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Medicine

Comparison of Efficacy of Intravenous Phenytoin and Intravenous Valproate in Childhood Seizure

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Abstract: A randomized control trial was undertaken for children of 2-12 years of age, suffering from seizures, generalized tonic-clonic, partial or in the form of status epilepticus to evaluate the efficacy and safety of IV phenytoin and IV valproate, as a second line agent after an intravenous injection of benzodiazepine. Children with simple febrile convulsion were excluded from the study. Clinical and socio-demographic parameters for the study were recorded on a predesigned proforma. Relevant investigation in the form of blood parameters, CSF study and neuroimaging were done accordingly. Data were entered into Microsoft excel datasheet and analyzed with SPSS-17.0 and medcalc- 12.7.3. There were no significant differences in the efficacy of phenytoin and valproate in controlling seizure from various etiologies like CNS infections, seizure disorder, intracranial granuloma etc. But, in cases of type of seizure like in status epilepticus and focal seizure with or without secondary generalization phenytoin is controlling more number of seizures than valproate. On the contrary, valproate controlled more number of generalized seizures than phenytoin. But there is no significant statistical difference between the two. Further studies in a larger population have to be done to identify its statistical significance.
Keywords: childhood seizure, efficacy, phenytoin, valproate.

INTRODUCTION

A seizure is defined as a transient, involuntary alteration of consciousness, behavior, motor activity, sensation or autonomic function caused by an excessive rate and hyper synchrony of discharges from a group of cerebral neurons. A postictal period of decreased responsiveness usually follows most seizures.

Epilepsy describes a condition of susceptibility to recurrent seizures and if the seizure activity lasting longer than 30 minutes or consciousness is not regained between 2 seizure activities, it is termed as status epilepticus [1].

Seizure is the most common pediatric neurologic disorder, with 4-10% of children suffering at least one seizure in the first 16 years of life [2]. Athough childhood epilepsy is more likely to remit; the developmental and social impact of epilepsy may extend beyond childhood, affecting the individual's potential in cognitive, emotional and socioeconomic arenas [3]. Pharmacotherapy is cornerstone of management of childhood epilepsy. The goal of medical management is seizure freedom, with minimal or no adverse effects. For the rapid control of seizures, it is necessary to administer AED intravenously. Initial management of seizures should be attempted mainly with IV diazepam or lorazepam and the next line of treatment involves IV phenytoin, valproate, phenobarbital, midazolam or levetiracetam [4-7].

Traditionally IV phenytoin is used as a second line drug for managing acute episode of seizures. Fosphenyoin and phenytoin are listed as second monotherapy for the treatment of tonic-clonic seizure, both generalized and partial, psychomotor seizure, and in the management of status epilepticus [8, 9]. On the other hand, IV valproate was endorsed as after an initial trial of benzodiazepine for convulsive status, absence status, generalized tonic-clonic and partial seizure[10]. Even after studies showing individual efficacy and safety of IV valproate and IV phenytoin, there are limited discussion on comparative study between these two drugs. Our study aims to compare the efficacy and safety of these two in childhood seizure and children with status epilepticus.

MATERIALS AND METHODS

This prospective randomized control trial was undertaken in the Department of Pediatrics, R.G. Kar Medical College Hospital, Kolkata over the period of 2014-2015. Approval was taken from institutional ethics committee before starting the study. Study population was children belonging to age group 2 to 12 years with generalized tonic clonic seizures and partial seizures, admitted in our ward. Children with simple febrile seizure are excluded from our study. They are divided in 2 groups, 30 in number in each group. Informed consent was taken from the parent for each study case. Clinical and socio-demographic parameters for the study subjects were recorded on a predesigned proforma. After giving adequate supportive care in the form of airway, breathing and circulation management, all the Status epilepticus patients receive a single dose of IV benzodiazepines as a 1st line therapy to control seizures. Then as a 2nd line drug, loading dose of either IV Phenytoin or IV Valproate was given randomly. Then maintenance dose was given accordingly. If any seizure recurs half loading of corresponding drug was given. If still seizure persists then next level of management was initiated. Patient then investigated for relevant blood investigations, CSF study and neuro imaging accordingly.

The study was analyzed following standard statistical protocol. All data were collected, compiled and plotted in Microsoft excel power sheet. Thereafter it was subjected to statistical analysis with the help of SPSS software (version 17.0) and Medcalc (version 12.7.3). Microsoft word and Excel '10 were used to generate the tables, graphs etc. All tests were 2-tailed. A p-value of <0.05 was considered statistically significant for all analysis.

RESULTS

Our study was to compare efficacy between phenytoin and valproate in childhood seizure. We made two groups of patients, 30 numbers of patients in each group. One group received IV phenytoin and other group received IV valproate after initial stabilization and benzodiazepines, if required as in cases of status epilepticus. Both of the groups were matched for age and sex. Valproate controlled (28-controlled and 2-not controlled) seizures in more number of patients than by phenytoin (26 vs 4), without any significant statistical difference (χ^2 – 0.740). In our study population there were 15 girls, in which 7 received valproate and 8 received phenytoin. There is no statistically significant difference between two drugs and sex. No differences were found in two groups in terms of habitat and socioeconomic status also.

Most common cause of convulsion in our study group was infective, which constitute 31.67% of total cases. It was followed by seizure disorder (30%) and intracranial granulomas (23.33%). In our study all the cases of intracranial granulomas (neurocysticercosis, tuberculum), seizures were controlled by antiepileptic agents. In our study valproate controlled all of the patients with convulsion in infection (meningitis, encephalitis) and seizure disorder. In subjects who received phenytoin controlled only 90% of patients with infection and 78% of patients with seizure disorder, and rest of patient received valproate to control seizures. But this is not significant χ^2- 0.526 for infection and 0.235 for seizure disorder. The entire patients with cerebral palsy received valproate and convulsion of one subject was not controlled by valproate. In our population, there is no significant difference in the efficacy of phenytoin and valproate in various etiologies (Table 1).

Table-1: Distribution according to etiological type and response to the drug

Etiology	Response to the drug	Drug received				P value
		Phenytoin		Valproate		
Intracranial granulomas	Controlled	9	100%	5	100%	NS
	Not controlled	0	0%	0	0%	
Infective	Controlled	9	90%	9	100%	0.526
	Not controlled	1	10%	0	0%	
Seizure disorder	Controlled	7	77.8%	9	100%	0.235
	Not controlled	2	22.2%	0	0%	
Cerebral palsy	Controlled	0	0%	2	66.7%	NS
	Not controlled	0	0%	1	33.3%	
Miscellaneous	Controlled	1	50%	3	75%	0.600
	Not controlled	1	50%	1	75%	

Seizures in our study group were associated with various illnesses depending on etiology. But majority of patients didn't have any associated illness. Most common association was with fever. Irrespective of their associated illness, efficacy of phenytoin and valproate remains same (Table 2).

Table-2: Distribution of population according to associated illness and their response to the drug

Associated illness	Response to the drug	Drug received				P value
		Phenytoin		Valproate		
		N	%	N	%	
Fever	controlled	7	77.78%	10	90.90%	0.421
	Not controlled	2	22.22%	1	9.09%	
Developmental delay	controlled	1	100%	2	66.67%	0.750
	Not controlled	0	0%	1	33.33%	
Dystonia	controlled	0	0%	1	100%	NS
	Not controlled	0	0%	0	0%	
Hydrocephalous	controlled	1	100%	1	100%	NS
	Not controlled	0	0%	0	0%	
Hypoglycemia	controlled	0	0%	1	100%	NS
	Not controlled	0	0%	0	0%	
No associated illness	Controlled	17	89.47%	13	100%	0.345
	Not controlled	2	10.53%	0	0%	

In our study, Valproate controlled seizure in 89% of subjects with previous history of seizure, while phenytoin controlled 75% of subjects (χ^2 – 0.538). In the first episode valproate controlled seizures in 95.3% of subjects while phenytoin controlled seizures in 88.5 %,(χ^2 – 0.390). Regarding type of seizure, Valproate controlled 95.7% of subject and phenytoin controlled 84.0% of subjects in a generalized seizure, (χ^2 – 0.667). Phenytoin controlled all the case with focal with or without secondary generalization. Phenytoin and valproate does not have any significant difference in efficacy in the distribution of type of seizures (Table 3).

Table-3: Distribution of the population according to the type of seizures and response to the drug

Type of seizure	Response to the drug	Drug received				P value
		Phenytoin		Valproate		
Focal	Controlled	2	100%	3	75%	0.667
	Not controlled	0	0%	1	25%	
Generalized	Controlled	21	84.0%	22	95.67%	NS
	Not controlled	4	16.0%	1	4.33%	
Focal with secondary generalization	Controlled	3	100%	3	100%	0.201
	Not controlled	0	0%	0	0%	

Repeated attacks of convulsions were present in six patients. It has been seen that valproate has controlled seizure in more number of patients, if seizure is less than five minutes. Valproate controlled seizure in 95.7% of subjects and phenytoin controlled 84.2% if duration less than five minutes (χ^2 – 0.234). But if patient had status, phenytoin was preferred and more number of patients received phenytoin and thus number of controlled seizure were also increased. In our study, phenytoin controlled seizures in 83.3% of subjects, while valproate controlled 50% of patients, (fischer – 0.464) (Table 4).

Table-4: Distribution of study population according to duration of seizure and response to the drug

Duration of last seizure	Response to the drug	Drug received				P value
		Phenytoin		Valproate		
a(less than 5 minutes)	Controlled	16	84.21%	22	95.67%	0.234
	Not controlled	3	15.79%	1	4.33%	
b(5 to 30 minutes)	Controlled	5	100%	5	100%	NS
	Not controlled	0	0%	0	0%	
c(more than 30mnutes)	Controlled	5	83.33%	1	50%	0.464
	Not controlled	1	16.67%	1	50%	

Total three patients developed clinically recognizable adverse effects. All of them were attributed to phenytoin (thrombophlebitis-2, ataxia-1). Because of financial constraints, blood level of AED could not be done. As seizure may be precipitated by various metabolic derangements, and also seizure may cause various metabolic derangements we had assessed serum glucose level, electrolyte level in all the possible subjects. Only in 56.67% of the study population screened for electrolyte level. In them, 70.59% had normal levels and rest had abnormal values. Most common abnormality that we faced was sodium

imbalance either hypernatremia or hyponatremia. They constitute 11.67% of study population. Only one had hypoglycemic attack.

In our study seizure were controlled in 90.00% of total subjects. In rest, two were expired and seizures in others were controlled by additional AED and discharged in stable conditions. Both phenytoin and valproate have similar discharge rate (96.67%). Both groups have one death each (Fig 1).

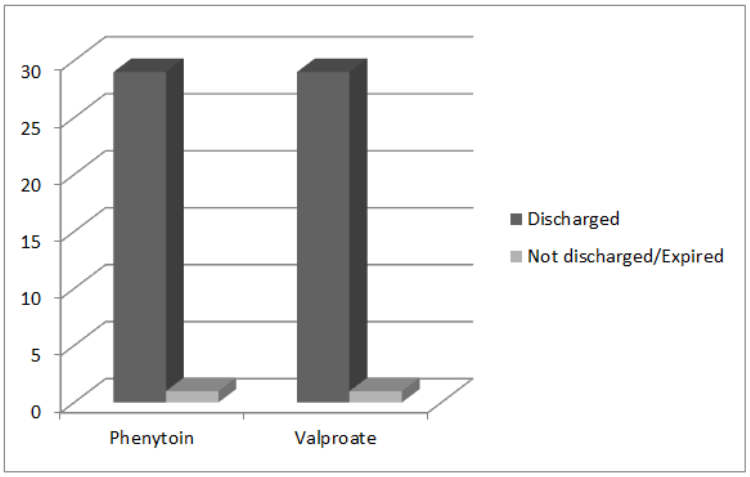

Fig-1: outcome of the patient receiving phenytoin and valproate

DISCUSSION

A seizure is a paroxysmal event due to abnormal excessive or synchronous neuronal activity in the brain. Childhood seizure is broad heterogeneous group of seizures which includes seizure of various etiologies including infective, metabolic, neoplastic, genetic, idiopathic, etc. The treatment of seizure depends on type of seizure and duration of seizure. Here in our study we have compared the efficacy of phenytoin and valproate in childhood seizures. We took total sixty subjects, thirty subjects in each group. Age and sex were matched adequately between the group of patient receiving phenytoin and group receiving valproate. Subjects were later randomized accordingly. Patient was assessed clinically and with relevant investigations. The response to the drug was assessed up to discharge from our hospital. Two of our patient were expired due to intractable seizures whose seizures were not at all got controlled by multiple AEDs.

In our study, we have seen that valproate is as efficacious as phenytoin in controlling seizure. Valproate controlled seizures marginally more patients than phenytoin, but couldn't get any statistical evidence to prove valproate is superior to phenytoin (χ^2 - 0 .754). De Silva *et al*. [11] have reported that phenytoin, valproate, phenobarbitone and carbamazepine have similar outcome even after following up for 3 years. Turnbull *et al*. [12] reported that both phenytoin and valproate has no difference in efficacy in adults with recent onset epilepsy irrespective of their type. They suggested initial choice of anti epileptic agents is determined by adverse effects than efficacy. On contrary to our study Misra *et al*. [13] reported that valproate is more effective than phenytoin in controlling status epilepticus. This difference may be due to small sample size of status epilepticus. Alvarez *et al*. [14] reported that efficacy of valproate, phenytoin and leviteracetam in controlling status epilepticus is similar. Gilad *et al*. [15] demonstrated that there is no significant difference between phenytoin and valproate in status epilepticus and acute repetitive seizures in adult. Agarwal *et al*. [16] showed that IV valproate is as efficacious as IV Phenytoin in controlling benzodiazepine refractory seizures.

Both phenytoin and valproate controlled seizures irrespective of the type of seizures, number of seizures, and duration of seizures in our study. Tudur smith *et al*. [17] also demonstrated that the interaction between treatment and seizure type is insignificant. In our study type of seizure doesn't have any statistical significance in efficacy of IV phenytoin and IV valproate. Though phenytoin controlled all the patients with focal seizure, valproate controlled only 75% of its subjects with seizures of focal onset but sample sizes of both groups were small. Shakir[18] also demonstrated that valproate can be used as anti epileptic drug in various types of epilepsy as it has got similar efficacy of phenytoin.

Even after patient admitted because of various etiologies including meningitis, encephalitis, intracranial granulomas and tumors, seizure disorder and genetic disorders, phenytoin and valproate showed similar efficacies. In our study, infection, which includes meningitis, encephalitis, contributed majority of the seizures (32%), which was followed by seizure disorder (30%) and intracranial granulomas (23%) like neurocystisercosis, tuberculuma and cerebral palsy.

ADEM, genetic disorders contributed rest. Agarwal *et al*. [16] stated that infection including CNS infections and neuro cysticercoids is major etiology which causes status epilepticus in Indian scenario. But in western countries non compliance to the AED or under dosage of AED contribute majority of cases which was followed by neurocystisercoids. In our study valproate controlled all of the patients with convulsion in infection and seizure disorder. In subjects who received phenytoin controlled only 90% of patients with infection and 78% of patients with seizure disorder, and rest of patient received valproate to control seizures. But this is non-significant (χ^2- 0.526 for infection and 0.235 for seizure disorder). Further studies with larger group are required to demonstrate any statistical significance.

In our study, seizures were most commonly associated with fever. Fever with convulsion is major presentation of intracranial infections. Also fever lowers seizure threshold of patient, and thus seizure get easily triggered in a patient with seizure disorder when they are having fever. Fever associated with one third of our subjects. It doesn't have significant difference in efficacy of phenytoin and valproate (χ^2-0.421). Developmental delay, dystonia, hypoglycemia, hydrocephalous were also associated with our patients. There is no statistical significance of efficacy of phenytoin and valproate in above mentioned associated illness.

Two of the patients were expired even after getting multiple AED through intravenously. One of them received phenytoin after benzodiazepines and other one received valproate after benzodiazepines. As seizures were not getting controlled both of the patients received either group of drug, and thus both patient received phenytoin and valproate. Later they received higher groups of drugs, and then required ventilator support and vasopressors. Due to limited resources, radio imaging couldn't be done. Both of the patients were having multiple metabolic derangements and corrective measures had been taken. But patients didn't respond to any of the measures and expired. Unfortunately, etiologies are unknown because of various constraints. Even in developed countries various case of seizure remains as unknown/ idiopathic, after the battery of investigation [19, 20]. But still we must take adequate measures to identify the etiology, if similar case happens, with necessary investigations.

In our study, two of the patient who received phenytoin developed thrombophlebitis but those who received valproate didn't develop any side effects. One patient, received phenytoin, developed ataxia. There was mild elevation of SGPT in patients who were receiving long term AED, more in valproate. Agarwal *et al*. [16] also reported mild elevation in SGPT in valproate receiver. They also reported higher incidence of serious side effects like respiratory distress, hypotension with phenytoin which is not detected in our study. Misra *et al*. [13] had demonstrated liver dysfunction and respiratory depression, electrolyte and blood glucose disturbances with valproate. Turnbull *et al.* [12] demonstrated that there is no difference in hematological and biochemical parameters between patient receiving phenytoin and valproate. We need further studies to confirm whether these metabolic derangements are due to drug or due to the brain damage caused by the seizure or any other cryptogenic cause which can attributable as a cause of seizure in future. Callaghan *et al.* [21] noticed various adverse effects with anti epileptic drugs. In their study valproate caused weight gain, drowsiness, aggressive behavior weight gain. They noticed rash, gum hypertrophy and ataxia in patients who receiving phenytoin. De Silva *et al*. [11] demonstrated higher incidence of adverse effects, in newly onset childhood seizures, in phenytoin comparing to valproate, and because of that, they had to withdraw the phenytoin in few patients and switched to another AED. Callaghan *et al.* [21] were changed AED including valproate, phenytoin, carbamazepine, if there was undesirable reaction was present. In our study no patient was switched over. Ataxia was controlled spontaneously. Shakir *et al*. [18] couldn't demonstrate any adverse effects in both phenytoin and valproate. This may be due small study population.

In our study, outcome of both group i.e. phenytoin and valproate is comparable (χ^2 - 0.754). Tudur smith *et al.* [17] has similar result. They didn't found any significant difference in outcome between phenytoin and valproate. Also they didn't found any supportive evidence for use of valproate for generalized tonic clonic seizure and phenytoin for focal seizure. But in our study it has been seen that phenytoin controlled almost all the focal seizure in its group, but valproate control only 75% of focal seizure without secondary generalization in its group(χ^2 0.667). It may be due low sample size (n=4) in valproate group. On contrary to our study Misra *et al*.[13] demonstrated that valproate is better than phenytoin in controlling seizure in status epilepticus in a small randomized control trial. Gilad *et al*. [15], Agarwal *et al*.[16] reported that valproate and phenytoin have equal efficacy in controlling seizures in status epilepticus in single centre randomized trial. Callaghan *et al*. [21], Malik *et al*. [22] concluded that both valproate and phenytoin are equally efficacious in controlling seizure in children. Callaghan *et al.* [21] demonstrated this in various childhood seizures while Malik *et al*. [22] demonstrated in status epilepticus. Alvarez [14] reported that phenytoin and valproate is equally efficacious as second line drug in controlling seizures. Cochrane database review by Tudur smith [17] concluded that there is no significant difference between efficacy of phenytoin and valproate. Finally Cochrane database review by Nolan *et al.* [23] in 2013 also reported the same result.

CONCLUSION

In conclusion, from our study we have tried to find out the efficacy of valproate and phenytoin in controlling seizure. In cases of status epilepticus and focal seizure with or without secondary generalization phenytoin is controlling more number of seizure than valproate. On the contrary, valproate controlled more number of generalized seizures than phenytoin. But there is no significant statistical difference between the two. Further studies in a larger population have to be done to identify its statistical significance.

LIMITATION

Our study was a single centre small group randomized trial. As groups were small it is recommended to repeat the study in a multicentre larger group trial for long term. In our study, follow up of the patient wasn't accounted as our subjects were assessed only during hospital stay. Our study was done in a year span, so number of patient was limited. Because of financial constraints, there was limitation in doing various investigations including radio imaging. As there was no bedside EEG monitoring available, seizure control was determined by clinically as physical termination of seizure. Blood level of AED couldn't be assessed because of lack of facility for the same and also for financial constraints. In our study we could not assess the efficacy of drug in other types of seizures like absence seizure and myoclonic seizures.

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