Changes in Cardiorespiratory Parameters during the Management of status Epilepticus in Children: A Prospective Randomized Controlled Study

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ABSTRACT

Introduction: Status epilepticus is a common pediatric neurological emergency. Study aimed to compare changes in hemodynamic parameters during the management of pediatric status epilepticus using different first line anticonvulsants.

Material and Methods: This prospective, randomized, study was done on Pediatric patients in the age group of 2 months to 16 years who present actively convulsing to the emergency department of pediatrics.

Results: The mean time to regain consciousness in phenytoin, levetiracetam and valproate groups was 122.3(± 45.4) minutes, 120.8(±42.8) minutes and 75.0(±30.7) minutes (mean±S.D) respectively. There was no significant difference in the three groups in various vital parameters like heart rate, systolic blood pressure, spo_2 and respiratory rate recorded at regular intervals in the acute stage (p value > 0.05).

Conclusion: All the three anticonvulsants studied are safe and efficacious, and there is no significant difference in the cardiorespiratory parameters of three groups, and the time to regain consciousness was less in valproate group in comparison to other groups.

Keywords: Cardiorespiratory Parameters, Levetiracetam, Phenytoin, Valproate, Status Epilepticus And Childhood Seizures

INTRODUCTION

Status epilepticus is a common pediatric neurological emergency that requires immediate and vigorous management and at times poses a therapeutic challenge to the treating physician. If not managed promptly, it may result in significant neuromorbidity and mortality.[1,2] The correct management strategy involves initial stabilization of vitals and prompt control of seizures, followed by evaluation and treatment of the underlying etiology.[3,4,5] The standard protocol for treatment of pediatric status epilepticus involves use of a benzodiazepine first followed by a long acting drug like phenytoin. Phenytoin remains the drug of choice for second-line therapy in status epilepticus that does not respond to lorazepam or diazepam and is also used for maintaining anti seizure effect after the initial therapy with diazepam.[6-8] But phenytoin carries high chance of potential side effects, medication interactions.[9] Despite the availability of a number of antiepileptic drugs that are approved for pediatric use, additional antiepileptic drugs that are effective and well-tolerated in children are still needed.

Approved by the Food and Drug Administration in 1997 in the treatment of status epilepticus, the use of intravenous valproate has been reported in an increasing number of studies, indicating relative ease of use, relatively good tolerability and suggesting that it may be efficacious[10-15]

Levetiracetam is another such drug with a broad-spectrum antiepileptic activity and a unique preclinical and pharmacological profile. In comparison with other IV anticonvulsants, levetiracetam has few known adverse effects, including a low risk of sedation, cardiorespiratory depression, or coagulopathy, and thus could be potentially useful in pediatric patients.[16] Currently, levetiracetam is approved by the United States Food and Drug Administration as adjunctive treatment for partial-onset seizures (POS) in patients ≥ 1 mo of age, myoclonic seizures in patients ≥12 yr of age with juvenile myoclonic epilepsy (JME), and primary generalized tonic-clonic seizures (GTCS) in patients ≥ 6 yr of age with idiopathic generalized epilepsy (IGE).[17] The European Medicines Agency (EMA) also approves the use of LEV as monotherapy in adolescence and adults ≥16 yr of age with newly diagnosed, partial-onset epilepsy with or without secondary generalization.[18]

The present study was devised to compare changes in hemodynamic parameters during the management of pediatric status epilepticus using different first line anticonvulsants.

MATERIAL AND METHODS

This prospective, randomized controlled study was conducted in the department of Pediatrics at Sher-i-Kashmir Institute of Medical Sciences, Srinagar during 2014-2017.

Pediatric patients in the age group of 1 month to 16 years who present actively convulsing (focal motor status or generalized convulsive status) to the emergency department of pediatrics were included in the study. All the concerned parents of the patients were informed about the purpose of the study and written informed consent was obtained from them. Also approval was taken from the hospital ethics

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How to cite this article: Mudasir Nazir, Sheeraz A. Dar, Wasim A. Wani. Changes in cardiorespiratory parameters during the management of status epilepticus in children: a prospective randomized controlled study. International Journal of Contemporary Medical Research 2019;6(5):E1-E5.

DOI: http://dx.doi.org/10.21276/ijcmr.2019.6.5.56

committee for the study.

Randomization

The patients who consented to participate in the study were then randomized into three groups. Randomization was done using a computer derived random-number sequence. One hundred and fifty pediatric patients of either sex, in the age group of 1 month to 16 years, who consented were enrolled in the study. The patients with following characteristic were excluded:

1. Age below 1 month
2. Children already receiving antiepileptic drugs
3. Children with evidence of meningitis or head trauma
4. Known hypersensitivity to drugs in study

All the enrolled patients were actively convulsing at admission. After proper assessment of airway and breathing IV access was established and iv diazepam @ 0.3mg/kg was given to control the seizures. Standard monitoring with recording of heart rate, blood pressure, respiratory rate and pulse oximetry (spo_2) was established in the mean time.

After obtaining written consent, a detailed assessment regarding type of seizures, any previous drug intake, and any history suggestive of meningitis and head trauma was recorded. After initial stabilization, patients were randomly assigned to three groups-

1. Phenytoin group –received iv phenytoin loading dose @20 mg /kg diluted in NS at a rate <1mg/kg/minute followed by maintainance dose of 5mg/kg day in two divided doses
2. Levetiracetam group – recieved iv levetiracetam loading dose 25mg/kg @ 3mg/kg/min followed by maintainance 25mg/kg/day divided 12hrly.
3. Valproate group- recieved iv valproate loading 25mg/kg @ 3mg/kg/min, followed by maintainance 20mg/kg/day in divided doses 12hrly.

The primary outcome variables included changes in respiratory rate, heart rate, blood pressure, and oxygen saturation at various time points in the three groups. Venous blood samples were drawn under aseptic conditions for measurement of a baseline haemogram, a liver function test, and analyses of blood urea, serum electrolytes, and blood sugar. Weight, height, and body mass index were calculated, and patients were examined for any neurologic deficits.

Monitoring

Pulse rate, respiratory rate, blood pressure, oxygen saturation, consciousness, and recurrence of seizures were monitored for a 24-hour period every 30 minutes for 1 hour, then hourly for 3 hours, and then every 2 hours for 12 hours, and then every 4 hours until 24 hours had passed. Patients were also monitored for development of any adverse to the given drugs.

STASTISTICAL ANALYSIS

The observed data was entered in the computer to analyze with the help of MS, Excel and SPSS version 15 for windows. The primary outcome measure is presented as mean and SD and statistically significant difference was evaluated using one way ANOVA. Statistically significant difference of qualitable variables among three groups was evaluated using Chi square/ Fischers exact test. A p value of <0.05 was considered as significant and a p-value less than .001 ($p<0.001$) as highly significant.

RESULTS

A total of 150 patients with status epilepticus were included in the studyunder three groups: phenytoin, valproate and levetiracetam groups. The mean(±SD) age of patients was 4.87(±3.84 years, 104 were males and 46 were females. The mean weight and height of our patient population were 14.27±6.83 kgs and 101±39.9 cms respectively. the most common type of seizure in our patients was generalized in 113 patients and focal in 37 patients. The demographic and clinical characteristics of the patients in different groups are given in table-1.

The cardiorespiratory parameter were: heart rate, systolic BP, respiratory rate and spo2, recorded at 0(basal), 30 and 60 minutes. The comparison of these parameters in different groups is given in table-2. The mean time to regain consciousness was 105.7±39.2 minutes in our patients, with intergroup comparison given in table-3 and table-4. The patients in valproate group regained consciousness earlier than both phenytoin and levetiracetam group patients on overall comparison and also in generalized seizure group. The time to regain consciousness after focal seizures was less in patients of valproate group as compared to the patients from phenytoin group. Although sample size is too small to draw any conclusions in focal seizures.

DISCUSSION

Standard management of seizures involves initial control of active seizures, followed by use of longer acting drugs, most

Parameter	Phenytoin (n=50)	Levetiracetam (n=50)	Valproate (n=50)	P value
Age(years)±SD	5.17±3.71	4.98±4.14	4.45±3.68	0.624
Gender	M=35,F=15	M=36,F=14	M=33,F=17	0.803
Weight(kg) ±SD	14.73±6.4	14.68±7.15	13.55±7.03	0.62
Height(cm) ±SD	107.5±44.96	99.69±40.87	96.54±35.20	0.38
Head Circumference (cm) ±SD	45.65±4.56	46.05±4.64	45.69±4.57	0.89
BMI(kg/m^2)	14.08±1.45	14.18±1.91	14.37±1.36	0.65
Seizure type	G=37,F=13	G=37,F=13	G=39,F=11	0.87
G-generalized, F-focal				

Table-1: Comparison of clinical characteristics in study population

Parameter		Phenytoin (n=50)	Levetiracetam (n=50)	Valproate (n=50)	P value
Heart rate	Basal ±SD	125±23	126±24	127±19	0.439
	30 min±SD	112±20	115±21	118±17	0.222
	60min±SD	109±19	111±20	115±17	0.179
Systolic BP (mmHg)	Basal ±SD	93±10	91±10	95±11	0.187
	30 min±SD	93±10	91±10	95±11	0.236
	60min±SD	89±9	87±9	91±10	0.159
Respiratory Rate	Basal ±SD	28±5	29±6	29±4	0.243
	30 min±SD	25±5	26±6	26±4	0.599
	60min±SD	25±5	26±5	25±4	0.691
Saturation (SPO_2)	Basal ±SD	95±3.4	95±3.5	94±3.6	0.351
	60min±SD	98±0.9	99±0.8	98±0.6	0.074

Table-2: Comparison of cardiorespiratory parameteres in study population

Seizures	Phenytoin	Levetiracetam	valproate	P value
Total (n=150)	122.34±45.406	120.82±42.796	75.04±30.657	<0.0001
Generalized seizures (n=113)	122.19±46.93	124.46±41.45	74.03±30.82	<0.0001
Focal seizures (n=37)	122.8±42.54	110.46±46.55	78.64±31.27	0.039

Table-3: Comparison of time taken to regain consciousness

Comparison	P value		
	Total	Generalized	Focal
Phenytoin vs levetiracetam	>0.05	>0.05	>0.05
Phenytoin vs valproate	<0.001	<0.001	<0.05
Levetiracetam vs valproate	<0.001	<0.001	>0.05

Table-4: Comparison of time taken to regain consciousness with intergroup comparison

often intravenous. Active seizures are usually controlled with shorter acting agents like benzodiazepines.[19] Longer acting agents are started latter to augment seizure control and to prevent recurrence. Long term anticonvulsant treatment is started after two or more generalized unprovoked seizures or focal seizures. To attain rapid antiepileptic drug levels intravenous loading doses are employed initially. Currently phenytoin is the most commonly used iv agent in the setting of acute seizure treatment in children.[20] But phenytoin carries a high risk of side effects and drug interactions[21-24], engendering a need for newer drugs which are both effective and well tolerated. IV formulations of Levetiracetam and valproate have recently been approved for use in children and can be used as alternatives to phenytoin in the treatment of seizures and epileptic syndromes, especially in patients allergic to the latter and in progressive myoclonic epilepsy.[20,25,26] Lack of life threatening cardiovascular, neurological or local adverse effects makes them useful in emergency situation as well. The efficacy of levetiracetam and valproate in acute repetitive seizures and status epilepticus has been demonstrated in a number of studies, both in adults and pediatric patients.[15,27-30] The present study compares changes in hemodynamic parameters during administration of iv phenytoin, iv levetiracetam and iv valproate for acute seizure management in children. We included children with a second generalized convulsive status or a focal seizure status only, because they require long-term antiepileptic therapy. According to the standard seizure management protocol, intravenous Diazepam was administered to control active seizures. The duration of action for diazepam is 20-30 minutes.

All the three groups were comparable in age and sex distribution and in various anthropometric parameters like weight, height, head circumference and body mass index. No statistically significant difference in primary outcome was observed in different age groups (1 month- 1 year, 1-5 years, 5-16 years) signifying that all the three drugs were equally safe in acute seizure control in different age groups ($p<0.05$). F Brigo et al in a review of five RCTs to evaluate efficacy and safety of intravenous valproate in the treatment of status epilepticus (including generalized convulsive status epilepticus), concluded that compared with phenytoin, valproate had statistically lower risk of adverse effects, with no differences in seizure freedom at 24 hours. This review suggests that IV valproate has a better tolerability than IV phenytoin in treatment of generalized convulsive status epilepticus, without any statistically significant differences in terms of efficacy.[31]

The mean time to regain consciousness in phenytoin, levetiracetam and valproate groups was 122.3(± 45.4) minutes, 120.8(±42.8) minutes and 75.0(±30.7) minutes (mean±S.D) respectively. Patients in valproate group regained consciousness earlier than both phenytoin and levetiracetam group patients($p<0.0001$). In the study by Anuradha et al in which patients initially received iv diazepam, no difference in time taken to regain consciousness was observed between valproate and phenytoin groups.[30] Yu et al found that the time taken for mental status recovery after iv valproate was less than 60 min in all patients with status epilepticus.[29] However,

in their study iv diazepam was not used before valproate loading. To the best of our knowledge no such comparative study was available for iv levetiracetam.

There was no significant difference in the three groups in various vital parameters like heart rate, systolic blood pressure, spo_2 and respiratory rate recorded at regular intervals in the acute stage (p value > 0.05). Significant respiratory depression was not reported in any patient in this study. Our findings were consistent with the findings of Yu et al[29] who concluded that there was no change in cardiorespiratory parameters after rapid iv infusion of valproate. Ramael S et al used iv levetiracetam in their study and found no significant change in cardiorespiratory parameters.[32]

Adverse un-wanted side effects reported in our study were somnolence in two patients in levetiracetam group at one week follow up. The age of both the patients was less than three months. The effects were not severe to warrant drug discontinuation. One patient from valproate group had drug induced hepatotoxicity (transamonitis) at three months follow up requiring drug discontinuation. The age of the patient was 11 months. Four patients in phenytoin group had drowsiness and two had episodes of ataxia after every dose of oral phenytion at 1 week follow up.

Pharmacokinetic studies have established a benign safety profile for levetiracetam. Li et al prospectively analyzed 120 patients There was a side effect incidence rate of 47.5% which included somnolence, dysphoria, nervousness, somnipathy, astitia, and debilitation.[22-25] Valproate is known to cause liver dysfunction on long term use, especially in children less than 3 years of age but intravenous infusions have been found to be very safe in a number of studies. When the safety profiles of valproate and levetiracetam are compared with phenytoin, the former two drugs are preferred both in emergency and long term use. In our study, patients from phenytoin group had no serious adverse effects other than drowsiness and ataxia in few. So phenytoin was better tolerated in our patients both as infusion and as long term maintainance, as compared to poor tolerance reported in other studies.[12-18]

CONCLUSION

There was no significant difference in the three groups in various vital parameters like heart rate, systolic blood pressure, spo_2 and respiratory rate recorded at regular intervals in the acute stage. Moreover, all the three anticonvulsants studied are safe and efficacious, although the time to regain consciousness was less in valproate group in comparison to other groups.

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Source of Support: Nil; **Conflict of Interest:** None

Submitted: 04-04-2019; **Accepted:** 09-05-2019; **Published:** 30-05-2019