache (5.6%). behavioral problems (5.6%), fever (5.6%), drowsiness (4.8%), worsen neurological condition (4.8%) while lesser side effects were observed in patient on levetiracetam and these were: hypotension (2.4%) and worsen neurological conditions (2.4%). In few of the subjects on levetiracetam ataxia (1.6%), headache (1.6%), behavioral problems (1.6%), fever (1.6%) were also observed (Table 5). Egunsola O et al, on the safety of levetiracetam in pediatric patients with epilepsy, reported that behavioral problems and somnolence were the most prevalent adverse event.[19] Respiratory depression requiring nasal oxygen and ataxia were the adverse effects noted following fosphenytoin administration in Senthilkumar CS et al, study while in the levetiracetam group behavioral change in the form of irritable cry and thrombocytopenia were noted.[15]

CONCLUSION

Levetiracetam may be an effective alternative to phenytoin as a second line drug in the management of benzodiazepine resistant convulsive status epilepticus in children. The overall rates of adverse events were low and mild in severity, suggesting a fairly safe profile for levetiracetam in actual clinical context.

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