e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2023; 15 (6); 1215-1222

Original Research Article

Comparative Analysis between Valproate and Phenytoin in Convulsive Status Epilepticus in Pediatric Population

Prashant Kariya

Assistant Professor, Department of Pediatrics, Vedantaa Institute of Medical Sciences, Palghar, Maharashtra

Received: 10-04-2023 / Revised: 11-05-2023 / Accepted: 05-06-2023

Corresponding author: Dr Prashant Kariya

Conflict of interest: Nil

Abstract

Introduction: Status epilepticus (SE) is a common neurological emergency in children that calls for prompt and aggressive treatment and occasionally presents a therapeutic challenge to the attending physician. The main anti-epileptic impact is brought about by voltage-dependent sodium channels being inhibited. Phenytoin reduces sodium input into neurons, which reduces excitability, by acting on the intracellular portion of the ion channel. Since action depends on both use and concentration, it should start as soon as an effective concentration is attained. The most frequent neurologic emergency, generalized convulsive status epilepticus (GCSE), accounts for 1% to 2% of all visits to the emergency room. Any seizure lasting more than 30 minutes is considered to be in the status epilepticus (SE), regardless of whether awareness is affected or whether subsequent seizures occur without a break in consciousness.

Aims and Objectives: To compare the efficacy between valproate and phenytoin during status epilepticus among children.

Methods: A randomized double-controlled study was conducted on 100 pediatric patients who visited the outpatient department. Injections of sodium valproate (Valprol, 5 mL per 500 mg, Intas Pharmaceuticals, India), and sodium phenytoin (Ciroton, 2 mL per 100 mg, Ciron Pharmaceuticals, India) were used. The baseline characteristics were determined before the drug treatment and the outcome assessment factors were assessed after the drug treatment of each group at prescribed dosage and duration. required statistical analysis was conducted.

Results: The patients were divided equally into 2 groups phenytoin and valproate. Males are more in valproate group (60%). Generalized convulsive seizure are mostly seen in valproate group (90%) compared to phenytoin group (76%). Hypocalcemia is seen mostly in phenytoin (12%) than valproate (10%). The primary outcome is seen in 90% of phenytoin group and 82% in valproate group. The phenytoin group had a greater rate of additional medicine to control the seizure after control of the seizure by study drug (21.3%) compared to the valproate group (11.6%).

Conclusion: This study has demonstrated that phenytoin and valproate are equally effective in reducing seizure frequency in the treatment of paediatric convulsive status epilepticus

Keywords: Phenytoin, Valproate, Epilepticus, Convulsion, Seizure.

Introduction

In the first 16 years of life, 4.3% to 10.2% of children experience at least one seizure, making seizures the most prevalent pediatric neurological condition. Children under the age of 3 have the highest occurrence, and older kids have a lower

incidence. Status epilepticus (SE) is a common neurological emergency in children that calls for prompt and aggressive treatment and occasionally presents a therapeutic challenge to the attending physician [1]. It may cause substantial neuromorbidity and mortality if not treated right once. Since most seizures end quickly, seizures that last longer than five minutes should likely be evaluated as SE. According to estimates, SE will manifest in 1.4% to 16.2% of epileptic patients during the course of their lives [2]. The most frequent neurologic emergency, generalized convulsive status epilepticus (GCSE), accounts for 1% to 2% of all visits to the emergency room. Any seizure lasting more than 30 minutes is considered to be in the status epilepticus (SE), regardless of whether awareness is affected or whether subsequent seizures occur without a break in consciousness [19]. Seizures lasting more than five minutes are typically regarded as constituting an operational definition allowing for rapid treatment [3]. In actuality, seizures last on average under two minutes, and only 40% of those lasting between ten and thirty-nine minutes end without medical intervention. In addition to the number and length of seizures, the definition of GCSE has expanded to include the quantity and variety of medicines. There are four stages of GCSE: imminent, established, refractory, and super-refractory [4,5].

There is sometimes a postictal state lasting several minutes after a single generalized tonic-clonic seizure, during which the seizure threshold is markedly increased. By making this adjustment, homeostasis is restored and overexcitation is stopped. These defense mechanisms break down during GCSE, causing seizures to follow one another or possibly become self-sustaining [6,7]. Although the exact mechanism behind this is uncertain, current discoveries provide potential theories. Inhibition mediated by gamma-aminobutyric acid class A (GABAA) is less efficient, although glutamate's excitatory effects are increased. This affects the timing of anticonvulsant medication during GCSE and how GCSE develops into refractory GCSE, among other things [8,9].

Maintaining an airway and vital signs, notably blood pressure, is part of the initial care of GCSE. As cerebral blood flow depends on systemic pressure, arterial blood pressure should be kept above 120 mm Hg; pressures below 90 mm Hg must be avoided as a drop in glucose and oxygen may cause brain damage [18]. Monitoring the patient's temperature is important, and fever should be actively treated. The majority of febrile GCSE cases are in pediatric patients, and bringing body temperature back to normal reduces neurologic morbidity. Establishing intravenous (IV) access is necessary. Intraosseous delivery may be an option if IV access is not accessible [10,11].

Persistent generalized convulsions that last at least five minutes or two seizures with no full regaining of consciousness in between are signs of impending GCSE. A benzodiazepine may cause an impending GCSE to end spontaneously (BDZ). The preferred treatment for this stage is benzodiazepines, albeit the precise chemical substance utilized depends on the formulation accessibility and administration route. A BDZ fails to stop seizures when an established GCSE arises [12]. With no complete recovery of consciousness in between seizure occurrences, this is characterized by at least 30 minutes of intermittent or continuous seizures. Phenytoin (PHT), phenobarbital (PB), fosphenytoin (fPHT), or valproate are typically used as treatments (VPA). Levetiracetam and lacosamide have also been utilized recently, particularly when standard medications were unavailable due to drug shortages [13].

The main anti-epileptic impact is brought about by voltage-dependent sodium channels being inhibited. Phenytoin reduces sodium input into neurons, which

reduces excitability, by acting on the intracellular portion of the ion channel. Since action depends on both use and concentration, it should start as soon as an effective concentration is attained [14,15]. Numerous processes have been proposed, yet the exact mechanism of action remains unknown. VPA may enhance glutamic acid decarboxylase, decrease succinic acid decarboxylase and GABA-transaminase, and potentiate postsynaptic GABA. In order to prevent depolarization-induced, prolonged repeated firing, it may also block voltage-gated sodium channels and low-threshold T-type calcium channels [16,17].

Materials and methods

Study design

A randomized double-controlled study was conducted on 100 pediatric patients who visited the outpatient department of our hospital during the period of one year. A computer-generated, unstratified block randomization was utilised, with blocks that might be three, six, or nine squares in size. The allocation of random numbers was done by a person who was not involved in the study. Individual assignments were put into three-part alphanumeric coded serial numbers opaque sealed envelopes (SNOSE). A slip of paper with instructions for preparing the study medication was enclosed in the envelope.

Unaffiliated nursing staff produced the study drug concentration of 5 mg/mL in 0.9% normal saline dilution in the syringe after opening the packaging. The same alphanumeric identifier and study drug dose (4 mL per kg over 20 minutes) were written on each syringe. The identity of the patient was concealed from the person who produced the study drug. In this trial, injections of sodium valproate (Valprol, 5 mL per 500 mg, Intas Pharmaceuticals, India), and sodium phenytoin (Ciroton, 2 mL per 100 mg, Ciron Pharmaceuticals, India) were utilised. The trial medications were provided by the Institute's main pharmacy. Prior to seizure control, the participants, treating physicians, nurses who administered the medications, as well as the researchers and study staff, were oblivious of the treatment assignments.

Inclusion and Exclusion Criteria

Children with convulsive status epilepticus (tonic, clonic, tonic-clonic, and myoclonic, focal or generalised), aged three months to twelve years, were included.

Children with the following conditions were excluded from the study (i) recent or active hemorrhage from any site. (ii) non-convulsive status epilipticus. (iii) liver or kidney diseases. (iv) neurosurgery and head injury in past one month. (v) suspected allergy to drugs. (vi) platelet count less than 50,000. (vii) children with known epilepsy already on medication with valproate and levetiracetam for more than a month. (viii) known or suspected mitochondrial disorders.

Statistical analysis

All patients' data were examined in accordance with the groups to which they were assigned (Intention to treat). The Kolmogorov Smirnov Z test was used to determine whether the data were normal. Oneway analysis of variance (ANOVA) was used to compare continuous data with proportions using the Chi-square test, and Kruskal-Wallis was used to analyse continuous data with non-normal distribution. A P value of less than 0.05 was regarded as statistically significant for all two-tailed tests. Data analysis was done using Epi Info 7 (7.0.9.7, CDC, Atlanta, GA) and SPSS version 20.0 (IBM SPSS Statistics, Armonk, NY).

Ethical approval

The patients were given thorough information about the study by the authors. The patient's permission has been gotten. The concerned hospital's ethical committee has accepted the study's methodology.

Results

Table 1 shows the baseline characteristics of patients. The patients were divided equally into 2 groups phenytoin and valproate. Males are more in valproate group (60%). Generalized convulsive seizure are mostly seen in valproate group (90%) compared to phenytoin group (76%). Hypocalcemia is seen mostly in phenytoin (12%) than valproate (10%). Developmental delay mostly seen in valproate group (22%).

Table 1: Baseline characteristics of children in treatment groups

Characteristics	Phenytoin group (n= 50)	Valproate group (n= 50)	p-value
Age (months)	45 (44)	58 (45)	0.33
Male	27 (54)	30 (60)	0.90
*(cm) head circumference	-1.8 (2.1)	-1.2 (2.0)	0.33
*Body mass index, z score	46.7 (4.3)	48.5 (3.6)	0.17
Duration of seizure, prior to enrollment (min)	11 (11-24)	11 (11-16)	0.58
Fever history	33 (66)	22 (44)	0.14
Classification of status epilepticus, n (%)			0.45
Generalized convulsive	38 (76)	45 (90)	
Focal motor	8 (16)	4 (8)	
Focal onset evolving into bilateral convulsive SE	6 (12)	4 (8)	
Family history of seizure disorder	6 (12)	4 (8)	0.39
Developmental delay	7 (14)	11 (22)	0.61
Hypocalcemia	6 (12)	5 (10)	0.77
Abnormal CT head (n= 75)	4/24 (16)	4/17 (18)	0.38
MRI brain (n= 65)	6/13 (43)	3/14 (16)	0.44
Electroencephalographic abnormality	16/ 28 (57)	18/ 30 (60)	0.98
Cerebrospinal fluid pleocytosis	15 (30)	11 (22)	0.28
Etiology			0.29
Acute	23 (46)	11 (22)	
Remote	12 (24)	11 (22)	
Acute or remote	2 (4)	4 (8)	
Febrile status epilepticus	4 (8)	4 (8)	
Unknown (i.e., cryptogenic)	11 (22)	25 (50)	

The primary outcome is seen in 90% of phenytoin group and 82% in valproate group. The phenytoin group had a greater rate of additional medicine to control the seizure after control of the seizure by study drug (21.3%) compared to the valproate group (11.6%). 44% of patients were moved to the paediatric intensive care unit; the phenytoin group's mean stay was considerably shorter (table 2).

Table 2: Outcome in children with convulsive status epilepticus in treatment group

Outcome	Phenytoin group (n= 50)	Valproate group (n= 50)	p-value
Primary outcome, n(%)	45 (90)	41 (82)	0.39
Secondary outcomes			
Time to control seizure (min), mean (SD)	1 (2)	1 (2)	0.43
‡Additional drug to control seizure, n(%)	6 (12)	8 (16)	0.39
$Additional drug to control seizure, n (%)	10/ 47 (21.3)	5/ 43 (11.6)	0.34
Mechanical ventilation, n (%)	11 (22)	8 (16)	0.48
Length of mechanical ventilation (d), mean (SD)	3 (1.5)	8 (5.8)	0.09
PICU shifting, n(%)	22 (44)	11 (22)	0.05
Hospital stay (d), mean (SD)	6.3 (4.3)	5.8 (5.6)	0.56
PICU stay (d), mean(SD)	2 (4)	6 (12)	0.006
Functional status (at discharge), n (%)			0.47
GOS score-1	-	2 (4)	
GOS score-3	-	2 (4)	
GOS score-4	12 (24)	16 (32)	
GOS score-5	38 (76)	31 (62)	
#Functional status (at 3 mo), n (%)			0.07
GOS score-3	-	-	
GOS score-4	4 (8)	15 (30)	
GOS score-5	45 (90)	35 (70)	
Mortality, n (%)	-	2 (4)	-
Adverse event, n (%)	2 (4)	-	-

Discussion

To get antiepileptic medication concentrations that are therapeutic, intravenous loading is necessary. Phenytoin might not be the best choice; valproate, the preferred medication for most epilepsy cases, might. A total of 100 kids (3–12 years old) with motor focal seizures or second-episode generalized seizures were randomly assigned to either valproate or phenytoin. Diazepam was given to patients who were convulsing when they were seen. Monitoring was done for pulse rate, respiration rate, oxygen saturation, blood pressure, seizure recurrence, and consciousness. Seizure control for 24 hours was the main indicator of success. Cardiorespiratory parameter changes served as secondary outcome measures. The study reports Cardiorespiratory parameters did not alter significantly over time. Therefore, intravenous valproate is safe and effective, with a quicker return to awareness. For acute seizures, valproate can be used in therapy regimens [20].

The two neurological emergencies that affect children the most frequently are status epilepticus and acute protracted seizures. Depending on their length and causes, such events have significant rates of morbidity and mortality as well as poor long-term consequences. As a result, such seizures call for prompt treatment with the proper anticonvulsant dosages. The most widely used anticonvulsants for treating status epilepticus and acute protracted seizures are benzodiazepines, phenytoin, and phenobarbital. These drugs do, however, have a number of well-known side effects. Prior research on both adults

and kids has demonstrated the effectiveness and safety of valproate fast infusion in managing status epilepticus. In kids with status epilepticus and acute protracted seizures, the goal was to evaluate the efficacy and safety of quick-loading valproate compared to intravenous phenobarbital. In conclusion, quick loading of valproate is efficient and secure in managing acute protracted convulsive seizures and convulsive status epilepticus in children. An appropriate option for ending status epilepticus and acute protracted seizures in children should be intravenous valproate [21].

The effectiveness of phenytoin, levetiracetam, and valproate in treating pediatric convulsive status epilepticus was recently compared in a study. The percentage of patients whose convulsive status epilepticus was under control 15 minutes after the trial medication infusion ended was the primary outcome [19]. The secondary outcomes were the duration of ventilation, length of hospital stay, frequency of adverse events, need for additional medications to manage seizures, and functional level at three months. According to the study's findings, phenytoin, levetiracetam, and valproate all controlled pediatric convulsive status epilepticus equally well [22].

There is currently a shortage of evidence-based information to help manage patients with status epilepticus (SE) who are resistant to benzodiazepines. In randomized research, patients with SE resistant to benzodiazepines were compared to the effects of intravenous (IV) phenytoin and intravenous valproate (IV VA). As efficient as IV phenytoin is IV VA. It is more user-friendly, more tolerated, and an option to IV phenytoin for patients with benzodiazepine-refractory SE, particularly those with the cardio-respiratory disease. The superior results in patients with shorter SE durations (2 h) point to the urgent necessity for therapy [23].

The two neurological emergencies that affect children the most frequently are status epilepticus and acute protracted seizures. Depending on their length and causes, such events have significant rates of morbidity and mortality as well as poor long-term consequences. As a result, such seizures call for prompt treatment with the proper anticonvulsant dosages. The most widely used anticonvulsants for treating status epilepticus and acute protracted seizures are benzodiazepines, phenytoin, and Phenobarbital [20-22]. These drugs do, however, have a number of well-known side effects. In children with status epilepticus and acute protracted seizures, the goal was to evaluate the efficacy and safety of quick-loading valproate with those of intravenous phenobarbital. In conclusion, quick loading of valproate is efficient and secure in managing acute protracted convulsive status epilepticus and convulsive seizures in children [23,24].

Conclusion

This study has demonstrated that phenytoin and valproate are equally effective in reducing seizure frequency in the treatment of paediatric convulsive status epilepticus, with a comparable neurological outcome at three-month follow-up. The percentage of patients whose convulsive status epilepticus was under control 15 minutes after the trial medication infusion ended was the primary outcome. Secondary outcomes were the duration of ventilation, length of hospital stay, frequency of adverse events, need for additional medications to manage seizures, and functional level three months later (Glasgow Outcome Scale). Pediatric convulsive status epilepticus was equally well-managed by phenytoin and valproate.

References

1. McAbee GN, Wark JE. A practical approach to uncomplicated seizures in children. Am Fam Physician. 2000; 62:1109–16.

2. Vining EP. Pediatric seizures. Emerg Med Clin North Am. 1994;12:973–88.
3. Singhi S, Singhi P, Dass R. Status epilepticus: emergency management. Indian J Pediatr. 2003;70(Suppl 1): S17–22.
4. Hanhan UA, Fiallos MR, Orlowski JP. Status epilepticus. Pediatr Clin North Am. 2001;48:683–94.
5. Treatment of convulsive status epilepticus. Recommendations of the epilepsy foundation of America's Working Group on status epilepticus. JAMA. 1993;270:854–9.
6. Tullu MS, Mukhija V. Status epilepticus. In: Gupte S, editor. Recent Advances in Pediatrics. Special Volume 14. New Delhi: Jaypee Brothers; 2004. p. 1531.
7. Berg AT, Shinnar S, Testa FM, et al. Status epilepticus after the initial diagnosis of epilepsy in children. Neurology. 2004;63:1027–34.
8. Raj D, Gulati S, Lodha R. Status epilepticus. Indian J Pediatr. 2011;78:219–26.
9. Gulati S, Kalra V, Sridhar MR. Status epilepticus in Indian children in a tertiary care center. Indian J Pediatr. 2005;72:105–8.
10. Verrotti A, Ambrosi M, Pavone P, Striano P. Pediatric status epilepticus: Improved management with new drug therapies? Expert Opin Pharmacother. 2017;18:789–98.
11. Huff JS, Morris DL, Kothari RU, Gibbs MA. Emergency department management of patients with seizures: a multicenter study. Acad Emerg Med. 2001;8(6):622–628.
12. Capovilla G, Beccaria F, Beghi E et al. Treatment of convulsive status epilepticus in childhood: Recommendations of the Italian League Against Epilepsy. Epilepsia. 2013;54(suppl 7):23–34.
13. DeLorenzo RJ, Garnett LK, Towne AR et al. Comparison of status epilepticus with prolonged seizure episodes lasting from 10 to 29 minutes. Epilepsia. 1999;40(2):164–169.
14. Jenssen S, Gracely EJ, Sperling MR. How long do most seizures last? A systematic comparison of seizures recorded in the epilepsy monitoring unit. Epilepsia. 2006;47(9):1499–1503.
15. Lowenstein DH, Bleck T, Macdonald RL. It's time to revise the definition of status epilepticus. Epilepsia. 1999;40(1):120–122.
16. Shinnar S, Berg AT, Moshe SL, Shinnar R. How long do new-onset seizures in children last? Ann Neurol. 2001;49(5):659–664.
17. Wasterlain CG, Chen JW. Definition and classification of status epilepticus. In: Westerlain CG, Treiman DM, editors. Status Epilepticus. Cambridge, MA: MIT Press; 2006. pp. 11–16.
18. Lothman E. The biochemical basis and pathophysiology of status epilepticus. Neurology. 1990;40(5suppl 2):13–23.
19. DeLorenzo RJ, Towne AR, Pellock JM, Ko D. Status epilepticus in children, adults, and the elderly. Epilepsia. 1992;33(suppl 4):S15–S25.
20. Malamiri RA, Ghaempanah M, Khosroshahi N, Nikkhah A, Bavarian B, Ashrafi MR. Efficacy and safety of intravenous sodium valproate versus phenobarbital in controlling convulsive status epilepticus and acute prolonged convulsive seizures in children: a randomised trial. Eur J Paediatr Neurol. 2012 Sep;16(5):536-41.
21. Misra, U. K., Kalita, J., & Patel, R. Sodium valproate vs phenytoin in status epilepticus: a pilot study. Neurology, 2006;67(2): 340-342.
22. Vignesh, V., Rameshkumar, R. & Mahadevan, S. Comparison of Phenytoin, Valproate and Levetiracetam in Pediatric Convulsive Status Epilepticus: A Randomized Double-blind Controlled Clinical Trial. Indian Pediatr. 2020; 57: 222–227.
23. Agarwal, P., Kumar, N., Chandra, R., Gupta, G., Antony, A. R., & Garg, N. Randomized study of intravenous

valproate and phenytoin in status epilepticus. Seizure, 2007;16(6): 527–532.
24. Malamiri, R. A., Ghaempanah, M., Khosroshahi, N., Nikkhah, A., Bavarian, B., & Ashrafi, M. R. Efficacy and safety of intravenous sodium valproate versus phenobarbital in controlling convulsive status epilepticus and acute prolonged convulsive seizures in children: A randomised trial. European Journal of Paediatric Neurology, 2012;16(5): 536–541.