ORIGINAL ARTICLE

COMPARATIVE ASSESSMENT FOR THE EFFICACY OF VALPROATE AND PHENYTOIN FOR CONTROLLING SEIZURES IN PATIENTS OF CONVULSIVE STATUS EPILEPTICUS: A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT:
Purpose: the present study was conducted to compare the efficacy of valproate and phenytoin for controlling seizures in patients of convulsive status epilepticus. **Methods:** It was conducted in the Department of Pediatrics, Guru Gobind Singh Medical College and Hospital, Faridkot. All children (n=60) aged 2-14 yrs who remained refractory to infusion of lorazapam were the target population of this study and divided into two groups phenytoin (Group A)and valproate (group B). **Results:** Overall, 56.7% of the patients were male and 43.3% of the patients were females in group A and 60% of the patients were male and 40% of the patients were females in group B. Mean time to regain consciousness was found higher among group A. Statistical test applied were chi-square and student t-test. **Conclusion:** intravenous valproate was comparable to intravenous phenytoin in terms of efficacy. Time to regain consciousness and time to control seizure was significantly briefer with valproate than with phenytoin.
Keywords: Seizures, Phenytoin, Valproate

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INTRODUCTION

Status epilepticus (SE) is a commonly encountered pediatric neurological emergency. It is defined as continuous seizure activity or recurrent seizure activity without regaining consciousness lasting for more than 30 minutes. [1] It is important to start measures aimed at controlling the acute seizures if they do not stop within a few minutes. Therefore, for practical reasons, this definition has been recently modified by the Epilepsy Foundation of America's Working Group on Status Epilepticus: particularly for generalized seizures. Any seizure activity persisting for more than 5 minutes is considered to be SE and has to be treated accordingly.[2,3]

Status epilepticus has an incidence of about 20/100,000 for the Caucasian population in industrialized countries. [4] It has a bimodal distribution, with the highest incidence during the first year of life and after the age of sixty. Thus, among children, infants (< 1 year of age) have the highest incidence of SE.[5]Though there is no epidemiological data for India, but SE is estimated to be more common here. It also poses a more serious problem in India because of a higher frequency of CNS and systemic infections, infestations, stroke, malnutrition, injury, treatment

gap and poor compliance to antiepileptic drugs (AEDs). [6]

It is associated with high morbidity and mortality. Most of the mortality is secondary to the underlying etiology rather than to the seizures. The main predictors of outcome are age at presentation, duration of status, etiology and severity of the underlying disease. The risk of complications increases substantially with duration (>60 minutes).There may be acidemia, hypoglycemia or hypotension in the short term and mental, cognitive and movement disorders or new neurological deficits in the long term. The sooner and quicker the treatment begins, the better is the prognosis and lesser are the complications viz. metabolic acidosis, respiratory arrest, aspiration pneumonia, neurogenic pulmonary edema.[7] The reported overall mortality is about 22.1 % in adults and 3 to 7 % in children. However, mortality in cases with symptomatic SE is higher and in children it is 20%. Neurological sequelae - motor or cognitive deficits - have been found in 9 to 28% and subsequent epilepsy in 23 to 30% of children.[8]

Various studies have been done comparing phenytoin and Valproate as second line agents for control of SE in adults. However, there are few such studies in children. Hence, this study was planned to compare the efficacy of valproate and phenytoin for controlling seizures in patients of convulsive status epilepticus.

MATERIALS AND METHOD

The present study titled "Comparative Efficacy of Intravenous Valproate and Phenytoin as a Second Line Therapy in Convulsive Status Epilepticus in Children" was conducted in the Department of Pediatrics, Guru Gobind Singh Medical College and Hospital, Faridkot. All children aged 2-14 yrs presenting with status epilepticus were administered two doses of intravenous lorazepam at interval of 5 minutes. Those patients who remained refractory to this treatment were the target population of this study.

Study Population: A total of 60 such patients were studied. For calculating the required minimal sample size, we had considered the 88% success rate of Valproate.[45]To provide the results within 15 percent allowable error and 90 percent confidence limits, the minimum sample size required was calculated to be 23 patients per group. So we took 30 patients in each group.

Group A: 30 patients were given intravenous valproate in doses of 30 mg/kg as loading dose diluted 1:1 with normal saline at the rate of 6mg/kg/min.[9]

Group B: 30 patients were given intravenous phenytoin in doses of 20 mg/kg as loading dose diluted 1:1 with normal saline at the rate of 1mg/kg/min.[9]

Informed written consent was taken from the parents / accepted legal guardian of the patients. There was random allocation of the study drugs among the patients. The randomization was achieved by computer generated random numbers.

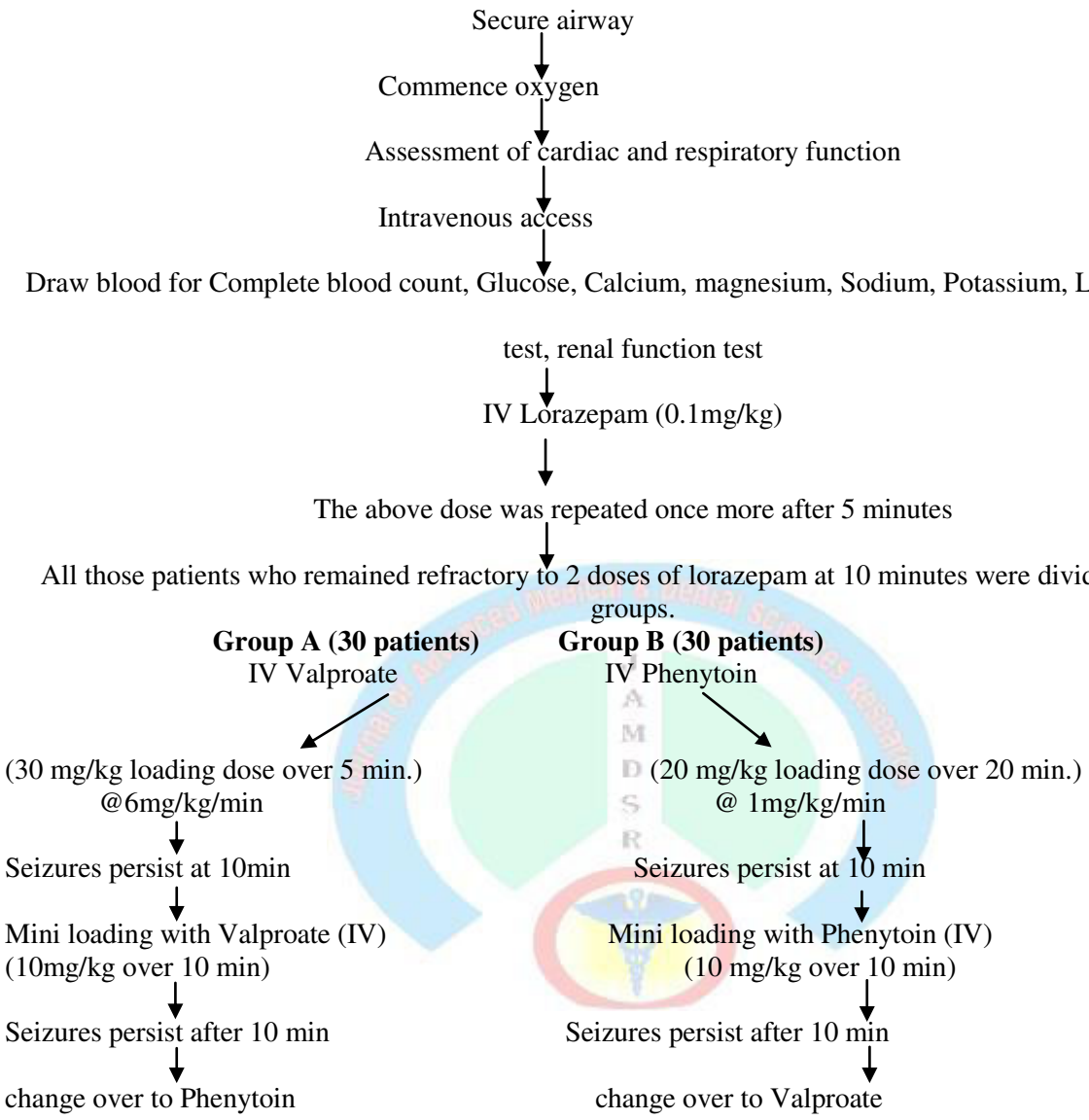
Inclusion criteria

- Patients in the group of 2 to14 years of either sex, presenting with convulsive status epilepticus (for the diagnosis of status epilepticus, any convulsive activity persisting for more than 5 minutes was taken as status epilepticus).
- Patients having withdrawal/non-compliance of anti-epileptic drug for more than 4 weeks were included.

Exclusion criteria

- Age less than 2 years.
- Patients of suspected mitochondrial disorders.
- Patients of renal failure.
- Patients of hepatic encephalopathy.
- Patients in non-convulsive status epilepticus.
- Patients in whom valproate or phenytoin was contraindicated.
- Patients with neurological emergencies requiring immediate surgical interventions (Head injury or subdural hematoma).
- Patients who had already received loading doses of phenytoin or valproate before reporting to this hospital.
- Patients having withdrawal/non-compliance of anti-epileptic drug less than 4 weeks.

The following protocol was followed in this study



Treatment was considered successful if all motor seizure activity ceased and there was no return of seizure activity in the next 12 hours. Maintenance dose of understudy drug (phenytoin or valproate) was given after 12 hours according to body weight of the patient.

Follow Up:

All the patients were followed for at least seven days or till discharge for seizure outcome, any adverse events and development of any new neurological sequel.

STATISTICAL ANALYSIS

The recorded data was compiled and entered in a spreadsheet computer program (Microsoft Excel 2010) and then exported to data editor page of SPSS version 20 (SPSS Inc., Chicago, Illinois, USA).

Descriptive statistics included computation of percentages, means and standard deviations. The statistical tests applied for the analysis were Pearson's chi-square test (χ^2) and students'ttest analysis. For all tests, confidence interval and p-value were set at 95% and ≤ 0.05 respectively.

RESULTS

Table 1 showed that out of 30 patients in group A, there were 19 patients in the age group 2 - ≤ 6 years(10 males,9 females);5 in the age group >6 -≤ 10years(3 males,2 females);and 6 in the age group >10 - ≤ 14 (4 males,2 females).Overall, 56.7% of the patients were male and 43.3% of the patients were females. **Table 2** Out of 30 patients in group B, there were 16 patients in the age group 2 - ≤ 6 years (7 males,9 females);12 in the age group >6 -≤ 10years(9 males,3 females);and 2 in the age group >10 - ≤ 14 (2 males, nil female).Overall,60% of the patients were male and 40% of the patients were females. **Table 3** shows that mean time to control seizures in valproate group was 13.93±1.67 min and in phenytoin group it was 23.46±6.43 min, p value was calculated which came out to be 0.023 which is statistically significant. **Table 4** depicted that mean time to regain consciousness in valproate group was 35.54±25.93 min and in phenytoin group it was 60.83±44.98 min, p value was 0.000 which is statistically highly significant. **Table 5:** revealed that out of 30 patients in group A 93.3% responded to IV VPA and out of 30 patients in group B 80% responded to IV PHT. The p value was calculated and found to be 0.127 which is non- significant.

Table 1: Age and Sex distribution of patients in group A

Age (in yrs)	Valproate Group		
	Male	Female	Total
2 - ≤ 6	10	9	19
	33.3%	30.0%	63.3%
>6 - ≤ 10	3	2	5
	10.0%	6.7%	16.7%
>10 - ≤ 14	4	2	6
	13.3%	6.7%	20.0%
Total	17	13	30
	56.7%	43.3%	100.0%

Table 2: Age and Sex distribution of patients in Group B

Age (in yrs)	Phenytoin Group		
	Male	Female	Total
2 - ≤6	7	9	16
	23.3%	30.0%	53.3%
>6 - ≤10	9	3	12
	30.0%	10.0%	40.0%
>10 - ≤14	2	0	2
	6.7%	.0%	6.7%
Total	18	12	30
	60.0%	40.0%	100.0%

Table 3: Mean Time to Control Seizures

Variable	Group	N	Mean	Standard Deviation	p-value
Time to control seizures(min)	A	28	13.93	1.67	0.023*
	B	24	23.46	6.43	

Test applied student t-test. * p value <0.05=significant

Table 4: Mean Time to Regain Consciousness

Variable	Group	N	Mean	Standard Deviation	p-value
Time to regain consciousness (min)	A	28	35.54	25.93	0.000*
	B	24	60.83	44.98	

Test applied student t-test. * p value <0.001= highly significant

Table 5: Comparison of Efficacy between the Groups

Variable	Group	Status Aborted (%)	p-value
Status Aborted (%)	A	93.3 (n=28/30)	0.127(NS)
	B	80 (n=24/30)	

Test applied- chi square test; NS=Non-Significant

DISCUSSION

In the present study, out of the 60 participants, 35 were males and 25 were females. In IV VPA group 17 (56.7%) were males and 13(43.3%) were females. In IV PHT group 18(60.0%) were males and 12(40.0%) were females. Thus both the groups were comparable in terms of number of males and females in each group.This was similar to a study conducted by Misra et al[6] in which number of males and females were comparable.

In the present study, the mean time to control seizures in IV VPA group was 13.93 min and in IV PHT group it was 23.46 min(p value=0.023, which was significant).However, Rai et al[10] (2011) observed the mean time to control seizure of 25.44±10.34 seconds in IV VPA group and 24.76±12.6 seconds in the IV PHT group (p=0.901, which was not significant).Our observations are similar to a study conducted by Arpita et al [11] (2014), in which time taken to abort initial seizure was significantly less (p<0.001) in IV VPA group (median 10 min IQR 5-10 min) as compared to IV PHT group (median 15 min with IQR 10-20 min).

In the present study mean time to regain consciousness in the IV VPA group was 35.54 per min and in the IV PHT group it was 60.83 min (p value = 0.015, which was significant). This is different from the observations made by Rai et al[10] in 2011. They found that in their patients who received valproate and were unconscious at presentation (n=23,46%) the mean time to regain consciousness after the drug infusion was 101.9 ±81.435 min (range,15-300 min). In those who received phenytoin were unconscious at presentation (n=22,44%) their mean time to regain consciousness after the drug infusion was 123.441±75.489 min (range 30-300 min) (p= 0.346,which is not significant).Nine patients in the valproate group and eight in the phenytoin group were not manifesting seizures at the time of their enrolment,and did not receive diazepam. The mean time to regain consciousness in those who received valproate only and phenytoin only were 58.33± 28.50 min (range 15-120 min) and 135.00 ±62.10 min (range ,60-240 min) respectively (p=0.010, which is significant). So the significantly shorter time to regain consciousness in the IV VPA group could be due to the fact that these patients did not receive DZP and hence its effect on level of consciousness was eliminated.

The difference in time to regain consciousness in our study and that of Rai et al[10]may be due to the fact that we have used IV lorazepam as the initial seizure aborting drug in place of IV DZP used by them. Lorazepam has a less sedating , longer acting anti-seizure effect as compared to DZP and therefore it is less likely to affect the sedation caused by the under trial drugs .

In present study, the percentage of patient in which status was aborted was 93.3% (28/30) in IV VPA group and 80%(24/30) in PHT group(p=0.127, which is not significant). This result is similar to the study of Misra et al[6] (2006) in which SE was aborted in 66% of patients with valproate, and in 42% of patients with phenytoin (statistically insignificant, at P > 0.05). Agarwal et al[12] (2007)in a randomized study of adults with benzodiazepine-refractory status epilepticus, reported that IV VPA

was successful in 88% of their patients, and IV PHT was successful in 84% of their patients($p>0.05$, which is not significant).

CONCLUSION

In this study, intravenous valproate was comparable to intravenous phenytoin in terms of efficacy. Time to regain consciousness and time to control seizure was significantly briefer with valproate than with phenytoin. With the proven superiority in this study of intravenous valproate vs intravenous phenytoin in terms of time to control seizure and time to regain consciousness, the inclusion of intravenous valproate can be recommended in treatment protocols for acute repetitive seizures and status epilepticus as a second line drug.

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