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Original Research Article.

Comparison of Safety and Efficacy of Sodium Valproate and Levetiracetam In Treatment of Status Epilepticus in 6 Months to 16 Years Age Group

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ABSTRACT

Background: Status epilepticus (SE) is a neurological emergency which can be life-threatening. Several medical regimens are used in order to control it. In this study, we intended to evaluate the clinical efficacy and tolerability of sodium valproate and levetiracetam in the control of SE.

Methods: This prospective study was conducted in 100 patients of status epilepticus aged 6 months to 16 years coming to pediatric emergency at Rajindra Hospital, Patiala. They were randomly divided into two groups, 50 patients received Sodium Valproate (VPA) and other 50 received levetiracetam (LEV). All patients were monitored for vital signs every 2 hr up to 12 hr. The patients were also followed up for 7 days regarding drug response and adverse effects.

Results: Efficacy of VPA and LEV in aborting seizures within 30 minutes was found to be 74% and 82% respectively. Hence, LEV was found to be more efficacious than VPA in controlling SE in children. VPA had more adverse effects than LEV with some patients having bradypnoea and dizziness. Hence, along with previously reported safety profiles and efficacy of LEV, it is suggested that LEV could be an appropriate (or even better) alternative to VPA as the first choice anti-convulsant for second line treatment of pediatric SE.

Conclusion: Levetiracetam is preferred to Sodium valproate for treatment and control of SE due to its higher tolerability and lower hemodynamic instability.

Keywords: Levetiracetam, Sodium Valproate, Status Epilepticus.

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INTRODUCTION

Status epilepticus (SE) is one of the most common neurological emergencies, which was previously defined as long- lasting or multiple seizures without recovery and regaining consciousness between intervals lasting for more than 30 min. This definition has been used in various studies for many years, but recently new studies proposed that for better definition, all epileptic seizures lasting more than 5 min require the same treatment as used for SE. In these patients, mechanisms for self-termination of seizures fail. Thus, seizures can usually last for several minutes with the high possibility of recurrence.[1]

ILAE redefined status epilepticus as an ongoing seizure activity due to failure of mechanisms responsible for seizure termination or initiation of mechanisms provoking ongoing seizures causing prolonged seizures after time point t1, and which can have long-term consequences after time point t2, with these time points being defined separately for convulsive status epilepticus, focal status epilepticus and absence status epilepticus. (Table 1)

According to ILAE 2015, any generalized tonic-clonic seizure lasting for more than 5 minutes is likely to be prolonged and warrants initiation of treatment. Any generalized tonic-clonic seizure lasting for more than 30 minutes may cause long-term consequences and requires aggressive management to prevent the same.[2] Status epilepticus (SE) represents a severe condition with significant mortality and morbidity[4] and its timely treatment is indicated to prevent potentially deleterious complications[5]. Unfortunately, high-level evidence is available only for the first-line medication; in particular, lorazepam has been shown to be more effective than phenytoin (PHT) or placebo.[6]

Table 1: Time points in status epilepticus

	Time After which if Seizures Do not terminate, Patient is considered in status Epilepticus (t1)	Time After which ongoing seizures have long term consequences (t2)
Convulsive Status epilepticus.	5 min	30 min
Focal Status epilepticus with impaired consciousness	10 min	> 60 min
Absence status epilepticus	10-15 min	Unknown

Therefore, intravenous benzodi- azepines are recommended as an initial approach.[7] However, because first-line therapy fails to control at least 35-45% of patients with SE[6]. Additional treatments are needed for whom convincing evidence is lacking. Historically, phenytoin (PHT) has been used before VPA as a second-line agent.[6] In view of mortality and morbidity, it is imperative that SE be treated promptly. However, despite more than 150 years of research, treatment of SE remains controversial and is largely based on empirical recommendations rather well conducted clinical studies. Currently, high level evidence is available only for the first line medications of SE which includes intravenous BZDs. Since, first line therapy fails to control many times, additional treatment is necessary for most patients. Some of the conventional agents being used as second line treatment include phenytoin and valproate. However, use of these drugs is limited by their toxicity. Therefore, there is a need for newer, more effective and less toxic drugs for management of SE. More recently, LEV has also been ascribed to treatment of SE but there is still a lack of well-designed clinical trials supporting its efficacy in SE.

AIMS AND OBJECTIVES

1. To compare the efficacy of Sodium Valproate and Levetiracetam as a second line anti-epileptic drug in status epilepticus.
2. To compare the safety and adverse reactions associated with Sodium Valproate and Levetiracetam.

MATERIALS AND METHODS

Study Site

Department of Paediatrics, Rajindra Hospital, Patiala.

Study Design

This was a prospective study.

Study Population

6 months to 16 years old patients presenting to Paediatric Emergency of Rajindra Hospital Patiala.

Inclusion Criteria

Patients who fulfilled the definition of SE, who were administered IV midazolam and gave written consent for participation in the study.

Exclusion Criteria

- Patients who were < 6 months old or > 16 years old.
- Patients with history of liver disease.
- Who were already taking VPA or LEV.
- Who had a prior history of allergy to VPA or LEV.
- Those with drug withdrawal seizures.
- Hypoglycaemic seizures.

Study Procedure

This study includes 100 patients who were referred to pediatric emergency of Rajindra Hospital Patiala from February 2020 to August 2021. Patients were only enrolled in the study after obtaining informed consent. As most of the patients were in altered sensorium, written informed consents were obtained from first degree relatives of the patients before inclusion in the study.

Randomization was done using a simple random sampling method in which the patients were assigned either VPA or LEV depending on the order of recruitment to the study. Odd number patients received VPA (n=50; group A) and even number patients received LEV (n=50; group B).

All patients received a bolus injection of Midazolam 0.1 mg/kg IV over 1 minute. Patients of group A received IV VPA at a dose of 20 mg/kg (rate: 5 mg/kg/min) after dilution with normal saline and patients of group B received IV LEV at a dose of 30 mg/kg (rate: 5 mg/kg/min). This was followed by maintenance doses of the respective drugs.

End Points

Primary end point was successful clinical termination of seizure activity within 30 minutes after initiation of drug infusion.

Secondary end points were reoccurrence of seizure within 24 hours after control of SE, drug related adverse effects, neurological outcome at discharge as assessed by Functional Independence Measure (FIM; good outcome if FIM score of 5-7, poor if 1-4), need for ventilatory assistance, and mortality during hospitalization.

Statistical Analysis

Data was represented as frequencies, %, mean ± standard deviation wherever applicable. Efficacy is assessed by comparing the seizure freedom rates at the end of study and safety was assessed by comparing adverse effects. Appropriate statistical tests were applied to analyse the data.

Table 2: Seizure Control Rates

Seizure Control Rates	Sodium Valproate (VPA)		Levetiracetam (LEV)		p value
	Patients	%	Patients	%	
Seizure Aborted within 30 minutes of Initiation of Drug	37	74%	41	82%	0.003 (S)
Seizure not Aborted within 30 minutes of Initiation of Drug	13	26%	9	18%	0.007 (S)
Total	**50**	**100%**	**50**	**100%**	

Table 3: Seizure Control Rates according to Cause of Seizure

Cause of Seizure	Sodium Valproate (VPA)			Levetiracetam (LEV)			p value
	N	Seizure Aborted within 30 minutes of Initiation of Drug	Seizure not aborted within 30 minutes of Initiation of Drug	N	Seizure Aborted within 30 minutes of Initiation of Drug	Seizure not aborted within 30 minutes of Initiation of Drug	
Development Malformation	0	0 (0%)	0 (0%)	1	1 (100%)	0 (0%)	0.001 (HS)
Febrile Seizure	19	16 (84.21%)	3 (15.79%)	15	12 (80%)	3 (20%)	0.039 (S)
Intracranial Hemorrhage	3	1 (33.33%)	2 (66.67%)	2	2 (100%)	0 (0%)	0.013 (S)
Malignancy	1	1 (100%)	0 (0%)	2	2 (100%)	0 (0%)	0.477 (NS)
Meningitis	12	11 (91.67%)	1 (8.33%)	17	15 (88.24%)	2 (11.76%)	0.026 (S)
Neuro-cysticercosis	1	1 (100%)	0 (0%)	0	0 (0%)	0 (0%)	0.001 (HS)
Poisoning	3	1 (33.33%)	2 (66.67%)	2	2 (100%)	0 (0%)	0.013 (S)
Tuberculoma	0	0 (0%)	0 (0%)	2	2 (100%)	0 (0%)	0.001 (HS)
Viral Encephalitis	3	3 (100%)	0 (0%)	2	2 (100%)	0 (0%)	0.659 (NS)
Not Known	8	3 (37.50%)	5 (62.50%)	7	3 (42.86%)	4 (57.14%)	0.049 (S)

Table 4: Seizure Control Rates according to Gender

Cause of Seizure	Sodium Valproate (VPA)			Levetiracetam (LEV)			p value
	N	Seizure Aborted within 30 minutes of Initiation of Drug	Seizure not aborted within 30 minutes of Initiation of Drug	N	Seizure Aborted within 30 minutes of Initiation of Drug	Seizure not aborted within 30 minutes of Initiation of Drug	
Female	22	18 (81.82%)	4 (18.18%)	22	18 (81.82%)	4 (18.18%)	0.696(NS)
Male	28	19 (67.86%)	9 (32.14%)	28	23 (82.14%)	5 (17.86%)	0.022(S)
Total	**50**			**50**			

Table 5: Seizure Control Rates according to Type of SE

Cause of Seizure	Sodium Valproate (VPA)			Levetiracetam (LEV)			p value
	N	Seizure Aborted within 30 minutes of Initiation of Drug	Seizure not aborted within 30 minutes of Initiation of Drug	N	Seizure Aborted within 30 minutes of Initiation of Drug	Seizure not aborted within 30 minutes of Initiation of Drug	
Convulsive Status Epilepticus	43	32 (74.42%)	11 (25.58%)	48	40 (83.33%)	8 (16.67%)	0.001 (HS)
Focal Status Epilepticus with Impaired Consciousness	6	5 (83.33%)	1 (16.67%)	2	1 (50%)	1 (50%)	0.006 (S)
Absence Status Epilepticus	1	0 (0%)	1 (100%)	0	0 (0%)	0 (0%)	0.001 (HS)

Table 6: Seizure Control Rates in different Age Groups

Cause of Seizure	Sodium Valproate (VPA)			Levetiracetam (LEV)			p value
	N	Seizure Aborted within 30 minutes of Initiation of Drug	Seizure not aborted within 30 minutes of Initiation of Drug	N	Seizure Aborted within 30 minutes of Initiation of Drug	Seizure not aborted within 30 minutes of Initiation of Drug	
6 Months - <2 Years	14	11 (78.57%)	3 (21.43%)	20	18 (90%)	2 (10%)	0.026 (S)
2-11 Years	31	22 (70.97%)	9 (29.03%)	23	18 (78.26%)	5 (21.74%)	0.002 (S)
12-16 Years	5	4 (80%)	1 (20%)	7	5 (71.43%)	2 (28.57%)	0.139 (NS)

Table 7: Comparison of efficacy according to Glasgow Coma scale

Cause of Seizure	Sodium Valproate (VPA)			Levetiracetam (LEV)			p value
	N	Seizure Aborted within 30 minutes of Initiation of Drug	Seizure not aborted within 30 minutes of Initiation of Drug	N	Seizure Aborted within 30 minutes of Initiation of Drug	Seizure not aborted within 30 minutes of Initiation of Drug	
Minor Brain Injury (13-15)	39	32 (82.05%)	7 (17.95%)	38	34 (89.47%)	4 (10.53%)	0.147 (NS)
Moderate Brain Injury (9-12)	3	3 (100%)	0 (0%)	3	3 (100%)	0 (0%)	0.134 (NS)
Severe Brain Injury (≤8)	8	2 (25%)	6 (75%)	9	4 (44.44%)	5 (55.56%)	0.006 (S)

Table 8: Adverse Effects of Drugs

Adverse Effect of Drugs	Sodium Valproate (VPA)		Levetiracetam (LEV)		p value
	Patients	Percentage	Patients	Percentage	
Hypotension	0	0%	1	2%	0.083 (NS)
Bradycardia	1	2%	1	2%	0.386 (NS)
Bradypnoea	1	2%	0	0%	0.083 (NS)
Vomiting	2	4%	0	0%	0.025 (S)
Headache	3	6%	2	4%	0.045 (S)
Dizziness	1	2%	0	0%	0.083(NS)
Raised Liver Enzymes	0	0%	1	2%	0.083(NS)
Absent	42	84%	45	90%	0.895 (NS)
Total	**50**	**100%**	**50**	**100%**	

Table 9: Secondary Outcome

Adverse Effect of Drugs	Sodium Valproate (VPA)		Levetiracetam (LEV)		p value
	Patients	Percentage	Patients	Percentage	
Intubated and Shifted to ICU for Ventilatory Assistance	4	8%	5	10%	0.185(NS)
Recurrence of Seizure within 24 hours after Control of SE	5	10%	7	14%	0.067(NS)
Death	4	8%	5	10%	0.185(NS)
Drug Related Side Effects	8	16%	5	10%	0.029 (S)
Discharge	29	58%	28	56%	0.871(NS)
Total	**50**	**100%**	**50**	**100%**	

Table 10: Final Outcome at Discharge

Adverse Effect of Drugs	Sodium Valproate (VPA)		Levetiracetam (LEV)		p value
	Patients	Percentage	Patients	Percentage	
Good (5-7)	42	84%	42	84%	0.894(NS)
Poor (1-4)	4	8%	3	6%	0.014 (S)
Death	4	8%	5	10%	0.020 (S)
Total	**50**	**100%**	**50**	**100%**	

RESULTS

Efficacy of VPA in aborting seizures within 30 minutes was found to be 74%. On the other hand, efficacy of LEV in aborting seizures within 30 minutes was found to be 82% in our study. There was a significant difference (p=0.003) found in efficacy of VPA and LEV. In our study, LEV is found to be more efficacious than VPA in controlling SE in children.

In VPA group, 100% efficacy seen in Malignancy, NCC and Viral encephalitis probably due to less number of cases. Apart from this, maximum efficacy was seen in Meningitis (91.67%) followed by febrile seizures (84.21%). Almost equal efficacy was seen in Poisoning (33.33%), Intracranial Hemorrhage (33.33%) and in case where no cause was found (37.50%).

In LEV group, 100% efficacy was found in Developmental malformations, Intracranial Hemorrhage, Malignancy, Poisoning, Tuberculomas and Viral encephalitis patients probably due to less number of cases. Apart from these, maximum efficacy was found in meningitis (88.24%) followed by febrile seizures (80%) and 42.86% in cases where no cause was found.

On comparison, It was found that LEV is as efficacious as VPA in controlling SE in patients of Malignancy (p=0.477) and Viral encephalitis (p=0.659). LEV has more efficacy in patients of poisoning (p=0.013), Intracranial Hemorrhage (p=0.013) and in patients where no underlying cause was found (p=0.049). VPA is found to be more efficacious in cases of Meningitis (p=0.026) and

febrile seizures (p=0.039). The efficacy of these drugs can not be compared in patients of Developmental Malformations and Tuberculomas as no cases were present in VPA group, and in cases of Neurocysticercosis where no case was present in LEV group. In our study, efficacy of VPA in controlling seizure activity in females was 81.82% and in males it was 67.86% as compared to efficacy of LEV which was found to be 81.82% in females and 82.14% in males. This comparison of efficacy has no statistically significant difference in females (p=0.696) and has statistically significant difference in males (p=0.022) proving that LEV is as efficacious as VPA in controlling SE in females and is more efficacious in males.

In this study, the efficacy of VPA was maximum in controlling Focal SE (86.49%) followed by Convulsive SE (74.42%) and Absence SE (0%). However, efficacy of LEV was found to be more in controlling Convulsive SE (83.33%) than Focal SE (50%) and there were no cases of Absence SE.

On comparison of efficacy, we found statistically significant difference in efficacy in all types of SE. This proves that LEV has more efficacy in controlling Convulsive SE whereas VPA has more efficacy in controlling Focal SE.

In this study, the efficacy of VPA was maximum in controlling Focal SE (86.49%) followed by Convulsive SE (74.42%) and Absence SE (0%). However, efficacy of LEV was found to be more in controlling Convulsive SE (83.33%) than Focal SE (50%) and there were no cases of Absence SE.

On comparison of efficacy, we found statistically significant difference in efficacy in all types of SE. This proves that LEV has more efficacy in controlling Convulsive SE whereas VPA has more efficacy in controlling Focal SE.

In our study, Maximum efficacy of VPA was found in moderate brain injury patients (100%) followed by mild brain injury patients (82.05%) and severe brain injury patients (25%). On the other hand, LEV also showed maximum efficacy in moderate brain injury patients (100%) followed by mild brain injury patients (89.47%) and severe brain injury patients (44.44%).

On comparison of efficacy, it was observed that both VPA and LEV had equal efficacy in controlling SE in minor and moderate brain injury patients, whereas LEV had more efficacy in severe brain injury patients. No literature was found to compare these results.

In VPA group, 1 patient (2%) had bradypnoea, 1 patient (2%) had bradycardia, 1 patient (2%) had vomiting, 6% patients had headache and 1 patient (2%) reported dizziness. In LEV group, 1 patient (2%) had hypotension, 1 patient (2%) had Raised Liver enzymes, 4% had Headache and 1 patient (2%) had bradycardia. On comparison, there was statistically significant difference (p=0.025) in incidence of headache between the two drugs i.e. VPA causing more headaches than LEV. There is no significant difference in both the drugs causing bradycardia (2% patients in each group). Rest of the adverse effects can not be compared as they were not present in both groups. LEV caused hypotension and raised liver enzymes in few patients and VPA caused bradypnea and dizziness in some patients. It was observed that adverse effects were very mild and less in number in both groups.

In VPA group, 8% of total patients needed intubation, seizures reoccurred in 10% of the patients within 24 hours after control and death was reported in 8% patients. 58% patients were discharged from the hospital 49 and 16% had adverse effects of VPA. In LEV group, 10% of patients needed intubation and ventilatory support, 14% of patients had reoccurrence of Seizures within 24 hours after control, Death was observed in 10% cases, 56% cases were discharged from the hospital and 10% of patients had adverse effects to LEV. On comparison, no significant differences were found between VPA and LEV group with respect to most of the secondary outcomes. However, VPA group had relatively more side effects than LEV group.

In our study, final outcome was measured using FIM score. In VPA group, final outcome was good in 84% patients and poor in 8% patients with 8% deaths. However, in LEV group 84% patients had good outcome while 6% patients had poor outcome and 10% patients expired. On comparison, both the drugs had equal proportion of patients (84% each) with good final outcome. However, there was statistically significant difference (p=0.014) in number of patients having poor final outcome in both groups (8% patients in VPA group and 6% patients in LEV group) which can be explained by slightly higher number of deaths in LEV group.

DISCUSSION

Comparison of Efficacy of VPA And LEV

Efficacy of VPA in aborting seizures within 30 minutes was found to be 74%. Our study results were comparable to the study conducted by Vincent Alvarez et al[6] (2011) in adult patients where efficacy of VPA in aborting seizures was 74.58% and Amiri-Nikpour MR et al[1] (2017) where efficacy was 78.18%. However, in contrast to our study, efficacy of VPA in other studies is mentioned below :

Table 11: Comparison with other studies

Author	Year of Study	Efficacy of VPA
U K Misra et al	2016	54.4%
Manjari Tripathi et al	2009	68.3%
Chu SS et al	2019	65.93%

This difference in efficacy can be justified by the difference in ethnic background of the patients, different sample size and different age wise distribution in our study as compared to above mentioned studies. Efficacy of LEV in aborting seizures within 30 minutes was found to be 82% in our study. The results in other studies were:

Table 12: Comparison with other studies

Author	Year of Study	Efficacy of VPA
Chu SS et al	2019	73.69%
Richard E Appleton et al	2020	70.00%
Mark D Lytle et al	2019	70.00%
Chakravarthi S et al	2015	59.00%
U K Misra et al	2016	76.3%
Nuzhat Noureen et al	2019	92.7%
Manjari Tripathi et al	2009	73.2%

Cessation rates as high as 85-95% have been reported but these studies have significant heterogenecity in design and outcomes[8,9]. Other possible explanation of differences in result are same as for VPA group (different sample size, different age group distributions).

There was a significant difference (p=0.003) found in efficacy of VPA and LEV. In our study, LEV is found to be more efficacious than VPA in controlling SE in children. Our results were not comparable to the other similar studies conducted by Kapur J et al[10] (2019), Brigo F et al[11] (2016) and Chu SS et al[12] (2019) which reported no significant difference between efficacy of these drugs. This can be explained by different ethnic background and different sample size of our study.

Comparison of Efficacy According to Gender

In our study, efficacy of VPA in controlling seizure activity in females was 81.82% and in males it was 67.86% as compared to efficacy of LEV which was found to be 81.82% in females and 82.14% in males. This comparison of efficacy has no statistically significant difference in females (p=0.696) and has statistically significant difference in males (p=0.022) proving that LEV is as efficacious as VPA in controlling SE in females and is more efficacious in males. We found no available data in the literature to compare this observation.

Comparison of Efficacy According to the Type of SE

In this study, the efficacy of VPA was maximum in controlling Focal SE (86.49%) followed by Convulsive SE (74.42%) and Absence SE (0%). However, efficacy of LEV was found to be more in controlling Convulsive SE (83.33%) than Focal SE (50%) and there were no cases of Absence SE.

On comparison of efficacy, we found statistically significant difference in efficacy in all types of SE. This proves that LEV has more efficacy in controlling Convulsive SE whereas VPA has more efficacy in controlling Focal SE. No relevant study could be found to compare these results.

Comparison of Efficacy According to Different Age Groups

In our study, Efficacy of VPA was maximum in age group of 12-16yrs (80%) followed by age group of 6m-<2yrs (78.57%) and 2-11yrs (70.97%). It was much higher than similar study conducted by James M Chamberlain et al[13] (2020) which was 34% in <5 yrs age group, 20% in 6-10yrs and 34% in 11-17yrs age group. This difference in observation can be explained by different sample size of studies, different ethnic background of the patients and different distribution of age groups.

The efficacy of LEV in controlling SE was maximum in age group of 6m–<2yrs (90%) followed by 2–11yrs (78.26%) and 12–16yrs (71.43%) age group. Our observed efficacy was higher than study done by James M Chamberlain et al[13] (2020) which was 37% in <5yrs age group, 39% in 6-10yrs and 40% in 11-17yrs age group. Another study by Stuart R Dalziel[15] (2019) showed 51% efficacy of LEV in <5yrs age group and 50% in >5 yrs age group. This difference in observation can be explained by different sample size of studies, different ethnic background of the patients and different distribution of age groups.

On comparison, the efficacy of LEV is found to be more in controlling SE in 6m-<2yrs and 2–11 yrs age group. However, equal efficacy is found in controlling SE in 12–16yrs age group. No similar study could be found to compare these results.

Comparison of Efficacy According to Glasgow Coma Scale

In our study, Maximum efficacy of VPA was found in moderate brain injury patients (100%) followed by mild brain injury patients (82.05%) and severe brain injury patients (25%). On the other hand, LEV also showed maximum efficacy in moderate brain injury patients (100%) followed by mild brain injury patients (89.47%) and severe brain injury patients (44.44%).

On comparison of efficacy, it was observed that both VPA and LEV had equal efficacy in controlling SE in Minor and Moderate brain injury patients, Whereas LEV had more efficacy in Severe brain injury patients. No literature was found to compare these results.

Comparison of Efficacy According to the Cause of SE

In VPA group, 100% efficacy seen in Malignancy, NCC and Viral encephalitis probably due to less number of cases. Apart from this, maximum efficacy was seen in Meningitis (91.67%) followed by febrile seizures (84.21%). Almost equal efficacy was seen in Poisoning (33.33%), Intracranial Hemorrhage (33.33%) and in case where no cause was found (37.50%). No literature was found to compare these observations.

In LEV group, 100% efficacy was found in Developmental malformations, Intracranial Hemorrhage, Malignancy, Poisoning, Tuberculomas and Viral encephalitis patients probably due to less number of cases. Apart from these, maximum efficacy was found in meningitis (88.24%) followed by febrile seizures (80%) and 42.86% in cases where no cause was found. These results were not comparable to the study done by Wani G et al[14] (2017) where efficacy of LEV was 40.4% in febrile seizures and 15.4% in meningitis.

Another study by Stuart R Dalzeal et al[15] (2019) reported 51% efficacy of LEV in controlling SE in febrile seizure patients. This difference is due to different sample size and different ethnicity of the patients.

On comparison, It was found that LEV is as efficacious as VPA in controlling SE in patients of Malignancy (p= 0.477) and Viral encephalitis (p=0.659). LEV has more efficacy in patients of poisoning (p=0.013), Intracranial Hemorrhage (0.013) and in patients where no underlying cause was found (p=0.049). VPA is found to be more efficacious in cases of Meningitis (p=0.026) and febrile seizures (p=0.039). The efficacy of these drugs cannot be compared in patients of Developmental Malformations and Tuberculomas as no cases were present in VPA group, and in cases of Neurocysticercosis where no case was present in LEV group.

COMPARISON OF SECONDARY OUTCOMES

VPA group

8% of patients needed intubation. This was comparable to the study by James M Chamberlain et al[13] (2020) where 11% patients were intubated. However, the intubation rates were much higher (31.7%) according to Manjari Tripathi et al[16] (2009) and 16.8% according to Kapur J et al[10] (2019). This was probably due to different sample sizes in these studies.

Seizures reoccurred in 10% of the patients within 24 hours after control. This was comparable to 9% reoccurrence in a study by James M Chamberlain et al[13] (2020) amd 11.2% as observed by Kapur J et al[10] (2019).

Death was reported in 8% patients, comparable to 8.4% mortality as observed by Vincent Alvarez et al[6] (2011). Less percentage of patients died in the studies by James M Chamberlain et al[13] (2020) (1%) and Manjari Tripathi et al[16] (2009) (4.8%) which can be explained by different ethnicity of patients and different sample sizes.

58% of patients were discharged in this group and 16% has side effects of VPA which are explained in details later in the discussion.

LEV Group

In this group, 10% of patients needed intubation and ventilatory support. This was comparable to 8% patients intubated in the study by James M Chamberlain et al[13] (2020). Need for intubation according to other studies were-

Table 13: Comparison with other studies

Author	Year of Study	Efficacy of VPA
Chakravarthi S et al	2015	18.18%
Mark D Lyttle et al	2019	30%
Stuart R Dalziel et al	2019	6%
Kapur J et al.	2019	14.2%
Suresh Kumar Angurana et al	2021	14.2%
Manjari Tripathi et al	2009	26.8%

These differences in results can be explained by different ethnic background of patients and different sample size in these studies.

Reoccurrence of Seizures within 24 hours after control is seen in 14% of patients. This was comparable to 10.7% by Kapur J et al[10] (2019), 9% by James M Chamberlain et al[13] (2020) and 9.7% patients by Suresh Kumar Angurana et al[17] (2021).

Death has been observed in 10% cases. This was comparable to 9.09% deaths observed by Chakravarthi S et al[18] (2015). Death percentages according to other studies were –

Table 14: Comparison with other studies

Author	Year of Study	Efficacy of VPA
Vincent Alvarez	2011	19.1%
Stuart R Dalziel	2019	0%
James M Chamberlain	2020	1%
Manjari Tripathi et al	2009	4.8%

We have 12% patients with adverse effects to LEV, similar to Cook R et al[19] (2019) and Mark D Lyttle et al[20] (2019). However, no adverse effects were observed by Nuzhat Noureen et al[21] (2019) and Chakravarthi S et al[18] (2015). All these differences in secondary outcomes can be explained by different ethnicity and different sample size of the studies.

On Comparison, no significant differences were found between VPA and LEV group with respect to most of the secondary outcomes. However, VPA group had relatively more side effects than LEV group. No literature is found to compare these results.

COMPARISON OF ADVERSE EFFECTS OF DRUGS

In VPA group, only 1 patient (2%) had bradypnoea. This finding was comparable to U K Misra et al[22] (2006) and Amiri-Nikpour MR et al[1] (2017) where also only 1 patient (4.3% and 1.8% respectively) had bradypnoea. 2% patients had bradycardia, 4% patients had vomiting, 6% patients had headache and 2% patients reported dizziness. Dizziness might be due to the use of Midazolam. Not much literature is found to compare these results, however we did not find any patients having raised liver enzymes whereas Amiri-Nikpour MR et al[1] (2017) reported raised liver enzymes in 5.4% patients and U K Misra et al[22] (2006) reported the same in 13.04% patients. This difference might be due to different sample size and different ethnicity of the patients.

In LEV group, 2% patients had hypotension which was comparable to the study by Mark D Lyttle et al[20] (2019) where also 2% patients had hypotension and Kapur J et al10(2019) where 0.7% patients had hypotension. Raised Liver enzymes were observed in 2% patients comparable to 0.7% patients in Kapur J et al10 (2019). Other adverse effects include Headache (4%) and bradycardia (2%). No literature is found to compare these results.

On comparison, there was statistically significant difference (p=0.025) in incidence of headache between the two drugs, VPA causing more headaches than LEV. There was no significant difference in both the drugs causing bradycardia (2% patients in each group). Rest of the adverse effects can not be compared as they are not present in both groups. LEV caused hypotension and raised liver enzymes in few patients and VPA caused bradypnea and dizziness in some patients. It was observed that adverse effects were very mild and less in number in both groups.

FINAL OUTCOME AT DISCHARGE

In our study, final outcome was measured using FIM score. In VPA group final outcome was good in 84% patients and poor in 8% patients with 8% deaths. However, in LEV group 84% patients had good outcome while 6% patients had poor outcome and 10% patients expired. This was comparable to the study done by Chakravarthi et al[18] (2015) where final outcome of LEV was good in 86.3% patients.

On comparison, both the drugs had equal proportion of patients (84% each) with good final outcome. However, there was statistically significant difference (p=0.014) in number of patients having poor final outcome in both groups (8% patients in VPA group and 6% patients in LEV group) which can be explained by slightly higher number of deaths in LEV group. No relevant study could be found to compare these results.

SUMMARY AND CONCLUSION

This was a prospective study, a randomised controlled trial done in Department of pediatric, Rajindra hospital Patiala to compare the efficacy and safety of VPA and LEV as a second line AED in status epilepticus in children. A total of 100 patients in the age group of 6m- 16 yrs of age presenting to pediatric emergency of Rajindra hospital Patiala were included in this study.

All the patients were quickly randomised into 2 groups by simple random sampling method and were assigned to either VPA or LEV depending on the order of recruitment to the study. Patients were enrolled in this study only after obtaining informed consent. As most of the patients were in altered sensorium, written informed consent were obtained from first degree relatives of the patients before inclusion in the study.

In our study 50 patients were given VPA and 50 patients were given LEV after midazolam infusion. There were 44% females and 56% males in both groups.

Efficacy of VPA and LEV in aborting seizures within 30 minutes was found to be 74% and 82% respectively. Hence, LEV found to be more efficacious than VPA in controlling SE in children.

In our study, efficacy of VPA in controlling seizure activity in females was 81.82% and in males it was 67.86% as compared to efficacy of LEV which was found to be 81.82% in females and 82.14% in males. It was observed LEV is as efficacious as VPA in controlling SE in females and is more efficacious in males.

In this study, the efficacy of VPA was maximum in controlling Focal SE (86.49%) followed by Convulsive SE (74.42%) and Absence SE (0%). However, efficacy of LEV was found to be

more in controlling Convulsive SE (83.33%) than Focal SE (50%) and there were no cases of Absence SE. On comparison, it was observed that LEV has more efficacy in controlling Convulsive SE whereas VPA has more efficacy in controlling Focal SE.

In our study, Efficacy of VPA was maximum in age group of 12-16yrs (80%) followed by age group of 6m–<2yrs (78.57%) and 2-11yrs (70.97%). The efficacy of LEV in controlling SE was maximum in age group of 6m-<2yrs (90%) followed by 2-11yrs (78.26%) and 12-16yrs (71.43%) age group. On comparison, the efficacy of LEV was found to be more in controlling SE in 6m–<2yrs and 2-11 yrs age group. However, equal efficacy was found in controlling SE in 12-16yrs age group.

In our study, Maximum efficacy of VPA was found in moderate brain injury patients (100%) followed by mild brain injury patients (82.05%) and severe brain injury patients (25%). On the other hand, LEV also showed maximum efficacy in moderate brain injury patients (100%) followed by mild brain injury patients (89.47%) and severe brain injury patients (44.44%).

On comparison of efficacy, it was observed that there is equal efficacy of VPA and LEV in controlling SE in Minor and Moderate brain injury patients, Whereas LEV has more efficacy in Severe brain injury patients.

In the present study, It was found that LEV is as efficacious as VPA in controlling SE in patients of Malignancy and Viral encephalitis. LEV has more efficacy in patients of poisoning, Intracranial Hemorrhage and in patients where no underlying cause was found. VPA is found to be more efficacious in cases of Meningitis and febrile seizures. The efficacy of these drugs can not be compared in patients Developmental Malformations and Tuberculomas as no cases were present in VPA group, and in cases of Neurocysticercosis where no case was present in LEV group.

In this study, no significant differences were found between VPA and LEV group with respect to most of the secondary outcomes. However, VPA group had relatively more side effects than LEV group. On comparison, VPA caused slightly more headaches than LEV. Both the drugs causing same proportion of bradycardia. LEV caused hypotension and raised liver enzymes in few patients and VPA caused bradypnea and dizziness in some patients. It was observed that adverse effects were very mild and were very few in both groups.

In our study, final outcome was measured using FIM score. In VPA group final outcome was good in 84% patients and poor in 8% patients with 8% deaths. However, in LEV group 84% patients had good outcome while 6% patients had poor outcome and 10% patients expired. On comparison, both the drugs had equal proportion of patients (84% each) with good final outcome. However, there was a statistically significant difference (p=0.014) in number of patients having poor outcome (8% patients in VPA group and 6% patients in LEV group) which can be explained by slightly higher number of deaths in LEV group.

In Conclusion, it was observed that LEV has higher efficacy than VPA-

- In controlling SE
- In male patients
- In Convulsive SE
- In 6m–<2 yrs and 2-11 yrs age group
- In severe brain injury patients (GCS≤8)
- In cases of poisoning and intracranial hemorrhage

Also, LEV has lesser adverse effects with some patients having hypotension and raised Liver enzymes. LEV group has more patients with poor outcome (FIM= 1-4)

On the other hand, VPA has more efficacy than LEV –

- In female patients
- In focal SE with impaired consciousness
- In Meningitis and febrile seizure patients

Also, VPA had more adverse effects than LEV with some patients having bradypnoea and dizziness. Hence, along with previously reported safety profiles and efficacy of LEV, it is suggested that LEV could be an appropriate (or even better) alternative to VPA as the first choice anti convulsant for second line treatment of pediatric SE.

LIMITATIONS

It was an open label trial. A double-blind design was way too complex in context of life threatening nature of SE.

- Small sample size of this study.
- Short term follow up.
- We did not confirm the presence or absence of seizure with an EEG. This approach is consistent with clinical practice because an EEG is generally not available on an emergency basis. However, purpose of this study was to revise and strengthen clinical practices and its findings will ultimately lead to strengthening of practices for using these drugs in SE.

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