ORIGINAL RESEARCH

Study of Comparing the Efficacy of Intravenous Levetiracetam Versus Intravenous Valproate inthe Management of Refractory Status Epilepticus in Children

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ABSTRACT

Background: Primary: To compare the rates of clinical seizure cessation at 15 min after intravenous bolus infusion in the two groups (valproate versus levetiracetam) of children aged 1-12 years with refractory status epilepticus (uncontrolled with initial BDZ and phenytoin bolus).

Materials and Methods: This study was conducted in Department of Pediatrics, Mamata medical college and General hospital Khammam. Study Period: Oct 2017 to Sept 2019. Study population: Children between 1 to 12 years with status epilepticus who had received diazepam followed by phenytoin infusion of 20 mg/kg and repeat 10 mg/kg. If status was still not controlled, they were labelled as refractory status epilepticus and enrolled in study. It was a Randomised controlled study.During the study period(Oct 2017to Sept 2019) a total of 1835 children visited emergency room, at our centre. Among them 259 children had seizures presenting feature. Fifty-seven children met the criteria for enrolment. Seven of these children could not be randomized. The remaining fifty children were randomized into two groups- group A received valproate (n=25) and group B received levetiracetam (n=25).

Results: The mean age of the patients was 45± 34 months and there was male preponderance (64%) seen in our study. The most common underlying etiology in both groups was acute central nervous system infections including meningoencephalitis and meningitis (40% in levetiracetam group and 64% in valproate group) Most children came with first time seizures and only few(20%) were known cases of epilepsy and on antiepileptics. Most of our children (56%) presented with generalised tonic clonic seizures. Duration of status before admission was different in both groups with median of 20 min and 30 min in levetiracetam and valproate group respectively and 40 % of patients had received some treatment for seizure before reaching us.

Conclusion: In this study no significant differences were observed between intra venous valproate and intra venous levetiracetam, in acute seizure control in children with SE refractory to Benzodiazepam and Phenytoin. Both the drugs were effective in more than 2/3rd of the children. Perhaps this might justify the use of a new protocol for management of refractory status epilepticus where in intravenous valproate or levetiracetam could be included before use of benzodiazepine or thiopentol infusion.

Keywords: Benzodiazepine, Seizures, Epilepticus, Meningoencephalitis, Valproate Versus Levetiracetam.

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INTRODUCTION

Convulsive status epilepticus (CSE) in childhood is a medical emergency and its aetiology and outcome mean that it should be studied separately from adult CSE.[1] Status epilepticus

(SE), is one of the most common neurologic emergencies among children associated with a high mortality and morbidity.

For operational purposes, status epilepticus is considered as a condition of prolonged seizure activity (more than 5 min) or persistent, repetitive seizure activity without recovery of consciousness in between episodes. Practically, any child who is brought seizing to the emergency room should be treated as status epilepticus.[2,3]Treatment should be initiated as early as possible; evidence has shown that once seizures persist for 5 to 10 minutes, they are unlikely to stop on their own in the subsequent few minutes.[4]

The annual incidence of pediatric SE worldover ranges from10 and 62 per 100,000. The highest incidence is in children less than 2 years of age, where it ranges from 135 to 156 per 100,000, with the greatest peak in the first year of life. If febrile SE is excluded, the incidence is decreased by 25% to 40%.[5-7] In developing countries like India the exact incidence is not known however, it is likely to be high due to high prevalence of epilepsy, central nervous system (CNS) infections, and long treatment gap. It has been observed that SE is refractory to current first-line(benzodiazepines)treatmentand second-line anticonvulsants (phenytoin, phenobarbital or valproic acid)in30 40% cases in adults.[8] In children, 9% to 10% of SE becomes refractory.[3] These nonresponsive cases are called Refractory status epilepticus (RSE) which is defined as an ongoing, intermittent or continuous seizure activity even after administration of adequate dosages of two first line anticonvulsant drugs.[3]

Drugs frequently used for seizure control in RSE are diazepam, midazolam infusion, and barbiturate coma. Diazepam infusion has been found to be effective but it is associated with a risk of respiratory depression and hypotension that require mechanical ventilation, vasopressor support, and intensive care. Also, it has been postulated that the Benzodiazepine receptors get internalized in prolonged status and therefore they are not very effective in prolonged seizures. Therefore, additional treatment options yielding a higher success rate and a better tolerability are desirable.[8] Newer drugs like valproate and levetiracetam which are effective in status epilepticus and with lesser side effects are being tried now.

Recently, leveteracetam, a newer antiepileptic with a novel mechanism of action has been approved for the treatment in refractory status epilepticus as an alternative drug by ILAE Task Force in 2008.[8] 8 Levetiracetam (LEV) has been found to be effective in focal as well as generalised epilepsies. Preliminary studies suggest that intravenous levetiracetam could have a potential place in the initial management of SE given its broad spectrum efficacy, limited side effects, and absence of drug interactions.[9,10] Although randomized controlled trials are lacking, use of levetiracetam is increasing in acute seizures and SE after parental consent. Very few studies comparing the efficacy of levetiracetam with other commonly used antiepileptic drugs in pediatric population are available. Hence, this study is planned to compare the efficacy of intravenous levetiracetam with intravenous valproate in the management of refractory status epilepticus.

Aims and Objectives

To compare the efficacy and safety of intravenous valproate versus levetiracetam in management of Refractory status epilepticus.

Objectives:

Primary objective:

To compare the rates of clinical seizure cessation at 15 min after intravenous infusion in the two groups (valproate versus levetiracetam) of children aged 1-12 years with refractory status epilepticus (uncontrolled with initial benzodiazepine and phenytoin bolus).

Secondary objectives:

- To compare the mean time taken to control seizure from the initiation of infusion in the two groups (valproate versus levetiracetam) of children aged 1-12 years with refractory status epilepticus (uncontrolled with initial benzodiazepine and phenytoin bolus)
- To compare the rates of additional antiepileptic use in the two groups (valproate versus levetiracetam) of children.
- To compare the rates of adverse events (hypotension, bradycardia, respiratory depression, ventilation, PICU stay, in hospital mortality) in the two groups (valproate versus levetiracetam).

MATERIALS & METHODS

Study settings: This study was conducted in Department of Pediatrics, Mamata medical college and General hospital Khammam.
Study Period: Oct 2017 to Sept 2019 (24 months).
Study population: Children between 1 to 12 years diagnosed as refractory status epilepticus as per standard definitions presented to pediatric emergency and pediatric intensive care unit are included in the present study.

Study design
Type: Randomised controlled study.
Primary purpose: Management of refractory status epilepticus
Method of randomization: Computer generated random number table.

Eligibility: All patients with Inclusion criteria

- Children aged 1 to 12 years old of either sex with ongoing clinical seizures(clonic, tonic, tonic clonic, myoclonic, focal or generalized)
- Clinical seizures despite use of one or more doses of benzodiazepines (IV, IN, Buccal) and IV Phenytoin of 30 mg/kg or includes those who respond to initial doses (30 mg/kg) of phenytoin but have recurrence within 6 hours of drug administration.

Exclusion criteria

- Non-convulsive status epilepticus
- Known or suspected cases of neurometabolic or mitochondrial disorders (unexplained developmental delay, and/or consanguinity, sib deaths, recurrent encephalopathy, recurrent vomiting, recurrent hypoglycemia, unexplained lactic or metabolic acidosis or hyperammonemia)
- Acute or chronic liver or kidney disease
- Head injury or neurosurgery in the past one month.
- Active or recent hemorrhage from any site
- Documented platelet count <50,000, or INR>2
- Known or suspected allergy or intolerance to either valproate or levetiracetam
- Patients of epilepsy already on LEV(>20mg/kg/day) or VPA(>20mg/kg/day)

Outcome Variables
Primary outcome variables:

- Proportion of children in either group who have Cessation of all clinical seizure within 15 min(130)of drug administration and no recurrence for the next 6 hours

Secondary outcome variables:

- Time taken to control seizure (minutes) from the initiation of infusion

- Proportion of children in either group who required additional drugs to abort ongoing clinical seizures
- Rates of adverse events (hypotension, bradycardia, respiratory depression, ventilation, PICU stay, in hospital mortality) in the two groups

Methodology

Patient flow:

Children between 1 to 12 years who presented to ER seizuring or those in ward who hadseizures >5 min whose seizures were not controlled after one or more bolus doses of diazepam/ midazolam/ lorazepam followed by phenytoin loading dose @30mg/kg were considered as having refractory status epilepticus or those responded to initial doses (30 mg/kg) of phenytoin , recurrence within 6 hours of drug administration in whom the use of AED was contemplated . After enrolment, children with refractory status epilepticus were randomised using computer generated random number table into two groups to receive either intravenous levetiracetam or valproate. Random assignments were kept in sealed envelopes and opened only after the child was enrolled in the study.

Treatment plan:

Treatment plan A: This group received intravenous levetiracetam @ 30mg/kg(128) diluted 1:1 in normal saline over 10 min. If theseizures were not controlled within 15 min of completion of drug administration those were considered to be primary treatment failure or if recurrence of seizure within 6 hours of drug administration were considered to be secondary treatment failure and the next line of treatment were followed based on the unit protocol.

Treatment plan B: This group received intravenous Valproate 30 mg/kg(4) diluted 1:1 in normal saline over 10 min. If the seizures were not controlled within 15 min of completion of drug administration(130) those were considered to be primarytreatment failure or if recurrence of seizure within 6 hours of drug administration were considered to be secondary treatment failure and the next line of treatment were followed based on the unit protocol.

Monitoring during therapy

Patients were attached to a monitor for continued measurements of heart rate (HR), oxygen saturation (SpO2) and non-invasive blood pressure (NIBP). Periodic documentation of respiratory rate, any respiratory distress, and any seizure recurrence were done. The time of drug administration was taken as 0 min and all measurements made with that reference.

Patients were assessed for persistence of clinically visible motor seizure activity at the end of 15 min, if seizures were persisted or recurred after an initial period of remission, it was considered as a failure of primary drug. All the clinical details were noted by the resident managing the case in ER and the time of seizure control were noted using digital clock in ER.

Drug safety

Any adverse effects during the trial were noted. A predetermined checklist was used based on all known adverse effects of Levetiracetam and valproate to evaluate for side effects. An independent data safety monitoring personal/committee reviewed the safety of the intervention during the trial.

Statistical Analysis

Baseline variables in the 2 groups were compared based on their distribution. Continuous variables were assessed by levene's test and compared by students t- test or Mann Whitney U test. P values <0.05 were considered significant. Categorical variables were assessed using Chi-square test or Fisher's exact test.

RESULTS

Age& sex distribution

The age and sex distribution of study population is as depicted in [Table 1]. Mean age of children in levetiracetam group was 44±36 months with median 30 months (IQR: 15-60 months) Mean age of children in valproate group was 45±31 months with median 36 months (IQR:21-66 months). Distribution of children in different age groups was as follows; 1-2 yrs(40%), 2-5 yrs (35%)and in > 5 yrs(25%) respectively.

There was no significant difference in the age of patients of two groups. [Table 1]

Table 1 : Comparison of demographic details between the study groups

S. No	Characteristics	Levetiracetam group N=25	Valproate group N=25	'P' value
1	Age in months Mean (SD)^	44±36	45±31	0.550
	Median (IQR)	30(15-60)	36(21-66)	0.550
	1 -2 yrs n (%)	12(48%)	9(36%)	0.690
	2-5 yrs n (%)	8(32%)	10(40%)	
	5-12 yrs n (%)	5(20%)	6(24%)	
2	Sex*			
	Male n(%)	17(68%)	15(60%)	0.556
	Female n(%)	8(32%)	10(40%)	

N = Number of patients , SD= Standard deviation , IQR= Inter quartile range , %= Percentage

* = Chi-Square Tests, ^ =Mann-Whitney Test

Male preponderance was seen in our study, 32(64%) of the total children were male. In levetiracetam group, 17(68%) were male and 8(32%) were female against 15(60%) were male and 10(40%) were female in valproate group. The difference between two groups was not significant.

Comparison of past history of seizure between study groups

In our study, 20(40%) children had past history of seizure among whom,13(65%) had generalized seizures and 7(35%) had focal seizures. In our study, 9(45%) children had structural lesions as cause for epilepsy followed by unknown cause 7(35%). Six teen children were already on AEDs with no significant difference between two groups.

The most common cause for refractory status epilepticus in our study was central nervous system infections. A total of 28(56%) children had central nervous system infection, out of these 26children had acute CNS infection and 2 children had CNS tuberculosis. Sixteen children had preexisting epilepsy,ten of whomidopathic epilepsy, and 6had remote symptomatic epilepsy. There was no significant difference between the two groups with respect to etiology of refractory status epilepticus.

In our study, 28 out of 50 patients had GTCS at presentation and 15 of them were in levetiracetam group and 13 in valproate group. Total 15 out of 50 patients had focal seizures at onset and 6 of them in levetiracetam group and 9 in valproate group and other types as listed in [Table 2]. There was no significant difference between two groups with respect to type of seizure at presentation.Mean duration of status epilepticus in levetiracetam group was

21±25 min with median 20 min and range of 7-30 minutes. Mean duration in valproate group was 50±52 min with median 30 min and range of 15-60 minutes. There was a significant difference with respect to duration of status epilepticus between two groups.

Mean number of seizures in this episode prior to hospitalization in levetiracetam group was 2 ± 2 with a median of 2 and with IQR of 1-4 episodes. Mean number of seizures in this episode prior to hospitalization in valproate group was 4 ± 5 with a median of 2.0 and with IQR of 1 - 3 episodes.

In levetiracetam group 5(20%) children had received AED prior to hospitalization among which 1(4%) received only one AED and 4(16%) had received 2 AEDs prior to hospitalization

In the valproate group significantly, more children had received AED prior to hospitalization compared with those in the levetiracetam group. Three (12%) received only one AED and 11(44%) had received 2 AEDs and 1(4%) had received multiple AEDs prior to hospitalization

At presentation 6 (12%) out of 50 children had shock out of which 5 were in levetiracetam group, 1 in valproate group, and 10 out of 50 children had ventilator requirement with 4 in levetiracetam group and 6 in valproate group with no significant difference between two groups with respect to shock and ventilation requirement.

14 out of 50 children had low GCS of <7 out of which 5 in levetiracetam group and 9 in valproate group. 21 out of 50 had GCS of 8-12 with 12 in levetiracetam group and 9 in valproate group and 15 had normal GCS. Sixteen out of 50 children had features of raised intracranial pressure with 6 of which in levetiracetam group and 10 in valproate group with no significant difference between two groups with respect to neurological findings at presentation.

Table 2: Comparison of clinical status at presentation to ER between the study groups

S. No	Characteristics	levetiracetam group N=25	Valproate group N=25	'P' value
1	Shock n (%)*	5(20%)	1(4%)	0.189
2	Ventilation*	4(16%)	6(24%)	0.480
3	Nervous system findings			
	GCS^	10±4	9±4	0.277
	<7	5(20%)	9(36%)	
	8-12	12(48%)	9(36%)	0.441
	13-15	8(32%)	7(28%)	
	Raised ICP n (%)*	6(24%)	10(40%)	0.225

N = Number of patients , SD= Standard deviation , IQR= Inter quartile range , %= Percentage, * = comparisons using Chi-Square Tests , ^ = comparisons using Mann-Whitney Test

Comparison of seizure cessation between 2 groups

In our study 39(78%) out of children got seizure cessation within 15 min of drug administration out of which 19 were in levetiracetam group and 20 in valproate group. In levetiracetam group 2(8%) had recurrence of seizure during hospital stay but no child had recurrence of seizure within 6 hours of drug administration whereas in valproate group 6(24%) had recurrence of seizure during hospital stay out of which 3(12%) children had recurrence of seizure within 6 hours of drug administration. There was no significant difference between two groups with seizure cessation and seizure recurrence.
In our study main primary outcome (control of seizures in 15 min after drug administration and the seizure free period for 6 hours post drug) between levetiracetam group(76%) and valproate group (68%) were not significant with p value of 0.529.

Secondary Outcome:
Mean duration of seizure cessation was 278±127 seconds with a median of 240 sec (IQR 120-300 seconds) in levetiracetam group and mean duration of seizure cessation was 314±206 seconds with a median of 300 sec (IQR- 120-600 seconds) in valproate group.
In levetiracetam group 8 (32%) children had requirement of additional drugs after levetiracetam administration whereas in valproate group 11 (44%) children had requirement of additional drugs after valproate with no significant difference between two groups.
Within one hour of drug administration 11(22%) out of 50 had respiratory depression out of which 4 were in levetiracetam group and 7 were in valproate group and 3 out of 50 children had shock within which 1 was in levetiracetam group and 2 were in valproate group. There was no significant difference between two groups with respect to adverse events.

Table 3: Comparison of secondary outcome between study groups

S. No	Characteristics	levetiracetam group N=25	Valproate group N=25	'P' value
1	Time of seizure cessation-seconds^- Mean±SD (%) Median	278±127 240(120-300)	314±206 300(120-600)	0.511
2	Requirement of additional drugs after study drug n (%)*	8(32%)	11(44%)	0.273
3	Adverse events within 1 hour of drug administration n (%)*	4(16%)	7(28%)	0.306
4	Shock n (%)*	1(4%)	2(8%)	1.000
5	New onset Respiratory depression n (%)*	4(16%)	7(28%)	0.306
6	Bradycardia*	Nil	Nil	-

N = Number of patients , SD= Standard deviation , IQR= Inter quartile range , %= Percentage,* = comparisons using Chi-Square Tests, ^ =Mann-Whitney Test

Comparison of seizure recurrence after SE refractory to study drugs between 2 groups
Mean duration of seizure recurrence was 600±170 minutes in levetiracetam group where in valproate group had mean mean duration of seizure recurrence was 500±470 minutes with no significant difference between two groups.
Total duration of status epilepticus in levetiracetam group was <1 hour in 18(72%) children,1-2hours in 3(12%), 2-5 hours in 3(12%) and > 5hours in 1(4%) child. Total duration of status epilepticus in valproate group was <1 hour in 13(52%) children,1-2hours in

7(28%), 2-5 hours in 4(16%) and > 5hours in 1(4%)children. There was no significant difference between two groups with duration of status epilepticus.

Among children who had treatment failure with levetiracetam that is seizures uncontrolled/ partial control 1(4%) child SE got aborted with valproate,3(12%) with midazolam and 1 (4%) with thiopentone and 1 child didn't respond to any AEDs whereas in valproate group and among children who had seizures uncontrolled/ partial control that is treatment failure with valproate 8(32%) children got aborted with levetiracetam ,1(4%) with midazolam and 1 (4%) with thiopentone.

In levetiracetam group 11(44%) had adverse events after status epilepticus during hospital stay among which 2(8%) had shock, 10(40%) had been ventilated among which 5(20%) had ventilation associated pneumonia, 2(8%) had pneumothorax, 10(40%) had sepsis, 1(4%) had fungal infections, 3 (12%) had deranged

coagulogram and 5 (20%) had azotemia and 2(8%) had azotemia and 2(8%) had transaminitis 2(8%) had neurological sequelae.

Table 4: Comparison of adverse events during hospital stay after study drug administration between the 2 groups

S. No	Chracteristics	Levetiracetam group N=25	Valproate group N=25	'P' value*
1	Adverse events n (%)	11(44%)	9(36%)	0.564
2	Shock n (%)	2(8%)	3(12%)	1.000
3	Sepsis n (%)	10(40%)	6(24%)	0.225
4	Ventilated n (%)	10(40%)	12(48%)	0.554
5	Ventilation associated pneumonia n (%)	5(20%)	3(12%)	0.702
6	Pneumothorax n (%)	2(8%)	1(4%)	1.000
7	Fungal infections n (%)	1(4%)	0(0%)	1.000
8	Neurological sequelaen(%)	2(8%)	1(4%)	1.000
9	Deranged PTI n (%)	3(12%)	4(16%)	1.000
10	Azotemia n (%)	5(20%)	2(8%)	0.417
11	Transaminitis n (%)	2(8%)	1(4%)	1.000

N = Number of patients , SD= Standard deviation , IQR= Inter quartile range , %= Percentage, * = comparisons using Chi-Square Tests, PTI= Prothrombin index

In valproate group 9(36%) had adverse events after SE during hospital stay among which 3(12%) had shock,12(48%) had been ventilated among which 3(12%) had ventilation associated pneumonia, 1(4%) had pneumothorax, 6(24%) had sepsis,4 (16%) had deranged coagulogram and 2 (8%) had azotemia and 1(4%) had transaminitis 1(4%) had neurological sequelae. There was no significant difference in adverse events between two groups.

In our study 9(18%) children out of 50 died 7 were in levetiracetam group and 2 were in valproate group with sepsis,shock and raised ICP were the common causes of death in 4 out of 9 children expired out of which 3 were in levetiracetam group and 1 were in valproate group and other causes of death as per listed in [Table 4]. In 4 children outcome could not be ascertained as parents decided to withdraw medical care(left against medical advice). There was no significant difference in their overall outcome between two groups.

Mean duration of hospital stay in levetiracetam group was 12±12 days with a median of 10 days and range of 1-40 days, whereas the mean duration of hospital stay in valproate group was 12±10 days with a median of 10 days and range of 1-35 days. There was no significant difference in duration of hospital stay between two groups.

DISCUSSION

Design and setting of the study:

This study was conducted in the pediatric emergency and intensive care unit of the Department of Pediatrics, Mamata medical college and General hospital Khammam. The study was designed as a parallel group, open label, randomised controlled trial. There are only few studies of the use of intravenous levetiracetam in treatment of status epilepticus in children. This is a randomised controlled study in children, which was designed to compare the efficacy of intravenous levetiracetam with valproate for treatment of refractory status epilepticus.

Demographic details:

The mean age of the patients in this study was 45± 34 months. Most of the children in the study were less than 5 year old [1-2yrs old (42%), 2-5 yrs(36%)]. This was reflective of the overall higher preponderance of this age group to have seizures. Additionally the occurrence of status is also more common in the younger children (<5 years).[11]

The male preponderance of 67% and 60% in LEV and VPA group respectively is similar to previous studies of refractory status epilepticus,[4]and other studies done by Nishiyama et al(11)(M:F: 1.3:1) and Phillips et al.[12] This may be due to the cultural higher health care seeking behaviour for male children or it may reflect an actual higher incidence of SE in boys. This later observation needs confirmation in further studies.

CNS infections were the main cause of refractory status epilepticus and more than half the patients had meningoencephalitis. This too is similar to the previousstudies of refractory status epilepticus by Singhi et al.[13]Only 20% of patients in our study were known cases of epilepsy and were receiving anticonvulsants which is similar to the previous studies of refractory status epilepticus by Singhi et al.[4] However, this is different from studies by Philips et al,[14] where majority of the children were known cases of epilepsy and were already on anticonvulsants. The setting of their trials was different. Since infections are less common in developed countries, so infections contributing to status epilepticus also appear less common.

More than half the patients in thestudy had generalized seizures. While few studies have had similar observations others researchers have found focal seizures to be more common in their cohorts.[4,11,14]

Control of status epilepticus

The number of children in whom refractory status epilepticus was controlled within 15min of drug administration was similar in both the levetiracetam and valproate groups (p= 0.73). Refractory status epilepticus was successfully controlled within 30 minutes in 80% of children in the sodium valproate group in the previous studies of refractory status epilepticus.

Efficacy of LEV in control of status epilepticus in our study was similar to the adult study done by (73.2%) Tripathi et al was similar to other studies.[15,16]

One needs to consider the context of use of IV Lev in these reports. Direct comparisons are therefore difficult. Ina recent systematic review of all studies using LEV as second line AED in SE,data from ten studies were reviewed.[17] Of the ten studies, seven were retrospective observational, two were prospective observational, and one was prospective randomized. The studies described a total of 334 patients. The efficacy of LEV ranged from 44% to 94%, with

higher efficacy reported in the retrospective studies. The authors concluded that the evidence for use of LEV as an alternative stage two AED in SE is limited. The higher efficacy reported in retrospective studies indicates possible publication bias, and caution is advised when the results of these retrospective studies are considered in clinical decision- making. We have used the drug as third agent after failure of benzodiazepines and phenytoin. Reports of its use in phenytoin unresponsive patients are scarce. However in a recent report in adults with SE by Tripathi et al,a 73.2% response rate was observed.[16]

Time taken for status control after giving study drug

Time taken for control of refractory status epilepticus after drug administration was similar in both the LEV and VPA groups (median 240 and 300 seconds respectively). Median time for refractory status epilepticus control in VPA group was similar to studies by Uberall et al (2-6 min) and KainT Yu et al (8min).[14,15]

Breakthrough Seizures

There was higher incidence of breakthrough seizures in VPA group 6(24%) when compared to LEV group 2(8%), but there was no significant difference between two groups [p=0.247]. This higher incidence of breakthrough seizures in VPA group is similar to previous study done by Singhi et al(50%).[4] Majority of patients who had received valproate in our study required a repeat bolus of 10 mg/kg and 10(33%) patients received levetiracetam to control refractory status epilepticus. Uberall et al,[15] had reported that only 5(17%) of 31 patients with status epilepticus control had required second bolus of valproate.

Adverse events within 1 hour of drug administration

Children of both groups developed respiratory depression and shock after receiving bolus dose with similar frequency (p=0.564). Findings in children receiving valproate were different to previous studies by Campiston et al, Uberall et 14 where no child developed respiratory depression after receiving valproate.

Outcome of patients

Mortality in patients with refractory convulsive status epilepticus was slightly higher (18%) in the present study when compared to previous study of refractory status epilepticus done by Singhi et al.[4] Higher mortality in our study is similar to Misra et al(30.3%) and another study by Banerjee et al(25%).[18] Various other studies using different treatment modalities have reported variable mortality in refractory status epilepticus patients. Parviainen et al(using Thiopentol), (140) using continuous midazolam infusion found no death in their study patients.

Strengths of the study

The current study has certain strengths. Firstly, the inclusion criteria were objective and reproducible in a different setting as a predefined and published set of criteria were used. Secondly, it was a comparative study, and the two groups were comparable in terms of age group, gender distribution, etiology and pre-existing developmental delay and the side effects associated with the two drugs were also analysed.

Limitations of the study

This study had certain limitations. Firstly, baseline valproate group had longer duration of status epilepticus when compared to levetiracetam group in our study. The efficacy of drugs depends on the etiology and duration of status epilepticus prior to hospitalisation.This difference may have influenced the low response rate in the VPA group.Secondly, this study

could not achieve the estimated sample size leading to a decrease in the power of the study.Thirdly, results of the study cannot be extrapolated to infants. Fourthly, we did not do continuous EEG monitoring in our patients. A continuous VEEG monitoring is the gold standard for monitoring response in SE. Though desirable this facility is often unavailable in resource limited countries like India.

CONCLUSION

In this study no significant differences were observed between IV VPA and IV LEV, in acute seizure control in children with SE refractory to BDZ and PHT. However, both the drugs were effective in more than 2/3rd of children with RSE.

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