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A COMPARATIVE STUDY BETWEEN INTRAVENOUS SODIUM VALPROATE AND PHENYTOIN SODIUM AS SECOND-LINE TREATMENT OF STATUS EPILEPTICUS IN CHILDREN

Paediatrics

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ABSTRACT

Objectives- To demonstrate the efficacy of intravenous (IV) valproate as the second-line therapy for controlling seizures in patients of Status Epilepticus (SE) and to compare it with IV phenytoin.

Material And Methods- Children aged 2 yrs–12 yrs, admitted in Pediatric emergency ward and PICU with status epilepticus were included in the study. This was a hospital based randomized control clinical study.

Results- Total 60 children aged 2-12 yr were included in the study. In the group that received IV valproate, 100% seizure was controlled in children presented within 2 hrs, whereas in the group that received IV phenytoin 70.83% of patients presenting within 2 hrs had seizure controlled. (p value 0.008)

Conclusion- Sodium valproate was found better in comparison to phenytoin in controlling SE with seizure duration <2hrs and in reducing recurrence of seizure within 12 hours.

KEYWORDS

Status epilepticus, Children, Valproate, Phenytoin

INTRODUCTION

Status epilepticus (SE) is a medical emergency that should be anticipated in any patient who presents with an acute seizure. It is defined as continuous seizure activity or recurrent seizure activity without regaining of consciousness lasting for more than 5 minutes[1].

The most common type is convulsive status epilepticus (generalized tonic, clonic, or tonic-clonic). Approximately 10-25% of children with epilepsy have at least one episode of status epilepticus (SE) during the course of their disease[2,3,4].

Traditionally, based on a long clinical experience, and case controlled studies, intravenous (IV) phenytoin has been used as the second drug. 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[5]. It may be used as the second-line anti-epileptic drug (AED) in SE with a good seizure control[6]. But there is no randomized comparative study to the best of our knowledge till now.

Hence, we planned a randomized study to demonstrate the efficacy of IV Valproate as the second line therapy for controlling seizures in patients of SE refractory to diazepam, and to compare it with IV phenytoin. This study aims to investigate the efficacy of both medications in the treatment of SE as the second-line AED.

MATERIAL AND METHODS

The study was conducted in the Pediatric Medicine Department of a rural tertiary care hospital in West Bengal. The duration of the study was one year from March 2014 to February 2015. Children of two to 12 years age group, who were admitted in Pediatric emergency ward and Pediatric Intensive Care Unit (PICU) with status epilepticus, were included in the study. Those with a definite history of any allergic reaction to IV phenytoin or IV valproate, or any contraindications in giving these drugs were excluded from the study. All patients received IV diazepam or lorazepam as a first line medication before starting other AED.

This was a hospital based randomized control study (single blinded study). The children were randomized into two groups. One group received Intravenous (IV) valproate (20 mg/kg as loading dose at rate of 40 mg/min after dilution with normal saline) and the other IV phenytoin (20 mg/kg, max. rate of 50 mg/min after dilution with normal saline).

In our study patients of SE were defined as continuous or repeated seizure activity for more than 5 minutes without recovery of consciousness as defined in another study done by Walker MC *et al*[7].

Treatment was considered successful when all motor or electroencephalography (EEG) seizure activities ceased within 20 min after beginning of the drug infusion. The response was compared between the two groups in terms of significance using Wilcoxon rank sum or student t-test (for quantitative data) and Fisher's exact tests or Chi-square test (for qualitative data) whichever applicable. P value of <0.05 was taken as statistically significant for analysis.

RESULTS

Total 60 children aged 2-12 years were divided into 2 groups- sodium valproate group (V) and phenytoin sodium group (P). In every group there were 30 patients (Figure 1).

In V group 60% patients were male and in P group 53.3% were male. Mean age of V group of patients was 7.1 years and mean weight was 22 kg. For P group of patients mean age was 6.6 years and mean weight was 20.6 kg. In both patient groups(V and P) most common cause of SE was central nervous system (CNS) infection.

In V group of patients 90% seizure was controlled, but in P group of patients 70 % seizure was controlled. In the V group 100% seizure was controlled in children presented within 2 hrs, whereas in the P group 70.83% of patients presenting within 2 hrs, had seizure controlled. Here the differences between these two groups of patients (V and P) were statistically significant (p value 0.008) and it concluded that V group of patients had better seizure control if presented within 2 hrs. But in case children presented with SE of more than 2 hours, there is no statistical difference between these two groups (p value 0.889)(Table 1).

In V group of patients 76.66% patients had no recurrence of seizure in less than 12 hrs, whereas in P group of patients only 36.66% patients had no recurrence of seizure within 12 hrs. The P value was 0.002 which is statistically significant (<0.05). So, valproate is better than

phenytoin in controlling recurrence of seizure within 12 hrs (Table 2). In the V group 6.66% patients died and in P group death was 20%.

Figure 1. Showing the flow of patients

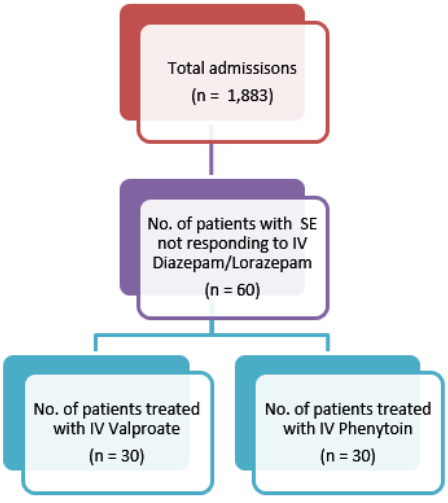

Table 1. Showing distribution of patients presenting within 2 hours and more than 2 hours and their relationship with seizure control

Group	Seizure controlled presented within <2 hr	Seizure not controlled presented within <2 hr	Seizure controlled presented > 2 hr	Seizure not controlled presented > 2 hr	Total
Sodium valproate	20 (100%)	0	7(70%)	3(30%)	30
Phenytoin sodium	17 (70.83%)	7 (29.17%)	4(66.67%)	2 (33.33%)	30
P value	0.008		0.889		
Total	37	7	11	5	60

Table 2. Showing distribution of patients and recurrence of seizure in <12 hr

Group	Seizure recurred in <12 hr	No recurrence in < 12 hr	Total	P value
Sodium valproate	7(23.33%)	23(76.66%)	30	0.002
Phenytoin sodium	19(63.33%)	11(36.66%)	30	
total	26(43.33%)	34(56.66%)	60	

DISCUSSION

Most of the patients were male in both groups. A study conducted by Agarwal P. *et al*[8] on patients of status epilepticus also showed male predominance. We used IV Valproate in doses of 20 mg/kg as loading dose, similar dosing was also used in a study done by Limdi *et al*[9]. IV Valproate was used at rate of 40 mg/min, similar dosing was used in other studies[10,11,12].

In our study the most common cause of status epilepticus was CNS infection i.e. 17 (56.67%) in both valproate and phenytoin group followed by inflammatory granuloma [in V group 5(16.67%) and in P group 4(13.33%)]. In the study by Agarwal P. *et al*[8] the most common etiology of SE was antiepileptic drug noncompliance or withdrawal in 12 (24%) patients in valproate group and 14 (28%) in phenytoin group, while the other etiologies included inflammatory granuloma [12 (24%) in valproate group and 12 (24%) in phenytoin group], CNS infections [10 (20%) in valproate group and 12 (24%) in phenytoin group].

In the present study, status epilepticus was interrupted successfully in 90% of patients in Group V and 70% of patients in Group P ($p > 0.05$). Czapinski and Terezynski[13] in 1998 reported an 80% success rate in interrupting SE in a series of 20 adult patients using IV Valproic acid in a bolus dose of 15 mg/kg followed by an infusion of 1 mg/kg/h. Peters and Pohlmann-Eden[14] have reported 85.6% success in controlling SE in a series of 102 adult patients using IV VA. Similarly in study by Tiamkao *et al*[15] status epilepticus was controlled successfully in 88% in Valproate Group and 84% in Phenytoin Group ($p > 0.05$).

In our study 33.33% of Group V and 20% of Group P were having duration of SE >2 h at the time of presentation. This delay in presentation might be attributed to the lack of awareness amongst the general public, inadequacy of medical and health services in this part of the world. The response to treatment was significantly better in patients having SE <2 hrs than SE >2 hrs in both the groups. Limdi *et al*[16] also got similar results.

In our study there was significant difference in recurrence of seizure within 12 hr between group V and group P. But in study by Agarwal P. *et al*[8] there were no significant differences between the treatments by valproate and phenytoin with respect to recurrence during the 12 h study period. The difference between our study and study by Agarwal et al could be due to the differences in the study population and etiology of SE.

In our study mortality in V and P groups were 6.66% and 20% respectively without any statistical significance. Approximately 89% of patients who died during or after status epilepticus was as a result of the etiology of the status, whereas only 2% of deaths were directly attributable to the status epilepticus itself[17]. In our study, one patient (3.33%) in group V and two patients (6.66%) in P group left against medical advice.

Limitations of our study were that the sample size was small, it was a single blinded study and facilities for video EEG monitoring, metabolic and genetic testing were not available.

CONCLUSION

Status epilepticus (SE) in children requires proper and prompt treatment to prevent morbidity and mortality. Early seizure control prevents neurological sequelae and improves outcome. Sodium valproate was found better in comparison to phenytoin in controlling SE with seizure duration <2hrs, in reducing recurrence of seizure within 12 hours and between 12 to 24 hours. It was also safer than phenytoin in terms of respiratory depression. But more studies are needed in the pediatric population to compare the efficacy of these two AEDs.

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