



A comparative study to assess the efficacy of i.v valproate and i.v phenytoin as first line therapy in childhood status epilepticus

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Abstract

Background: Status epilepticus (SE) implies prolonged single seizure or multiple episodes of seizures lasting more than 30 min without regaining consciousness in between. Status epilepticus is a medical emergency and should be treated promptly to prevent morbidity and mortality. The pharmacological treatment is strictly a step up type starting from initial drug and going to higher drug sequentially in case of failure of previous drug to control seizure. Most of the existing medications are associated with several disadvantages and unfavorable side-effects. Sodium valproate is an anti-epileptic drug with several applications in different types of seizures such as absence, tonic-clonic, and myoclonic seizures and it is also effective in several types of partial epilepsy. Numerous studies have shown that intravenous sodium valproate may be a potential antiepileptic drug (AED) to be effective in SE. It may be used as a first-line AED in SE with a good seizure control.

Objectives: To compare the efficacy of i.v valproate versus i.v phenytoin as first line therapy in childhood status epilepticus in age group 1-15 yrs and to observe the incidence of various specific side effects of valproate and phenytoin. Other objectives were to observe any correlation of seizure control to patient characteristics like age, gender, diagnosis, seizure type, duration of seizure prior to admission and family/previous history of seizure disorder.

Methods: This prospective study was conducted on 100 children admitted with status epilepticus in the department of Pediatrics, Government Medical College, Amritsar. Children were divided into 2 groups A and B and were alternatively given loading dose (20mg/kg) of i.v valproate and i.v phenytoin respectively after initial short acting benzodiazepine midazolam (0.2 mg/kg) i.v / i.m as rescue medication. The efficacy of the two drugs were compared in terms of the following parameters:

1. Time to control seizure.
2. Number of patients having seizure recurrence.
3. Extent of cardiorespiratory compromise, if any in terms of hypotension and respiratory depression.
4. Drug specific adverse effects were also noticed.
5. Duration of hospital stay: included discharged, expired, as well as patients who left against medical advice.

Also any correlation of the seizure control to patient characteristics like age, gender, seizure etiology, seizure type, duration of seizure prior to admission and previous/family history of seizure disorder were studied.

Results: The mean time of seizure control in valproate group was 6.30 ± 1.02 mins and in phenytoin group was 6.80 ± 0.94 mins. Seizure recurred in 8% of patients in valproate group and 20% of patients in phenytoin group. No patient in either valproate or phenytoin group had significant cardiorespiratory compromise in the form of hypotension, respiratory depression or any drug specific adverse effects during the hospital stay.

Conclusion: We found i.v valproate as more efficacious compared to i.v phenytoin as first line therapy in status epilepticus in children 1-15 yrs of age with regard to time taken to control seizure ($p=0.044$). Since the oral drug of choice for long term use in various types of seizures nowadays is valproate, shifting from i.v to oral drug may be more convenient in case of valproate than in phenytoin. We found valproate to be superior and safe in our study and conclude that valproate can be used in suitable patients as first line therapy alternative to phenytoin in status epilepticus.

Keywords: valproate, phenytoin, comparative efficacy, status epilepticus.

Introduction

Status epilepticus (SE) implies prolonged single seizure or multiple episodes of seizures lasting more than 30 min without regaining consciousness in between.¹ Impending status epilepticus refers to any seizure lasting more than 5 minutes¹. Many believe that even a shorter period of seizure activity causes significant neuronal injury and that seizure self-termination is unlikely after 5 minutes.² Consequently, Lowenstein and others have suggested a duration longer than 5 minutes as a part of the criterion for SE.² The incidence of status epilepticus ranges between 10 and 60 per lakh population in various studies. Status epilepticus is most common in children younger than 5yrs of age with an incidence in this age group of >100 per lakh children.³

Status epilepticus is a medical emergency and should be treated promptly to prevent morbidity and mortality. The sooner and quicker the treatment of SE begins, the better is the prognosis and less chances of complications such as metabolic acidosis, respiratory arrest, aspiration pneumonia, neurogenic pulmonary edema, and lactic acidosis⁴.

Presently, the initial treatment of SE after the primary procedures, includes stabilization of Airway Breathing Circulation (ABC) alongside seizure control with benzodiazepines like midazolam, diazepam or lorazepam. Subsequent pharmacological treatment includes phenytoin,

and phenobarbital (in case phenytoin does not control the condition) and in later stages midazolam infusion, pentobarbital, valproate, paraldehyde and other newer drugs like levetiracetam, lacosamide and topiramate. The treatment is a step up type starting from initial drug and going to higher drug sequentially in case of failure of previous drug to control seizure⁵.

Most of the existing medications are associated with several disadvantages and unfavorable side-effects. Intravenous phenytoin is highly alkaline and is associated with pain and tissue irritation. Intravenous infusion of phenytoin may cause serious problems at the injection site such as the purple glove syndrome. Furthermore, since phenytoin contains propylene glycol, it can lead to a fall in blood pressure and cardiac arrhythmias⁶. Although new drug compounds such as Fosphenytoin are soluble in the injection solvent and do not bring about complications at the site of injection (as phenytoin does), their effectiveness is limited in the control of myoclonic, atonic, and absence seizures⁷.

Sodium valproate is an anti-epileptic drug with several applications in different types of seizures such as absence, tonic-clonic, and myoclonic seizures and it is also effective in several types of partial epilepsy. Intravenous sodium valproate has a convenient loading dose method for the treatment of SE with no drowsiness⁸. Various studies showed that intravenous sodium

valproate may be a potential AED to be effective in SE. It may be used as a first-line AED in SE with a good seizure control⁹. Unlike phenytoin, sodium valproate can be used safely and has no potential major cardiovascular compromises such as cardiac arrhythmia or hypotension¹⁰. Sodium valproate therefore may be an appropriate drug as the first-line treatment in SE. Currently intravenous phenytoin is the most common medication used to treat SE as the first step in pharmacological treatment. The purpose of our study was to compare the efficacy of sodium valproate and phenytoin as first line drugs in the treatment of SE in children 1-15yrs of age.

Materials and Methods

This prospective study was conducted on 100 children admitted with status epilepticus in the department of Pediatrics, Government Medical College, Amritsar.

Inclusion criteria:

1. Age group 1-15 yrs
2. Patient presenting with status epilepticus irrespective of etiology and seizure type.
3. Patient not having any significant cardiorespiratory compromise on admission.

Exclusion criteria

1. Patient already receiving antiepileptic drugs.
2. Known hypersensitivity to any of the two drugs. Those with preexisting liver

Respiratory depression was defined as fall in respiratory rate less than normal for that age¹³ i.e

1-5 years	20-30
5-10 years	15-20
>10 years	15-18

4. Drug specific adverse effects were also noticed. In case of valproate, the side effects considered were signs of liver damage like nausea, vomiting, upper stomach pain, or loss of appetite, low fever, dark urine, clay-colored stools or jaundice and even asymptomatic elevation of

disease were excluded from the valproate group.

3 Family history of febrile seizures.

Children were divided into 2 groups A and B and were alternatively given loading dose (20mg/kg) of i.v valproate and i.v phenytoin respectively after initial short acting benzodiazepine midazolam (0.2 mg/kg) i.v / i.m¹¹ as rescue medication. In case seizures were not controlled after loading dose of either of these drugs, we followed step up treatment shifting to I.V Phenobarbitone as next line drug and Midazolam infusion or other drugs after that as per protocol mentioned in introduction and review of literature.

The efficacy of the two drugs was compared in terms of the following parameters:

1. Time to control seizure. It was calculated from the start of drug administration to the point of complete cessation of motor activity associated with seizure.
2. Number of patients having seizure recurrence. It was defined as repeat episode of seizure within a time less than the half life of the drug administered.
Half life of phenytoin:- 12-24 hours¹²
Half life of valproate:-10-15 hours¹²
Average half life for both drugs is 12 hrs and that was taken as time for recurrence.
3. Extent of cardiorespiratory compromise, if any in terms of hypotension and respiratory depression.
Hypotension was defined as systolic BP < [70+(age*2)] mm Hg.¹³

hepatic transaminases. In case of phenytoin, the side effects like nausea, vomiting, constipation, dizziness, drowsiness, slurred speech, ataxia, swollen or tender gums, sleep problems (insomnia), nervousness, tremors, or rash were considered.

5. Duration of hospital stay: included discharged, expired, as well as patients who left against medical advice.

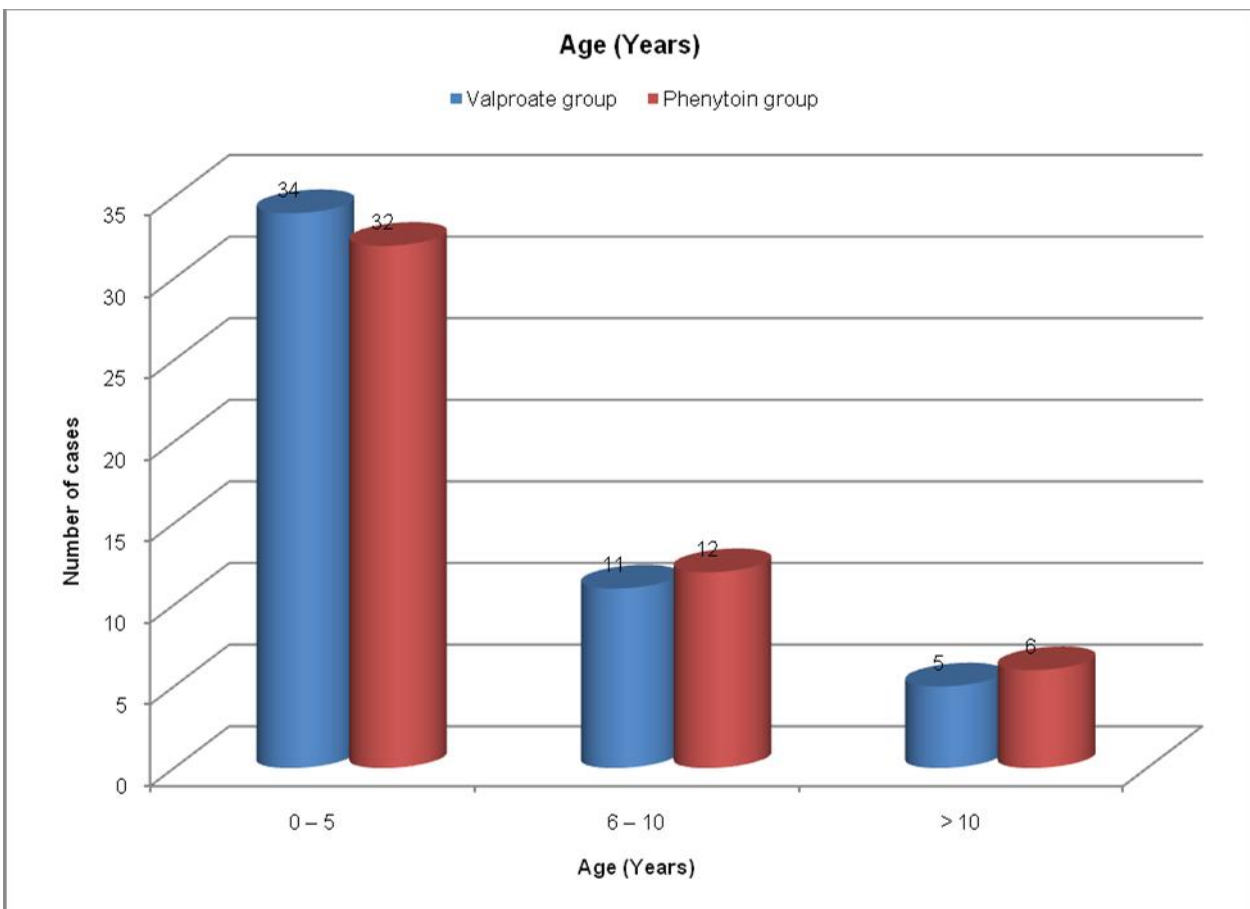
Also any correlation of the seizure control to patient characteristics like age, gender, seizure etiology, seizure type, duration of seizure prior to admission and previous/family history of seizure disorder was studied. Results so recorded were analysed statistically. p-value was

considered as a parameter to assess significance of various observations and results.

Results

In the valproate group mean age of presentation was 4.65 ± 4.07 yrs and that in phenytoin group was 5.02 ± 3.56 yrs as shown in Fig 1.

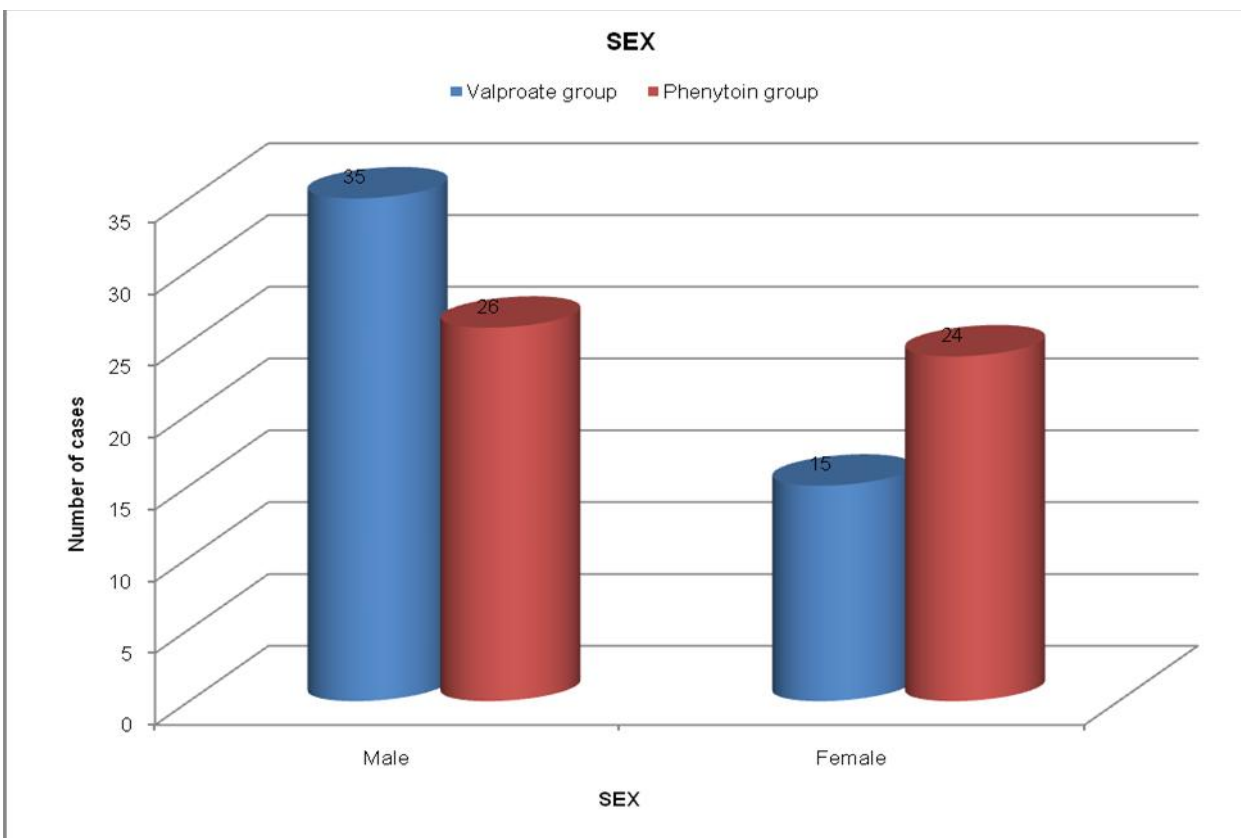
Fig 1.



In the valproate group 70% of patients were males and 30% were females. In phenytoin group 52%

were males and 48% were females as shown in Fig 2.

Fig 2.



The underlying etiology of seizures was diagnosed as shown in Table 1.

Table 1

Diagnosis	Valproate group N(%)	Phenytoin group N(%)	Total
Cerebral palsy	1(2%)	0	1
Complex partial	1(2%)	0	1
Dengue encephalitis	1(2%)	0	1
Downs syndrome	1(2%)	1(2%)	2
Dyselectrolytemia	1(2%)	1(2%)	2
Encephalitis	10(20%)	14(28%)	24
Hepatic encephalopathy	0	5(10%)	5
Intracranial bleed	1(2%)	0	1
Meningitis	7(14%)	7(14%)	14
MRCP	1(2%)	3(6%)	4
NCC	3(6%)	1(2%)	4
Pachygyria	1(2%)	0	1
Posthead trauma	1(2%)	0	1
Seizure disorder	18(36%)	15(30%)	33
Stroke	1(2%)	0	1
TBM	2(4%)	2(4%)	4
Viral encephalitis	0	1(2%)	1
Total	50	50	100

The type of seizures at presentation were as shown in Table 2.

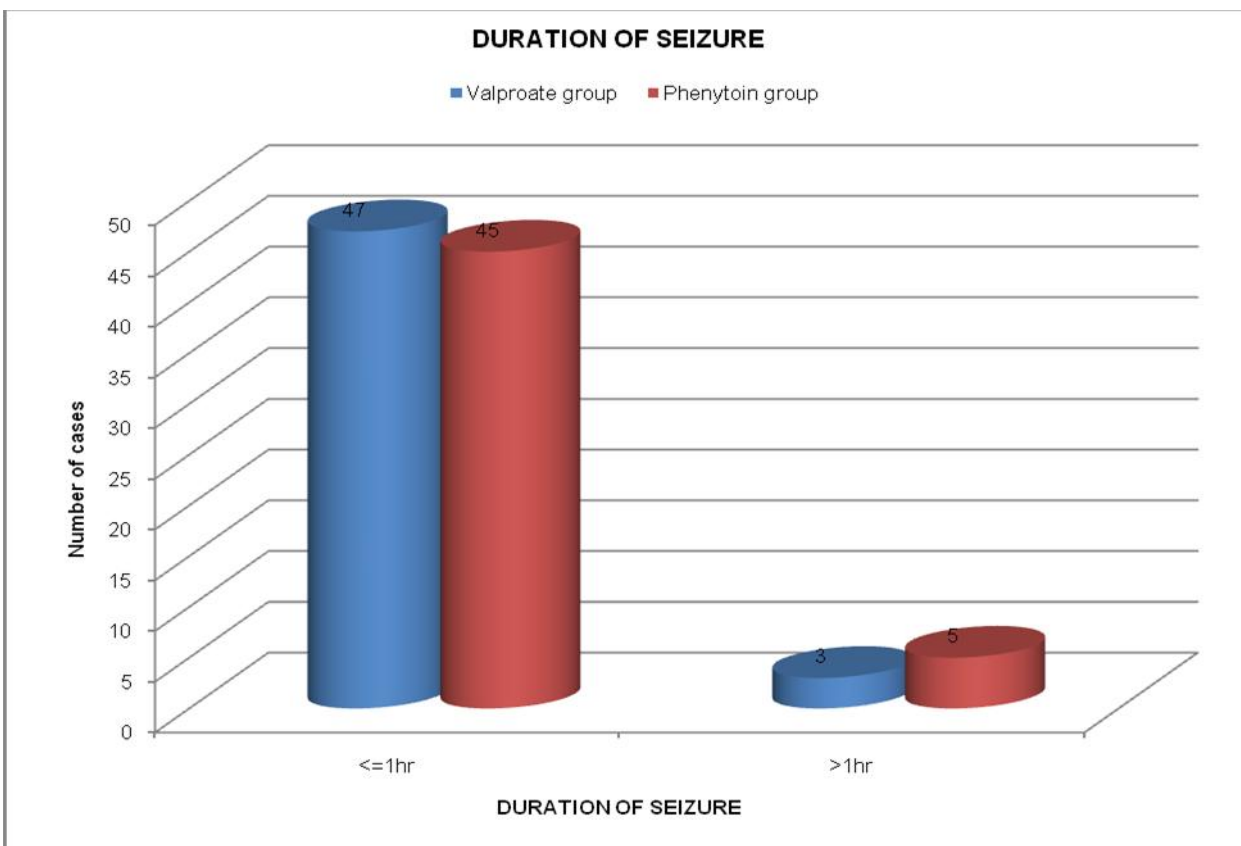
Table 2

Type of seizure	Valproate group N(%)	Phenytoin group N(%)	Total
Clonic	6(12%)	6(12%)	12
Complex partial	2(4%)	1(2%)	3
Focal	2(4%)	0	2
GTCS	23(46%)	37(74%)	60
Multifocal clonic	7(14%)	2(4%)	9
Myoclonic	1(2%)	0	1
Partial	1(2%)	1(2%)	2
Simple partial	4(8%)	2(4%)	6
Tonic	4(8%)	1(2%)	5
Total	50	50	100

The mean duration of ongoing seizure at initial presentation was **40.30 ± 25.06** mins in valproate

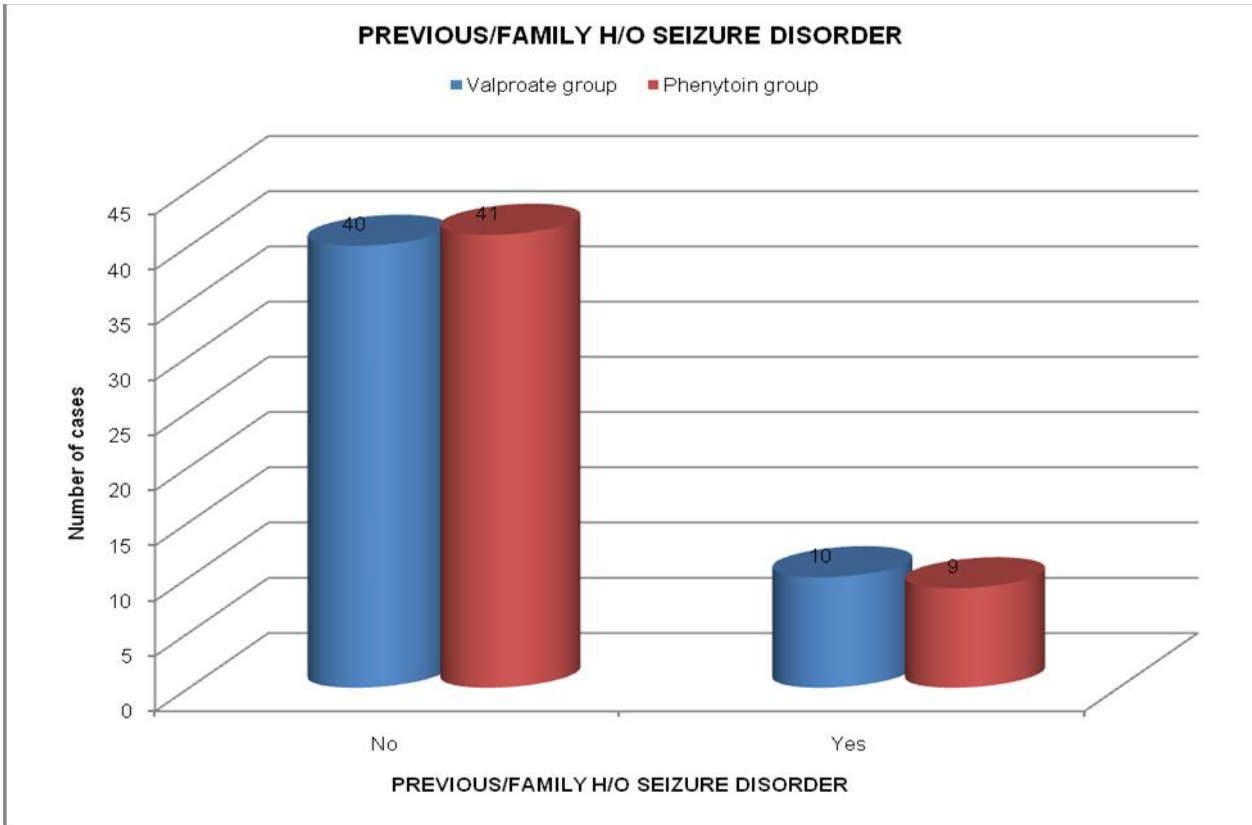
group and **45.20 ± 28.52** mins in phenytoin group as shown in Fig 3.

Fig 3.



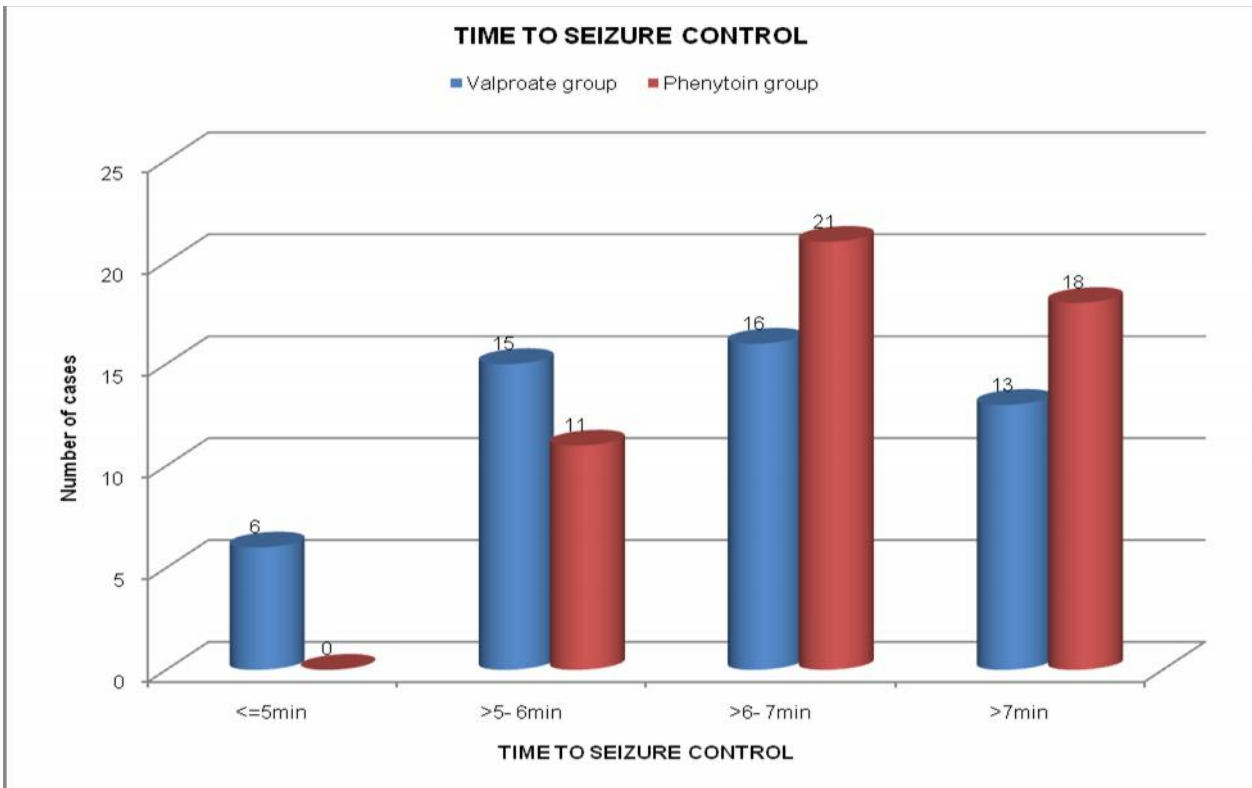
20% of patients in the valproate group and 18% of patients in phenytoin group had family

history/previous history of seizure disorder as shown in Fig 4.



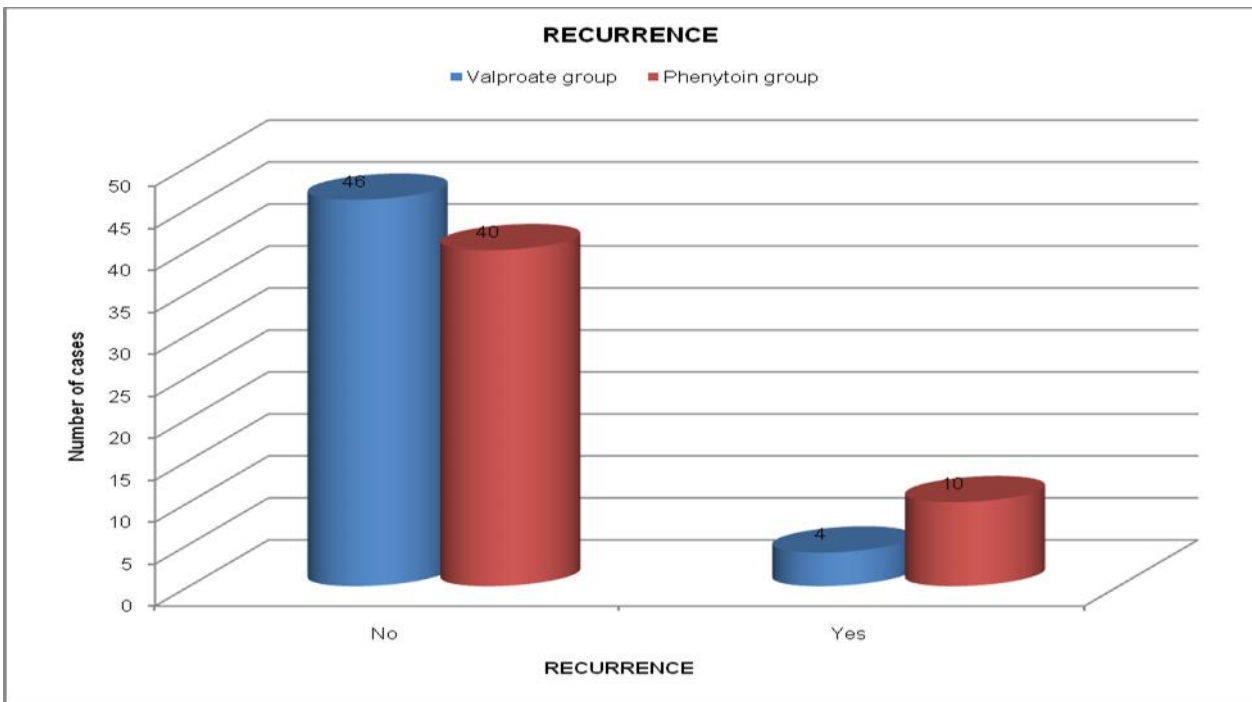
The mean time of seizure control in valproate group was 6.30 ± 1.02 mins and in phenytoin group was 6.80 ± 0.94 mins as shown in Fig 5.

Fig 5.



Seizure recurrence occurred in 8% of patients in valproate group and 20% of patients in phenytoin group as shown in Fig 6.

Fig 6.

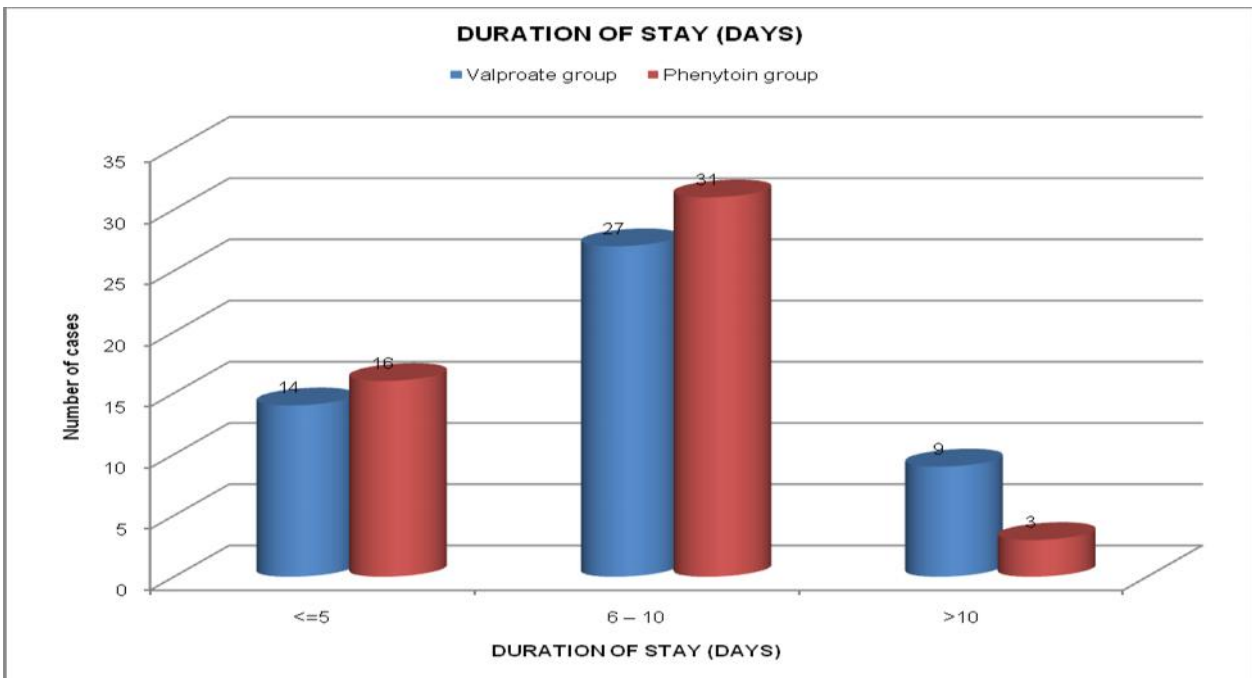


No patient in either valproate or phenytoin group had significant cardiorespiratory compromise in the form of hypotension or respiratory depression during or after the intravenous bolus administration of these drugs.

No patient in either valproate or phenytoin group had any drug specific adverse effects during the hospital stay.

The mean duration of hospital stay was 8.56 ± 4.90 days in valproate group and 7.46 ± 2.67 days in the phenytoin group as shown in Fig 7.

Fig 7.



Discussion

Statistically p value < 0.05 was considered significant. The following analysis was made:

Drug parameters:-

Time to control seizure

Valproate was found to be more efficacious than phenytoin in terms of time taken to control seizure irrespective of the underlying etiology. Mean time of seizure control in valproate group as 6.30 ± 1.02 mins. whereas in phenytoin group it was 6.80 ± 0.94 mins.

The calculated p -value being 0.044 was statistically significant.

6 out of 50 patients in the valproate group showed seizure control in ≤ 5 min compared to no such patients in the phenytoin group. Owing to the quicker and higher tissue distribution of valproate after intravenous bolus compared to phenytoin, the patients treated with valproate may have shown quicker seizure resolution. Further, with regard to time of seizure control, there was no correlation with other variables like underlying etiology or the duration of seizure prior to admission. Similar study by Shorvon et al in 2003 assessing the comparative efficacy of valproate and phenytoin showed intravenous sodium valproate to be more efficacious to intravenous phenytoin as first-line therapy. A study comparing the efficacy of sodium valproate and phenytoin in status epilepticus in 2006 by Misra et al also showed similar results regarding better efficacy of valproate although the criteria for assessment were different compared to our study. Percentage of patients showing seizure termination was the criteria used by Misra et al rather than time to control seizure as in our study. However the results were similar. In 2011, a study assessing the comparative efficacy and safety of intravenous valproate and phenytoin in children by Rai A, Aggarwal A, Mittal H and Sharma S also showed valproate to be superior in terms of time to regain consciousness in patients with deranged sensorium at presentation. Our study did not include this criteria for assessment. Also seizure control was assessed over a period of 24

hrs after starting the drug whereas in our study this period was 12hrs. The results in terms of efficacy of valproate were similar nevertheless. Other studies by Raad et al 2007, Agarwal et al 2007, Kanner et al 2008 and Somsak et al 2013 found valproate as non inferior to phenytoin in SE patients.

Recurrence

Out of 50 patients treated with phenytoin, 10 had repeat seizure within 12hrs, the time duration equivalent to 1 half life of the drug. The valproate group showed repeat seizure in 4 out of 50 patients.

This difference was statistically insignificant (p value = 0.084)

However the recurrence in valproate group was found to be 8% compared to 20% in phenytoin group which was quite less. Similar studies by Agarwal et al 2007 and Rai A et al 2011 also included the seizure recurrence criteria in the respective studies and found similar results to our study. The time period of assessment of recurrence was different in the 2 studies being 12 hrs in Agarwal et al and 24hrs in Rai A et al. The difference in the recurrence was found to be statistically insignificant as per our study. The underlying etiology may have contributed to recurrence with cases of meningitis, encephalitis and hepatic encephalopathy showing higher recurrence rates compared to less recurrence rates in seizure disorder, epilepsy and neurocysticercosis. There is a need to have more prospective studies in this regard preferably taking patients of a particular etiology and evaluating the risk of recurrence.

Short term/immediate adverse effects

Our analysis showed no incidence of any immediate adverse effects with either valproate or phenytoin. Blood pressure and respiratory rate evaluated after the drug administration showed no significant fall compared to the normal baseline evaluation at the time of admission. Similar studies by Agarwal et al 2007, Kanner et al 2008,

showed similar results to ours. However studies by Misra et al 2006 and Ahmad et al 2013 showed significant cardiovascular compromise in phenytoin group compared to valproate.

Further evaluation may be needed in case of patients presenting with significant cardiovascular compromise since our study included patients who were hemodynamically stable at admission.

Specific adverse effect

Our study showed no risk of developing any drug specific adverse effects with either valproate or phenytoin with regard to short term intravenous usage of these drugs.

Further our study showed no correlation of the seizure control to patient characteristics like age, gender, seizure etiology, seizure type, duration of seizure prior to admission and previous/family history of seizure disorder.

The mean duration of hospital stay in valproate group was 8.56 ± 4.90 days which was more than that in phenytoin group equal to 7.46 ± 2.67 days. The difference was statistically insignificant (p-value=0.182). Similar study by Somsak T et al 2013 also showed similar results to ours with no significant difference in duration of hospitalization in patients treated with valproate or phenytoin.

The duration of hospitalization in our study was probably influenced by the underlying disease process with most cases of meningitis or encephalitis having longer duration of stay compared to epilepsy/seizure disorder patients. However the seizure free period during hospital stay was found to be more in valproate group as the recurrence rate was lower. Valproate, despite controlling seizure in a lesser time compared to phenytoin had no significant effect in reducing the hospital stay which largely depended on the underlying etiology of seizure.

We found i.v valproate as more efficacious compared to i.v phenytoin as first line therapy in status epilepticus in children 1-15 yrs of age with regard to time taken to control seizure(p=0.044).

There was no significant difference in recurrence rate of seizures after i.v bolus of valproate or phenytoin in status epilepticus.

There was no significant risk of hypotension or respiratory depression with valproate or phenytoin when given as a slow i.v bolus.

There was no significant risk of specific adverse effects of valproate or phenytoin with short term i.v use.

The efficacy of i.v valproate or i.v phenytoin had no significant correlation to age, gender of the patient, etiology, type of seizure, duration of ongoing seizures and family/previous history of seizure disorder.

There was no significant difference in the duration of hospital stay in patients treated with valproate or phenytoin. The duration of stay correlate with the underlying cause of seizure.

Therefore as per our study i.v valproate may be a better alternative to i.v phenytoin as first line therapy in status epilepticus in children 1-15yrs of age showing quicker resolution of seizure with no immediate adverse effects. Since the oral drug of choice for long term use in various types of seizures nowadays is valproate, shifting from i.v to oral drug may be more convenient in case of valproate than in phenytoin. We conclude that valproate can be used in suitable patients as first line therapy alternative to phenytoin in status epilepticus.

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Conflict of interest: None declared

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