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Research Article

Comparative study of efficacy and safety of intravenous sodium valproate with intravenous phenytoin sodium in the treatment of status epilepticus in children

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ABSTRACT

Background: Status Epilepticus (SE) is a common paediatric neurological emergency that requires immediate and aggressive management. The standard treatment of status epilepticus includes use of diazepam, midazolam, phenytoin sodium/phenobarbitone, diazepam infusion in sequential order. Unfortunately the current therapies mentioned above have considerable adverse effects. There was a continued search for alternative drug. We found out that intravenous (IV) sodium valproate is safe and effective in controlling paediatric SE. Objective: Compare efficacy and safety of intravenous sodium valproate with intravenous phenytoin sodium in the treatment of status epilepticus in children.
Methods: This prospective comparative study was done over a period of two years. Children admitted to paediatric intensive care unit who satisfy inclusion criteria were included in the study. Thirty two subjects were enrolled. The subjects were randomized. 17 patients in VPA group received intravenous (IV) valproate in dose of 30 mg/kg as loading dose followed by additional 10 mg/kg if not controlled and fifteen patients in PHT group received intravenous (IV) phenytoin in the doses of 20 mg/kg and an additional 10 mg/kg if not controlled. Children were clinically monitored for adverse events. Treatment was considered successful if seizures were controlled within 20 minutes.
Results: IV valproate was successful in 82.4% and IV phenytoin in 80% with P>0.05. In a cross over, out of 3 uncontrolled patients in PHT group, none of the children got controlled with VPA as 2nd choice. However in VPA group, out of 3 uncontrolled patients, one got controlled with phenytoin as 2nd choice. Recurrence was 2.5 times more with phenytoin (3/7) than valproate (2/7) with P=0.209.
Conclusions: It was observed that intravenous sodium valproate is as effective as intravenous phenytoin in treatment of paediatric status epilepticus. The drug was tolerated well with no clinically observed adverse effects.

Keywords: Status epilepticus, IV valproate, IV phenytoin

INTRODUCTION

Status Epilepticus (SE) is a common paediatric neurological emergency that requires immediate and aggressive management. If not managed promptly, it may result in significant neuromorbidity and mortality.[1] Approximately 10-25% of children with epilepsy have at least one episode of status epilepticus during the course of their disease.[2] SE is present nearly in all epileptic syndromes, even idiopathic ones, although it is more frequent in cryptogenic and symptomatic forms.[3]

Standard treatment of status epilepticus includes use of diazepam, midazolam, phenytoin sodium/phenobarbitone,

diazepam infusion in sequential order. Unfortunately the current therapies mentioned above have considerable adverse effects. Hence there is continued search for newer effective and safe drugs. Intravenous sodium valproate is a newer alternative in treating status epilepticus. Starting in the 1980s, the use of intravenous valproate has been reported in an increasing number of uncontrolled case series, indicating relative ease of use, relatively good tolerability and suggesting that it may be efficacious.[4] Few studies have tried sodium valproate in adult patients with status epilepticus and found it useful. The safety and tolerability of intravenous sodium valproate in adults are established by Devinsky et al.[5]

However studies in paediatric patients are sparse. Hence the present study was taken up to evaluate the efficacy and safety of intravenous sodium valproate in comparison with intravenous Phenytoin sodium in treating children with status epilepticus.

METHODS

This prospective comparative study was done at a tertiary care centre over a period of 2 years. Status epilepticus was defined as a single seizure or recurrent seizures lasting for more than 30 minutes during which consciousness is not regained.[6] Children aged between 3 years and 17 years with status epilepticus were included. Children with following criteria were excluded from the study: 1) Patients who had received intravenous phenytoin sodium or sodium valproate just prior to admission to control the seizure activity, 2) Pre-existing hepatic disease or significant hepatic impairment, 3) Children with cardiac complications like hypotension, cardiac arrhythmia, 4) Presence of metabolic derangements like hypoglycaemia, hypocalcaemia, hyponatremia or hypernatremia. 5) Hypersensitivity to either of the drug.

Children admitted to paediatric intensive care unit of the hospital who satisfied inclusion criteria were included in the study after obtaining informed consent from the parents. The subjects were randomly divided into Sodium valproate (VPA) and phenytoin (PHT) groups using standard random table. The relevant information like age, sex, past medical history, drug allergies, treatment with antiepileptic drugs, duration of current seizure activity and use of anticonvulsants prior to arrival was documented for all subjects at admission. Patients in VPA group received intravenous (IV) sodium valproate in dose of 30 mg/kg (Misra et al.[7]) as bolus over 6 minutes (5 mg/kg/min) followed by additional 10 mg/kg if not controlled and Patients in PHT group received intravenous (IV) Phenytoin in the dose of 20 mg/kg after dilution with normal saline over 20 minutes (max. rate of 50 mg/min) followed by additional 10mg/kg if not controlled. All other necessary treatment including fluids, electrolytes, calories, antipyretics for fever and antibiotics for infection was provided as required. Monitoring: Continuous heart rate, blood pressure, respiration and adverse effects were monitored. Drugs were given under supervision and continuous cardiac monitoring. Once seizures are controlled, the maintenance dosage of the respective drug was started and continued. Laboratory evaluation: 1) Metabolic work up which includes random blood sugar, serum calcium and serum electrolytes done to rule out metabolic causes of SE. 2) Liver function tests were done prior to initiation of sodium valproate therapy. 3) Platelet counts and coagulation tests were done before initiation of therapy. 4) CT scan brain, EEG and CSF analysis was done for some patients to determine the etiology. Status epilepticus was considered to end at the time when convulsive seizure ceased and the patient subsequently regained consciousness after sometime. Status epilepticus was considered on-going when seizures were clinically evident or when the patient remained unconscious and subsequently had a convulsive seizure requiring treatment with an antiepileptic drug. We changed the therapy if life-threatening seizures were continued as per the standard protocol used in management of status epilepticus. All patients were followed for next 24 hours for seizure outcome and adverse events. Treatment was considered successful when all motor events ceased within 20 minutes after the beginning of the drug infusion. A cross over was done to other group if seizures were not controlled after 2nd loading dose.

Statistical Methods:[8-10] Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). 90% Confidence Interval has been computed. Chi-square test and Fisher Exact test has been used to find the significance of study characteristics/outcome between two groups.

RESULTS

Totally 1882 children were admitted to paediatric intensive care unit of the hospital during the study period. Total patients with status epilepticus who were assessed for eligibility were 44, out of which 12 were excluded, 8 of them did not meet the inclusion criteria, 2 patients refused to participate and 2 patients in VPA group had already received anticonvulsant prior to arrival. 32 children were finally available for the analysis, 17 (53.2%) children received Sodium valproate and 15 (46.8%) received phenytoin randomly.

The mean age of presentation was 5.83 ± 2.96 years (Figure 1). The study characteristics were comparable between two groups and are statistically similar between both the groups (Table 1). The most common cause of SE in this study was cryptogenic (37.5%) who presented with generalized seizures and subsequent investigations were normal except for abnormal EEG in few patients. This was followed by febrile status (9.4%), neurocysticercosis (9.4%) and viral encephalitis (9.4%) (Table 2). In PHT group out of 15 subjects, 12 (80%)

were controlled and 3 (20%) were not controlled (Treatment failure). In VPA group out of 17 subjects, 14 (82.4%) were controlled and 3 (17.6%) were not controlled (Table 3). Out of the controlled subjects (26), 2 (16.7%) of them in PHT group and 3 (21.4%) in VPA group required 2nd dose. Outcome is statistically comparable in both the groups with P=1.000 (Table 4). A crossover was done as seizures were not controlled within 20 minutes. All 3 uncontrolled valproate patients received phenytoin, out of which 2 were not controlled and 1 was controlled with phenytoin as 2nd choice. In phenytoin group 3 uncontrolled patients received valproate, out of which none got controlled with valproate as 2nd choice. Recurrences are 2.5 times more likely in PHT group when compared to VPA group with P=0.209 (Table 5).

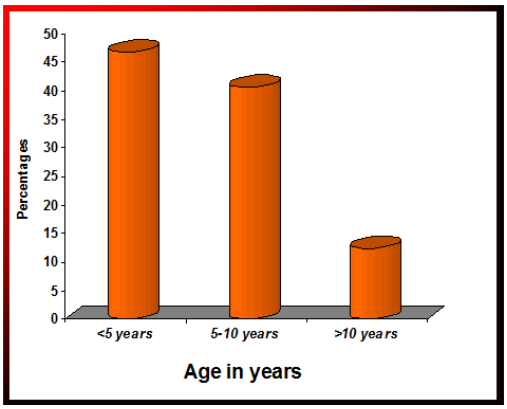

Figure 1: Age wise distribution of patients studied.

Table 1: Comparison of study characteristics.

Study characteristics	PHT (n=15)	VPA (n=17)	P value
Age in years; Mean ± SD	6.20 ± 3.34	5.50 ± 2.65	0.514
Male; No (%)	6 (40.0%)	12 (70.6%)	0.153
Female; No (%)	9 (60.0%)	5 (29.4%)	0.153
Treatment history; No (%)	1 (6.7%)	1 (5.9%)	1.000
GRBS mg/dl; Mean ± SD	120.60 ± 18.03	118.06 ± 13.46	0.652
Na; Mean ± SD	132.47 ± 7.65	136.88 ± 7.49	0.110
K; Mean ± SD	4.34 ± 0.76	4.18 ± 0.49	0.470
Ca; Mean ±SD	8.43 ± 0.59	8.39 ± 0.36	0.824
SGOT; Mean ± SD	35.58 ± 10.21	59.29 ± 90.86	0.379
SGPT; Mean ± SD	37.67 ± 11.29	37.06 ± 16.49	0.913
Platelet counts, Mean ± SD	3.13 ± 0.74	3.34 ± 1.59	0.639
ABG (Acidosis); No (%)	3 (20.0%)	1 (5.9%)	0.319

Table 2: Etiology of status epilepticus.

Diagnosis	Number (n=32)	%
Cryptogenic	12	37.5
Febrile status	3	9.4
Neurocysticercosis	3	9.4
Acute encephalitis	3	9.4
Hypertensive encephalopathy	2	6.3
Down's with CAD	1	3.1
Fever triggered seizure	1	3.1
NDD	1	3.1
Porencephalic cyst	1	3.1
Post-traumatic	1	3.1
Seizures sec to infarct	1	3.1
Spastic CP	1	3.1
TBM	1	3.1
WAS	1	3.1

CAD: Congenital atlanto-axial dislocation, TBM: Tubercular meningitis, WAS: Wiskott Aldrich syndrome, NDD: Neurodegenerative disorder, CP: Cerebral Palsy

Table 3: Response to therapy.

Outcome	PHT (n=15)	VPA (n=17)	Total (n=32)
Not controlled	3 (20.0%)	3 (17.6%)	6 (18.8%)
Controlled	12 (80.0%)	14 (82.4%)	26 (81.3%)

Inference: Outcome is statistically comparable in both the groups with P=1.000

Table 4: Dose response.

Dose	PHT (n=12)	VPA (n=14)	Total (n=26)
Single dose	10 (83.3%)	11 (78.6%)	21 (80.8%)
Double dose	2 (16.7%)	3 (21.4%)	5 (19.2%)

Inference: Outcome is statistically comparable in both the groups with P=1.000

Table 5: Recurrence.

Recurrence	PHT (n=15)	VPA (n=17)	Total (n=32)	90% CI
No	10 (66.6%)	15 (88.2%)	25 (78.1%)	64.2-87.7
Yes	5 (33.3%)	2 (11.8%)	7 (21.9%)	12.3-35.8
<24 hours	3 (20.0%)	2 (11.8%)	5 (15.6%)	7.8-28.8
>24 hours	2 (13.3%)	-	2 (6.3%)	2.1-17.2

Inference: Recurrences are 2.5 times more likely in PHT group when compared to VPA group with P=0.209

DISCUSSION

During the study period 44 children presented with SE which constituted 25 per 1000 of total ICU admissions. A 10-year retrospective study of all patients developing seizures in Mayo clinic ICU reported 7 per 1000 ICU admissions.[11] Another 2-year prospective study of medical ICU patients noted 35 with seizures per 1000 admissions.[11]

In the present study most of the children were of younger age group with mean age of presentation was 5.83 ± 2.96 yrs. In our study 46.9 % of children were less than 5 yrs. This was comparable to a study by Shinnar et al.[12] with more than 40% paediatric SE in children <2 years of age. Reported age-specific incidences for SE are 0.051% for children <1 year of age, 0.029% for those 1-4 years old, 0.009% for those 5-9 years old, and 0.002% for those 10-15 year old.[13]

In the present study, status epilepticus was interrupted successfully in 82.4% (14/17) of valproate group. It was better than results of other studies (Table 6).

Table 6: Efficacy of sodium valproate in various studies.

Study	Loading dose VPA	Efficacy VPA
Misra et al.[7]	30 mg/kg	66% as 1st choice 79% as 2nd choice
Limdi et al.[15]	31.5 mg/kg	63.3% in SE
Uberall et al.[6]	20 to 40 mg/kg	78% for RSE
Kian-Ti Yu et al.[1]	25 mg/kg	100% for SE, 95% for acute repetitive seizures
Our study	30 mg/kg	82.4% in SE as 1st choice

In a study by P. Agarwal et al.[14] conducted at GSVM medical college, Kanpur on children and adults compared IV valproate with IV phenytoin and reported an efficacy of 88% (44/50) with valproate and 84% (42/50) with phenytoin. Efficacy of phenytoin in our study is in agreement with these results. Misra et al.[7] compared sodium valproate with phenytoin sodium in treating status epilepticus and found that intravenous sodium valproate is more effective than intravenous phenytoin sodium in controlling convulsive status epilepticus both as first (66% vs. 42%) and as a second choice (79% vs. 25%). Here dosage used was 30 mg/kg. In another study, Limdi et al.,[15] concluded efficacy of rapid administration of valproic acid for status epilepticus and reported an overall efficacy of 63.3% with favourable tolerance of rapid administration of intravenous sodium valproate.

In a study by Kian-T-Yu et al.[1] in Paediatric SE & acute repetitive seizures showed efficacy of 100%. Dose: 25 mg/kg @ 3 mg/kg/min & seizures were controlled within 20 minutes. Uberall et al.,[16] in their study on children with refractory status epilepticus concluded that intravenous sodium valproate is effective in treatment of paediatric refractory status epilepticus. They have reported an effective control in 78% of children with refractory status epilepticus. Here valproate was used after diazepam, phenytoin/phenobarbitone has failed with effective dose of 20-40 mg/kg.

The significantly better response to intravenous sodium valproate with favourable tolerability has been observed in our study compared to other studies. In this study, out of controlled group (26), 2 of them required 2nd dose in phenytoin group and 3 (21.4%) in valproate group. This was comparable to study by Uberall et al.,[16] Out of 41 children, 27 children (65.9%) responded immediately after initial VPA bolus, 4 (9.8%) with 2nd bolus. Children who required 2nd bolus in our study were those who presented with prolonged duration with acute symptomatic etiology (viral encephalitis). Out of 32 subjects, 6 (18.8%) were not controlled in total (3 in each group) which is considered as treatment failure. A crossover was done to other drug. Here only one patient was controlled with PHT as 2nd choice. None of them got controlled with valproate as 2nd choice unlike in a study conducted by Misra et al.,[7] VPA was more effective than PHT in controlling SE as 2nd choice (79% vs. 25%). It was observed there was better response to phenytoin than valproate as a 2nd choice. However the etiology in these patients were acute symptomatic GCSE like viral encephalitis and hypertensive encephalopathy where repeated convulsions were known to occur. There was no significant difference in response to SE after switching over to other drug in either of the group. 5 out of 32 subjects were refractory to both the drugs suggesting some common mechanism of antiepileptic drug activity

of both the drugs. In 5 patients (33.3%) of PHT group and 2 patients (11.8%) of VPA group had recurrence in less than 24 hours after successful ending of 1st episode of SE. 2 patients (13.3%) of phenytoin group had recurrence in more than 24 hours. Recurrence is 2.5 times more likely in phenytoin group than valproate group (P=0.209). Here it was observed that recurrence was seen in cases of symptomatic CSE like viral encephalitis, hypertensive encephalopathy where the pathologic process within the brain was responsible for the recurrence. This was similar to comparative study of intravenous sodium valproate and phenytoin done by P Agarwal et al.[14] where 6 patients (6/50) in valproate group and 8 patients in phenytoin group (8/50) had recurrence. IV valproate was well tolerated at infusion rate of 5 mg/kg/min. There was no evidence of any valproate related systemic side effects like cardiac conductance disturbances, hypotension pulmonary insufficiency and local effects. This is similar to previous studies. Limdi and Faught[15] described the safety of rapid infusion of valproic acid in doses ranging from 33.3 to 555 mg/min (median, 200 mg/min) without serious adverse effects. Venkataraman and Wheless[17] have also shown the safety of rapid loading doses of iv valproate (mean dose 24.2 mg/kg and target infusion rates 3 or 6 mg/kg/min). Wheless et al.,[18] in 2004 demonstrated that IV VPA administered to patients with epilepsy at rates of infusion of up to 6 mg/kg/min and doses of up to 30 mg/kg does not cause clinically significant negative effects on blood pressure and pulse rate and caused only mild to moderate reversible adverse events. This suggests valproate can be used safely in children with status epilepticus.

SE was controlled in 81.3% (26/32) patients in total. Overall mortality is noted in 6.3% (2/32) one in each group. Mortality, directly attributable to symptomatic CSE which includes viral encephalitis and chronic renal failure with hypertensive encephalopathy. Here the cause of death could be disease process itself and SE cannot be considered as a single most etiological factor for the mortality. The mortality is statistically similar between both the groups (P=1.000). This is comparable to studies which have reported overall mortality of 3%-7%,[13] but varies greatly according to the etiology of the SE. Reported mortality with cryptogenic or febrile SE is 0%-2%.[19] Conversely, among children with acute symptomatic etiologies, mortality increases to 12.5%-16%.[19] Anoxia and acute bacterial meningitis carry particularly high risks of mortality.[19] Similarly, the risk of mortality is higher for younger children, ranging 3%-22.5% for those <2 years of age.[19] This suggests improvement from previous studies reflecting improved care of patients.

CONCLUSION

Intravenous sodium valproate was found to be as effective as intravenous phenytoin in the treatment of children with status epilepticus. The drug was tolerated well with no observed adverse events, Hence it can be used safely as an alternative drug to phenytoin in patients with cardio-respiratory disease. The recurrence of the seizures after control of first episode with phenytoin was 2.5 times more than valproate.

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