RESEARCH PAPER

Comparison of Phenytoin, Valproate and Levetiracetam in Pediatric Convulsive Status Epilepticus: *A Randomized Double-blind Controlled Clinical Trial*

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Objective: To compare the efficacy of phenytoin, valproate, and levetiracetam in the management of pediatric convulsive status epilepticus.

Design: Randomized double-blind controlled clinical trial.

Setting: Pediatric critical care division in a tertiary care institute from June, 2016 to December, 2018.

Participants: 110 children aged three month to 12 year with convulsive status epilepticus.

Intervention: Patients not responding to 0.1 mg/kg intravenous lorazepam were randomly assigned (1:1:1) to receive 20 mg/kg of phenytoin (*n*=35) or valproate (*n*=35) or levetiracetam (*n*=32) over 20 minutes. Patients with nonconvulsive status epilepticus, recent hemorrhage, platelet count less than 50,000 or International normalized ratio (INR) more than 2, head injury or neurosurgery in the past one-month, liver or kidney disease, suspected or known neurometabolic or mitochondrial disorders or structural malformations, and allergy to study drugs; and those who were already on any one of the study drugs for more than one month or had received one of the study drugs for current episode, were excluded.

Outcome measure: The primary outcome was the proportion of patients that achieved control of convulsive status epilepticus at the end of 15 minutes after completion of the study drug infusion. Secondary outcomes were time to control of seizure, rate of adverse events, and the requirement of additional drugs to control seizure, length of ventilation, hospital stay, and functional status after three months (Glasgow Outcome Scale).

Results: The study was stopped after the planned mid-interim analysis for futility. Intention to treat analysis was done. There was no difference in primary outcome in phenytoin (31/35, 89%), valproate (29/35, 83%), and levetiracetam (30/32, 94%) (*P*=0.38) groups. There were no differences between the groups for secondary outcomes. One patient in the phenytoin group had a fluid-responsive shock, and one patient in the valproate group died due to encephalopathy and refractory shock.

Conclusions: Phenytoin, valproate, and levetiracetam were equally effective in controlling pediatric convulsive status epilepticus.

Keywords: *Anti-epileptic drugs, Management, Outcome Seizure*.

Trial Registration: CTRI/2016/05/006908.

Convulsive status epilepticus (CSE) is the most common time-bound pediatric neurological emergency worldwide, where delayed control is associated with neurological sequelae and risk of mortality [1]. Half of the children in an Indian emergency department had convulsive status epilepticus at their first presentation without having any history of prior seizure [2]. The available evidence supports that benzodiazepines should be the drugs of first choice for CSE [3]. Subsequently, intravenous phenytoin/ fosphenytoin remains the most used antiepileptic drug. The other reasonable options are valproate, levetiracetam and phenobarbital. There is insufficient evidence to support the use of one particular drug over the others [1,4,5]. Thus, we compared the efficacy of phenytoin, valproate, and levetiracetam in pediatric convulsive status epilepticus. We hypothesized that levetiracetam would be associated with better control of seizures as compared to phenytoin and valproate in pediatric convulsive status epilepticus.

Accompanying Editorial: Pages 211-212.

METHODS

This randomized, double blinded-controlled clinical trial was conducted in the Division of pediatric critical care of a tertiary-care academic institution between June, 2016 to

December, 2018. The institutional ethics committee approved the study and written informed consent was obtained from parents/legal guardians. Children aged 3 month to 12 years with convulsive status epilepticus (clonic, tonic, tonic-clonic, and myoclonic, focal or generalized) were enrolled. Children with either of the following conditions were excluded (*i*) non-convulsive status epilepticus, (*ii*) active or recent hemorrhage (less than one week) from any site, (*iii*) documented platelet count less than 50,000, or international normalized ratio more than two, (*iv*) head injury or neurosurgery in the past one month, (*v*) acute or chronic liver or kidney disease, (*vi*) suspected or known neurometabolic or mitochondrial disorders or structural malformations, (*vii*) known or suspected allergy to any of the study drugs, (*viii*) patient with epilepsy already on levetiracetam (more than 20 mg per kg per day) or valproate (more than 20 mg per kg per day) or phenytoin (more than 5 mg per kg per day) for more than one month, and (*ix*) patients who have received the appropriate dose of study drug(s) for the current episode of convulsive status epilepticus. Convulsive status epilepticus was defined as continuous seizure activity or recurrent seizure activity without regaining consciousness, lasting more than five minutes [6,7]. Status epilepticus and its etiology were classified as per International League Against Epilepsy guidelines [6].

A computer-generated and unstratified block randomization with variable block sizes of three, six, and nine were used. A person not involved in the study performed the random number allocation. Individual assignments were placed in sequentially numbered opaque sealed envelopes (SNOSE) with a three-component alphanumerical code. The envelope contained an instruction slip about the preparation of the study drug. Nursing personnel, who was not part of the research team, opened the envelope and prepared the study drug concentration of 5 mg/mL in 0.9% normal saline dilution in the syringe. Each syringe was labeled with the same alphanumerical code, and study drug dose (4 mL per kg over 20 minute). The person who prepared the study drug was blinded to the patient's identity. Injection phenytoin sodium (Ciroton, 2 mL per 100 mg, Ciron Pharmaceuticals, India), injection sodium valproate (Valprol, 5 mL per 500 mg, Intas Pharmaceuticals, India) and injection levetiracetam (Levesam, 5 mL per 500 mg, Abbott Ind. Ltd, India) were used in this study. The Institute's central pharmacy supplied the study drugs. The participants, treating doctors and nurses administering the drugs, as well as the investigators and research personnel, were unaware of the treatment assignments until control of seizure. Later, the study drug was unblinded to the treating team to continue maintenance therapy. The person who collected the data and entered it into the datasheet, and the study statistician were unaware of the treatment assignments until final analyses. At the time of analysis, another person not involved in the study and SNOSE preparation decoded the treatment assignment by using the code from the online stored datasheet.

Enrolled patients were managed by stabilizing the airway, breathing and circulation, and using intravenous lorazepam 0.1 mg/kg in the pediatric emergency room. Patients not responding to intravenous lorazepam received the study drug at the dose of 20 mg kg over 20 minutes as an intravenous infusion. If convulsions were not controlled with the study drug or there was recurrence of seizure after control by study drug, additional antiepileptic drugs were administered as per the treating team's discretion. The patients were shifted to the pediatric intensive care unit or ward for further management and etiological workup, as per unit protocol. Survivors were followed for three months post-discharge. The functional status was assessed using Glasgow outcome scale score, which ranges from one to five (higher the score better the neurological function).

The primary outcome was the proportion of patients who achieved control of convulsive status epilepticus at the end of 15 minutes after completion of study drug infusion (*i.e.*, 35 minutes after starting the study drug infusion). The secondary outcomes were (*i*) time (minutes) taken to control seizure from the initiation of study drug infusion, (*ii*) proportion of patients who required additional drug to abort clinical seizures, (*iii*) rate of adverse events, (*iv*) length of mechanical ventilation if ventilated; (*v*) hospital stays including pediatric intensive care stay, (vi) in-hospital mortality, and (*vii*) functional status at three months of follow-up by Glasgow Outcome Scale.

Based on a study by Mundlamuri, *et al*. [8], control of convulsive status epilepticus by phenytoin and valproate was found to be at 68%. We, therefore, assumed that levetiracetam might increase the control rate to 88%. With a two-sided alpha of 5% and 80% power, 68 patients were needed in each group (nQuery + nTerim3.0 version software). Interim analysis was planned at the end of 50% enrollment. The trial progress was reviewed yearly by the institute's ethics and data and safety monitoring committee, including an independent statistician who was also a physician. The trial had to be stopped prematurely after the planned interim analysis contended that it was futile to continue the study further.

Statistical analyses: Data of all the patients were analyzed according to their assigned groups (Intention to treat). The normality of data was checked with the Kolmogorov-Smirnov Z test. Continuous data were compared by one-way analysis of variance (ANOVA) if normally distributed

or by Kruskal-Wallis test if non-normally distributed and proportions with Chi-square test. All tests were two-tailed, and a *P* value <0.05 was considered statistically significant. SPSS version 20.0 (IBM SPSS Statistics, Armonk, NY) and Epi Info 7 (7.0.9.7, CDC, Atlanta, GA) were used for data analysis.

RESULTS

The study flow is depicted in ***Fig.*1**. The baseline characteristics and investigations were comparable in the study groups ***(Table* I)**. The median duration of seizure, before enrollment, was 10 minutes in each group. Seven (7%) of patients received normal saline bolus and six (6%) patients received vasoactive therapy. Five patients in each group received osmotherapy for cerebral edema. Antibiotics and antivirals were given in 40 (39.2%) and 16 (16%) patients, respectively (***Table* I**). Computerized tomography was done in 55 (54%) patients, and magnetic resonance imaging was done in 41 (40%) patients. Abnormalities were found in 18 studies, with tubercular involvement in two children and multiple neurocysticercosis in one child. Control of convulsive status epilepticus was higher in the levetiracetam group (94%) as compared to the phenytoin group (89%) and valproate group (83%), though statistically no difference was found (*P*=0.38). The mean time to control of seizure was three minutes (*P*=0.42). Additional drug to control the seizure after control of seizure by study drug was higher in the phenytoin group (26%) as compared to the valproate (14%) and levetiracetam (13%) groups. Twenty-eight patients (27.5%) were shifted to the pediatric intensive care unit; mean stay was significantly lower in the phenytoin group (***Table* II**). One patient died in the valproate group due to encephalopathy and refractory shock; this death was not thought to be due to the study drug. No intervention-related serious adverse event was noted, except for one patient in the phenytoin group who had a fluid responsive shock.

DISCUSSION

The present randomized controlled study found that phenytoin, valproate, and levetiracetam are safe and equally efficacious in the management of pediatric status epilepticus. Our study findings are consistent with recent controlled studies. A study in adults [8], compared phenytoin (20 mg per kg), valproate (30 mg per kg) and levetiracetam (40 mg per kg) after 0.1 mg per kg of lorazepam found that there was no difference in the control of generalized convulsive status epilepticus (68% *vs*. 68% vs. 78%) and 6% of levetiracetam group patients had postictal psychosis. A more recent study [9] in both children and adults, comparing fosphenytoin (20 mg of phenytoin

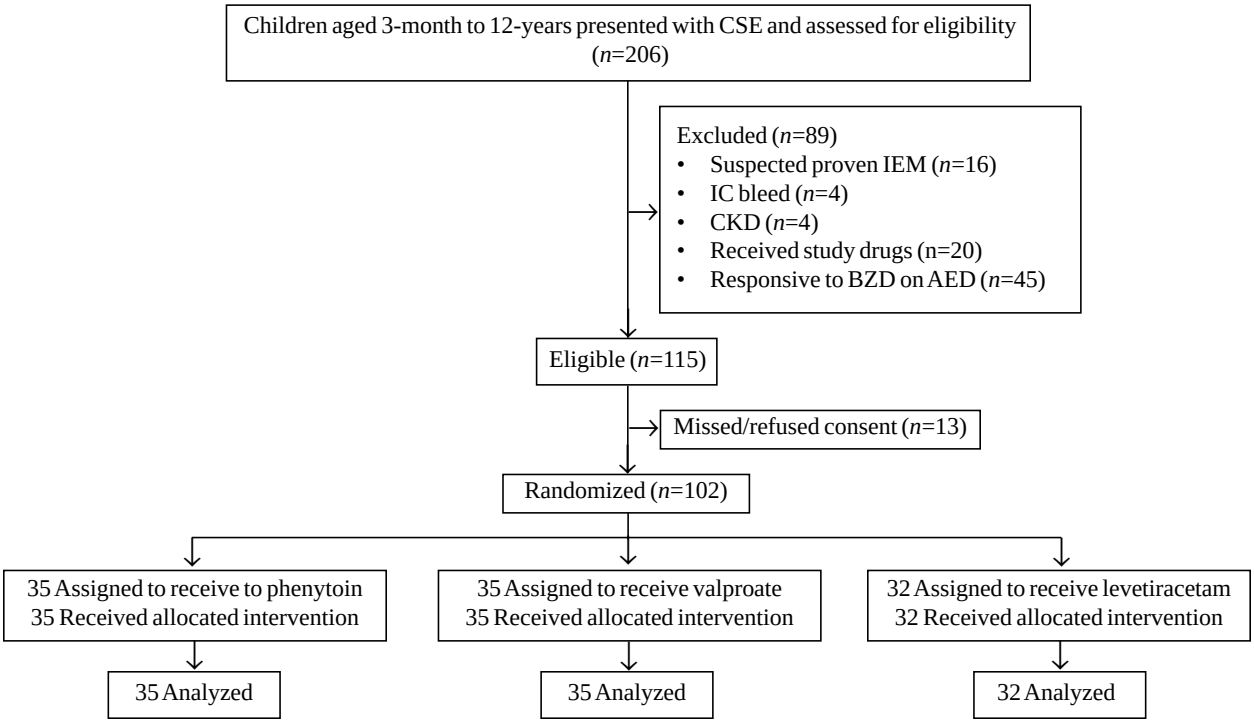

Fig. 1 *Study flow. CSE: Convulsive status epilepticus; IEM: Inborn error of metabolism; IC bleed: Intracranial bleed; CKD: Chronic kidney disease; BZD: Benzodiazepine; AED: Anti epileptic medication.*

TABLE I Baseline Characteristics of Children With Convulsive Status Epilepticus in the Three Treatment Groups

Variable	*Phenytoin group (n=35)*	*Valproate group (n=35)*	*Levetiracetam group (n=32)*	*P value*
*Age (mo)	44 (43)	59 (44)	58 (50)	0.32
Male	19 (54.3)	21 (60)	18 (56.2)	0.89
*Body Mass Index, z score	- 1.7 (2)	- 1.1 (1.9)	- 1.6 (2)	0.32
*(cm) Head circumference	46.4 (4.2)	48.3 (3.5)	47 (4.8)	0.16
#PRISM-III	5 (3 - 8)	4 (2-7)	3 (0-5)	0.17
#Duration of seizure, prior to enrollment (min)	10 (10 - 23)	10 (10-15)	10 (10-18)	0.57
Fever history	23 (66)	15 (43)	15 (47)	0.13
Classification of status epilepticus, n (%)				*0.44*
Generalized convulsive	26 (74)	31 (88)	24 (75)	
Focal motor	5 (14)	2 (6)	6 (19)	
Focal onset evolving into bilateral convulsive SE	4 (11)	2 (6)	2 (6)	
Family history of seizure disorder	4 (11)	2 (6)	1 (3)	0.38
Developmental delay	5 (14)	8 (23)	5 (16)	0.60
Hypocalcemia	4 (11)	3 (9)	2 (6)	0.76
Abnormal CT head (*n*=55)	4 / 23 (17)	3/16 (19)	1/16 (6)	0.37
‡MRI Brain* (*n*=41)	5 / 12 (42)	2/13 (15)	5/16 (31)	0.43
‡Electroencephalographic abnormality	15 / 27 (56)	17 /29 (59)	12/21 (57)	0.97
Cerebrospinal fluid pleocytosis	10 (29)	7 (20)	4 (13)	0.27
Etiology				*0.28*
Acute	16 (46)	7 (20)	14 (44)	
Remote	9 (25)	7 (20)	5 (16)	
Acute on remote	1 (3)	2 (6)	-	
Febrile status epileptics	2 (6)	2 (6)	2 (6)	
Unknown (*ie*, cryptogenic)	7 (20)	17 (48)	11 (34)	

*All values in no. (%) except *mean (SD) or #median (IQR); Hypocalcemia defined as ionized calcium less than one mmol/L or total serum calcium less than 8.5 mg/dL; PRISM: *Pediatric risk mortality score; CT: Computer tomography; MRI: Magnetic resonance imaging; ‡done during the follow-up.*

equivalent per kg), valproate (40 mg per kg) and levetiracetam (60 mg per kg), found that cessation of status epilepticus and improvement in the level of consciousness at 60 minutes of starting study drug infusion was similar in all three groups (45%, 46%, and 47%, respectively). The ConSEPT study [10] and the EcLiPSE study [1] compared 20 mg per kg phenytoin and 40 mg per kg levetiracetam. Clinical cessation of seizure activity in children with status epilepticus refractory to benzodiazepine was similar in both studies (60% *vs*. 50% and 64% *vs*. 70%, respectively) [1,10].

Isguder, *et al*. [11] reported that control of status epilepticus in pediatric patients was 71.8% with valproate and levetiracetam. The lower rate of seizure control could be due to a longer median duration of status epilepticus of 75 minutes, as compared to 10 minutes in our study.

A meta-analysis in pediatric status epilepticus found that valproate had a higher efficacy of 75.7% as compared to levetiracetam (68.5%) and phenytoin (50.2%) after administration of benzodiazepine [12]. Another meta-analysis of five randomized studies, which included one pediatric study (valproate *vs*. phenytoin), with insufficient information about random sequence generation and allocation concealment, found that there was no difference in clinical seizure control in both direct (valproate *vs*. phenytoin; 77% *vs*. 76% and levetiracetam *vs*. phenytoin; 72% *vs*. 68%) and indirect (levetiracetam *vs*. valproate; 72% *vs*. 77%) comparison [13]. Our study found a relatively higher control rate of seizure; as compared to other published studies [1,,8-13], possibly due to shorter duration of seizures before treatment in our study.

We found that the proportion of patients shifted to the pediatric intensive care unit was significantly higher in the phenytoin group. This could be due to the underlying illness in addition to the drug effects on neurological

TABLE II Outcome in Children With Convulsive Status Epilepticus in the Three Treatment Groups (*N*=102)

Outcome	*Phenytoin group (n=35)*	*Valproate group (n=35)*	*Levetiracetam group (n=32)*	*P value*
Primary outcome, *n* (%)	31 (89)	29 (83)	30 (94)	0.38
Secondary outcomes				
Time to control seizure (min), mean (SD)	3 (1.2)	3.2 (1.4)	3.1 (1.3)	0.42
[‡]Additional drug to control the seizure, *n* (%)	4 (11.4)	6 (17)	2 (6)	0.38
[$]Additional drug to control seizure, *n* (%)	8 / 31 (26)	4 / 29 (14)	4 / 30 (13)	0.35
Mechanical ventilation, *n* (%)	7 (20)	5 (14)	3 (9)	0.47
Length of mechanical ventilation (d), mean (SD)	2 (1.2)	7 (5.5)	3 (1.7)	0.08
PICU shifting, *n* (%)	15 (43)	7 (20)	6 (19)	0.04
PICU stay (d), mean(SD)	4 (2.4)	10 (4.5)	6 (3.7)	0.005
Hospital stay (d), mean (SD)	6.1 (4.1)	5.5 (5.4)	7 (7.4)	0.55
Functional status (at discharge), n (%)				*0.46*
GOS score-1	-	1 (3)	-	
GOS score-3	-	1 (3)	1 (3)	
GOS score-4	8 (23)	12 (34)	6 (19)	
GOS score-5	27 (77)	21 (60)	25 (78)	
[#]*Functional status (at 3 mo), n (%)*				*0.06*
GOS score-3	-	-	1 (3)	
GOS score-4	3 (9)	10 (29)	3 (9)	
GOS score-5	32 (91)	24 (71)	28 (88)	
Mortality, *n* (%)	-	1 (2.8)	-	-
Adverse event, *n* (%)	1 (2.8)*	-	-	-

*PICU: Pediatric Intensive Care Unit; GOS: Glasgow Outcome Scale; *fluid responsive shock, [#]n=34 for valproate group, [$]after control of seizure by study drug; [‡]no response to study drug.*

function. Valproate is reported to have a lower risk of cardiorespiratory compromise and a lack of sedative effect [14,15].

Our study had certain methodological differences from other similar studies. We assessed the absence of seizure 15 minutes after completion of study drug infusion, *i.e*. 35 minutes after starting the infusion, and the mean time taken to control of seizure was three minutes. We randomized the patients who did not respond to the benzodiazepine and used intention to treat analysis. This finding differs from the EcLiPSE study, which found that median time from randomization to the cessation of convulsive status epilepticus was similar in phenytoin and levetiracetam group (45-minute vs. 35-minute) and ConSEPT study assessed the clinical cessation of seizure activity five minutes after completion of infusion of the study drug with a different infusion time used for administration of study drugs (over five minutes and over 20 minutes) [1,10]. Another controlled study by Kapur, *et al*. [9] assessed the absence of seizure and recovery of consciousness after 60 minutes of starting the study drug infusion, and emergency unblinding before 60 minutes was considered a protocol deviation. Hence, the time limit followed for assessment of primary endpoint in our study is in line with the International League Against Epilepsy operational time point (t_1 and t_2) of status epilepticus [6].

Apart from the duration of seizure, age and underlying etiologies have a different impact on the prognosis of neurological outcome, even if assuming a similar seizure type [6]. In our study, these prognostic factors were not analyzed. Though it is difficult to differentiate the role of each of the prognostic factors, data from larger studies could allow for redefining of the risk of long-term neuromorbidity. Another strength of our study was that the neurological outcome at three-month was assessed. This is in contrast to six previous open-labeled controlled studies with valproate and two with levetiracetam, no follow-up details were provided [5]. Our study did not include the recovery of postictal consciousness, long term drug-related adverse effects, and behavioral assessment. Future studies with large sample size, preferably multicentric, should focus on children with different etiologies,

WHAT THIS STUDY ADD?

- Phenytoin, valproate, and levetiracetam at a dose of 20 mg/kg infusion over 20 minute were equally efficacious in the management of pediatric convulsive status epilepticus not responding to single dose of lorazepam, and patients had similar neurological outcome at three-month follow-up.

including liver and hematological diseases, with stratification of the duration of seizure and convulsive versus non-convulsive seizures.

In conclusion, our study shows that phenytoin, valproate, and levetiracetam are equally effective in controlling seizure in the management of pediatric convulsive status epilepticus with a similar neurological outcome at three-month follow-up.

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