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Original Research Article

Comparative efficacy of IV phenytoin, IV valproate and IV levetiracetam in childhood seizures

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ABSTRACT

Background: Seizures are the most common pediatric neurologic disorder, with 4% to 10% of children suffering at least one seizure in the first 16 years of life objectives to compare efficacy of IV phenytoin, IV valproate, and IV levetiracetam in childhood seizures between 2months to 16 years of age.
Methods: This prospective, randomized, study was done on pediatric patients in the age group of 2 months to 16 years who present actively convulsing to the emergency department of pediatrics.
Results: At 24 hours seizures were controlled in 44 (88%) patients out of 50 patients in phenytoin group, 39 (78%) out of 50 patients in levetiracetam group and 46 (92%) out of 50 patients in valproate group (p-value 0.115). The relative risk of seizure recurrence for levetiracetam and phenytoin groups when compared to valproate was 2.75 and 1.5, respectively.
Conclusions: Present study demonstrates that IV levetiracetam and IV valproate were comparable to IV phenytoin in terms of seizure control in acute setting. All the three are safe and efficacious. Time to regain consciousness was less in valproate group and long-term seizure control too was also better.

Keywords: Childhood seizures, Levetiracetam, Phenytoin, Status epilepticus, Valproate

INTRODUCTION

Seizures are the most common pediatric neurologic disorder, with 4% to 10% of children suffering at least one seizure in the first 16 years of life.[1] The incidence is highest in children younger than 3 years of age, with a decreasing frequency in older children.[2] Status epilepticus is a common pediatric neurological emergency that requires immediate and vigorous management and at times poses a therapeutic challenge to the treating physician. If not managed promptly, it may result in significant neuromorbidity and mortality.[3,4] Early termination of the seizure activity and meticulous supportive care can circumvent most of the deleterious effects of SE and limit the morbidity and mortality. The correct management strategy involves initial stabilization of airways, breathing and circulation, prompt control of seizures, evaluation and treatment of the underlying etiology.[5-7] The standard prototocol for treatment of pediatric status epilepticus involves use of a benzodiazepine first followed by a long acting drug like phenytoin. Benzodiazepines act as agonists at GABA receptors and potentiate inhibition of neuronal firing. They are potent and fast acting drugs which are used as

the initial therapy. Lorazepam is being preferred as the drug of choice for initial therapy. The dose is 0.05-0.1 mg/kg intravenous. Mean time for seizure cessation is 3 minutes. Duration of antiseizure effect is 12-24 hours. If lorazepam is not available, diazepam a short-acting but effective drug is administered. It should be followed within 20 minutes by a long acting drug such as Phenytoin. It should be given directly into the vein. The dose is 0.1-0.3 mg/kg at rate not greater than 2 mg/min for a maximum of 2 doses. Adverse effects of benzodiazepines include respiratory depression, hypotension and impaired consciousness. Among long acting agents currently phenytoin is the most common agent used in the setting of acute seizure prevention in children. It acts by stabilizing the neuronal membrane. Phenytoin remains the drug of choice for second-line therapy in SE that does not respond to lorazepam or diazepam and is also used for maintaining antiseizure effect after the initial therapy with diazepam. A loading dose of 20 mg/kg is infused slowly after diluting with saline at a maximum rate of 1mg/kg/min in children. It is advisable to avoid dextrose-containing solutions as diluents to prevent precipitation. ECG and blood pressure monitoring are recommended as the drug can cause arrhythmias and hypotension. The infusion can be repeated in a dose of 5mg/kg. As much as 30 mg/kg may be required to stop seizures in some patients.

Intravenous valproate can be used as an alternative to phenobarbital and phenytoin in the treatment of seizures and epileptic syndromes, especially in allergic patients and in progressive myoclonus epilepsy. Lack of life threatening cardiovascular, neurological, or local adverse effects supported its use in emergency conditions as well. Although intravenous valproate may be used as a second-line antiepileptic drugs in treatment of pediatric status epilepticus.[6,8-10] Less than three-year-old children are at a considerably increased risk of developing lethal hepatotoxicity, especially in those who have a history of hepatic disease, taken polytherapy of antiepileptic drugs, or with severe seizure disorders accompanied by mental retardation.[11]

Levetiracetam is another such drug with a broad-spectrum antiepileptic activity and a unique preclinical and pharmacological profile. Levetiracetam binds to a unique binding site in the brain, the synaptic vesicle protein SV2A. Because levetiracetam does not appear to affect normal brain physiology, it is believed to modulate SV2A function only under pathophysiologic conditions.[12] Levetiracetam is also known to selectively inhibit N-type calcium channels and to block the inhibition of GABA- and glycine-gated currents by negative allosteric modulators.[13,14]

The present study has been devised to compare efficacies of phenytoin, levetiracetam and valproate as second-line status epilepticus treatment in children and whether levetiracetam and/or valproate can offer a comparable or more efficious and safer modality of treatment for pediatric status epilepticus.

METHODS

This prospective, randomized, study was conducted in the Department of Pediatrics at Sher-i-Kashmir Institute of Medical Sciences, Srinagar, Jammu and Kashmir, India. This is an urban academic medical center in Srinagar, over a period of 3 years from January 1, 2012, through December 31, 2014.

Pediatric patients in the age group of 2 months to 16 years who present actively convulsing (focal motor status or generalized convulsive status) to the emergency department of pediatrics were included in the study. All the patients were informed about the purpose of the study and written informed consent was obtained from them. Also, approval was taken from the hospital ethics committee for the study.

Randomization

The patients who consented to participate in the study were then randomized into three groups. Randomization was done using a computer derived random-number sequence. 150 pediatric patients of either sex, in the age group of 2 months to 16 years, who consented were enrolled in the study. The patients with age below 1 month, children already receiving antiepileptic drugs, children with evidence of meningitis or head trauma and those with known hypersensitivity to study study drugs were excluded. All the enrolled pediatric patients were received actively convulsing. After proper assessment of airway and breathing IV access was established and iv diazepam at 0.3 mg/kg was given to control the seizures. Standard monitoring with recording of heart rate, blood pressure, respiratory rate and pulse oximetry (spo2) was established in the meantime. After obtaining written consent, a detailed assessment regarding type of seizures, any previous drug intake, and any history suggestive of meningitis and head trauma was recorded. After initial stabilization, patients were randomly assigned to three groups. Phenytoin group received IV phenytoin loading dose at 20 mg/kg diluted in NS at a rate <1 mg/kg/minute followed by maintenance dose of 5 mg/kg day in two divided doses. Levetiracetam group received IV Levetiracetam loading dose 25 mg/kg at 3 mg/kg/min followed by maintenance 25mg/kg/day divided 12hrly. Valproate group-recieved IV Valproate loading 25mg/kg at 3 mg/kg/hour, followed by maintenance 20 mg/kg/day in divided doses 12 hourly.

Venous blood samples were drawn under aseptic conditions for measurement of a baseline hemogram, a liver function test, and analyses of blood urea, serum electrolytes, and blood sugar. Weight, height, and body mass index were calculated, and patients were examined for any neurologic deficits.

Monitoring

Pulse rate, respiratory rate, blood pressure, oxygen saturation, consciousness, and recurrence of seizures were monitored for a 24-hour period every 30 minutes for 1 hour, then hourly for 3 hours, and then every 2 hours for 12 hours, and then every 4 hours until 24 hours had passed. Patients were also monitored for development of any adverse to the given drugs.

The observed data was entered in the computer to analyze with the help of MS, Excel and SPSS version 15 for windows. The primary outcome measure is presented as mean and SD and statistically significant difference was evaluated using one-way ANOVA. Statistically significant difference of qualitable variables among three groups was evaluated using Chi square/ Fischers exact test. A p-value of <0.05 was considered as significant and a p-value less than .001 (p<0.001) as highly significant.

RESULTS

A total of 150 patients were included in present study. After initial stabilization, patients were randomly assigned to three groups containing 50 patients each. At 24 hours seizures were controlled in 44 (88%) patients in Phenytoin group, 39 (78%) patients of levetiracetam group and 46 (92%) patients of valproate group.

Table 1: comparison of seizure control at 24 hours in three groups.

Category	Phenytoin (50)		Levetiracetam (50)		Valproate (50)		P-value
	N	%	N	%	N	%	
Controlled	44	88	39	78	46	92	0.1154
Not controlled	6	12	11	22	4	8	

On comparing the seizure control at 24 hours between the three groups the p value was 0.1154, which was not statistically significant as the p >0.05 (Table 1).

At 24 hours seizures were controlled in 44 (88%) patients in phenytoin group, 39 (78%) patients of levetiracetam group and 46 (92%) patients of valproate group. On comparing the seizure control at 24 hours between the three groups the p value was 0.1154, which was not statistically significant as the (p >0.05). The comparison of seizure control at 24 hours between individual groups was also obtained as shown in Table 2, Table 3 and Table 4. The comparison of seizure control at 24 hours between phenytoin and levetiracetam groups is statistically insignificant as the p value is > 0.05. The comparison of seizure control at 24 hours between levetiracetam and valproate groups was statistically insignificant as the p value is >0.05, but the relative risk was 2.75, which means the patients in Levetiracetam group were at marginally (2.75 times) higher risk of developing repeated seizures within 24 hours as compared to patients in valproate group.

Table 2: Comparison of seizure control at 24 hours between Phenytoin and Levetiracetam.

Category	Not controlled		Controlled		RR	P-value
	N	%	N	%		
Phenytoin (50)	6	12	44	88	0.546	0.287
Levetiracetam (50)	11	22	39	78		

Table 3: Comparison of seizure control at 24 hours between levetiracetam and valproate.

Category	Not controlled		Controlled		RR	P-value
	N	%	N	%		
Levetiracetam (50)	11	22	39	78	2.75	0.091
Valproate (50)	4	8	46	92		

The comparison of seizure control at 24 hours between phenytoin and valproate groups is statistically insignificant as the p value is >0.05. but the relative risk was 1.5, which means the patients in phenytoin group were at marginally (1.5 times) higher risk of developing repeated seizures within 24 hours as compared to patients

in valproate group. Comparison of time taken to regain consciousness in three groups was also obtained revealing the mean(±SD) time taken to regain consciousness in the Phenytoin group patients was 122.34(±45.406) minutes, where as in levetiracetam group it was 120.82(±42.796) minutes and in the valproate group it was 75.04(±30.657) minutes. The comparison of time taken to regain consciousness in the three study groups was statistically significant as the p value ANOVA is <0.05. At 3 months of follow up 7(14.28%) patients from phenytoin group, 14 (28.57%) patients from levetiracetam group and 2 (4%) patients from Valproate group had a repeated seizure. The comparison was statistically significant as the p-value was <0.05. The comparison of seizure control at 3 months between phenytoin and levetiracetam groups was obtained, revealing 85.72% in phenytoin group and 71.43% in levetiracetam group were well controlled. The difference is statistically insignificant as the p value is > 0.05.

Table 4: Comparison of seizure control at 24 hours between phenytoin and valproate.

Category	Not controlled		Controlled		RR	P-value
	N	%	N	%		
Phenytoin (50)	6	12	44	88	1.5	0.741
Valproate (50)	4	8	46	92		

Table 5: comparison of time taken to regain consciousness in three groups.

Variable	Study group	Mean± SD	95% CL	P value ANOVA
TTRC (min)	Phenytoin (50)	122.34±45.406	109.42-135.26	<0.0001
	Levetiracetam (50)	120.82±42.796	108.65-132.99	
	Valproate (50)	75.04±30.657	66.319-83.761	

Table 6: Comparison of seizure control at 3 months in the three study groups.

Category	Phenytoin (49)		Levetiracetam (49)		Valproate (50)		P-value
	N	%	N	%	N	%	
Controlled	42	85.72	35	71.43	48	96	0.0032
Not controlled	7	14.28	14	28.57	2	4	

Table 7: Comparison of seizure control at 3 months between phenytoin and levetiracetam.

Category	Not controlled		Controlled		RR	P-value
	N	%	N	%		
Phenytoin (49)	7	14.28	42	85.72	0.50	0.138
Levetiracetam (49)	14	28.57	35	71.43		

Table 8: Comparison of seizure control at 3 months between levetiracetam and valproate.

Category	Not controlled		Controlled		RR	P-value
	N	%	N	%		
Levetiracetam (49)	14	28.57	35	71.43	7.143	0.0009
Valproate (50)	2	4	48	96		

Table 9: Comparison of seizure control at 3 months between phenytoin and valproate.

Category	Not controlled		Controlled		RR	P-value
	N	%	N	%		
Phenytoin (49)	7	14.28	42	85.72	3.57	0.092
Valproate (50)	2	4	48	96		

Comparison of seizure control at 3 months between individual groups was also obtained as shown in Table 7, Table 8 and Table 9. The comparison of seizure control at 3 months between levetiracetam and valproate groups

was obtained, revealing 71.43% in levetiracetam group and 96% in valproate group were well controlled. The difference is statistically significant as the p value is <0.05, so the frequency of seizures in 3 months in valproate group was less as compared to levetiracetam.

The comparison of seizure control at 3 months between phenytoin and valproate groups was obtained, revealing 85.72% in phenytoin group and 96% in valproate group were well controlled. The differences are statistically insignificant as the p value is >0.05.

DISCUSSION

The present study compares efficacy of IV phenytoin, IV levetiracetam and IV valproate for seizure management in children and is, to the best of our knowledge, the only one available.

The primary outcome measure in our study was the cessation of seizure activity for 24 hours. At 24 hours seizures were controlled in 44 (88%) patients out of 50 patients in phenytoin group, 39 (78%) out of 50 patients in levetiracetam group and 46 (92%) out of 50 patients in valproate group (p-value 0.115). The relative risk of seizure recurrence for levetiracetam and phenytoin groups when compared to valproate was 2.75 and 1.5, respectively. This means valproate appears to be marginally better than the other two for acute seizure control, even though the difference was not statistically significant. The overall success rate of therapy in terms of efficacy was 88% in phenytoin group, 78% in levetiracetam group and 92% in valproate group. Misra UK et al, found that status epilepticus was aborted in 66% of patients with valproate, and in 42% of patients with phenytoin (P > 0.05).[10] In the study of Anuradha R et al, seizures were controlled in 80% in Valproate group and 92% in phenytoin group at 24 hours (p=0.2.03).[15] Goraya JS et al, found that 75% of patients who received IV levetiracetam for control of status epilepticus became seizure free and 25% had a >50% reduction in seizure frequency.[16] Abend NS et al, in their cohort of critically ill children with status epilepticus or acute repetitive seizures found that intravenous Levetiracetam resulted in either termination, temporary cessation, or reduction in ongoing seizure activity.[17]

The mean time to regain consciousness in phenytoin, levetiracetam and valproate groups was 122.3(±45.4), 120.8 (±42.8) and 75.0 (±30.7) minutes (mean±S.D) respectively. Patients in valproate group regained consciousness earlier than both Phenytoin and levetiracetam group patients(p<0.0001). In the study by Anuradha R et al, in which patients initially received iv diazepam, no difference in time taken to regain consciousness was observed between Valproate and Phenytoin groups.[15] Yu et al, found that the time taken for mental status recovery after IV valproate was less than 60 min in all patients with status epilepticus.[18] However, in their study iv diazepam was not used before valproate loading. To the best of our knowledge no such comparative study was available for IV levetiracetam.

Out of all patients in the three study groups only one patient from valproate group had a repeat seizure at the end of first week (p=0.372). A Rai et al, in their study found that none of the patients from either phenytoin or valproate group had a repeat seizure at the end of first week.[15] At 3 month follow up, 7 (14.28%) out of 49 patients in phenytoin group, 14 (28.57%) out of 49 in levetiracetam group and 2 (4%)out of 50 patients in valproate group had a seizure recurrence (p-value 0.0032 ANOVA). Valproate was significantly better for seizure control at 3 months than levetiracetam and the comparison between other groups revealed insignificant difference. Adverse un-wanted side effects reported in our study were somnolence in two patients in levetiracetam group at one week follow up. The age of both the patients was less than three months. The effects were not severe to warrant drug discontinuation. One patient from valproate group had drug induced transamonitis (hyperammonemia) at three months follow up requiring drug discontinuation. The age of the patient was 11 months.

This study has a number of limitations. Although EEG was done in all patients before hospital discharge, continuous EEG monitoring during acute phase was not possible. The serum drug levels were not done in all patients at different intervals except those who had a seizure recurrence.

CONCLUSION

This study demonstrated that IV levetiracetam and IV valproate were comparable to IV phenytoin in terms of seizure control in acute setting. All the three are safe and efficacious. Time to regain consciousness was less in valproate group and long-term seizure control too was also better. It appears that both levetiracetam and valproate can be effectively used in management of status epilepticus in emergency setting and Valproate is superior to phenytoin and levetiracetam in maintaining seizure control on long term basis. From the positive results in our study it can be concluded that levetiracetam and valproate can be recommended for inclusion in the treatment protocols of status epilepticus and as an initial loading dose in children requiring long term anticonvulsants. Although our experience with IV levetiracetam and IV valproate loading in pediatric seizure emergencies indicates that both are safe and effective, additional research is warranted to investigate further the use of these drugs for treating seizure emergencies in pediatric patients.

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