Efficacy and Safety of Intravenous Sodium Valproate in Convulsive Status Epilepticus in Children in Shahid Sadoughi Hospital

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Abstract

Objective

Status epilepticus (SE) is the most common pediatric neurologic emergency with high mortality and morbidity. There is no consensus on the drug of choice in the treatment of children. The purpose of this study was to evaluate the clinical efficacy and safety of intravenous sodium valproate as a third-line drug in the treatment of generalized convulsive SE of children.

Materials & Methods

In a retrospective study, medical records of those children who were admitted to Shahid Sadoughi Hospital of Yazd due to refractory generalized convulsive SE and were treated by intravenous sodium valproate as a third-line drug from 2009 to 2011 were evaluated.

Results

Six girls and five boys with a mean age of 5.12 ± 1.2 years (range: 3 - 9.6 years) were evaluated.

Intravenous valproate was effective for cessation of seizures in seven patients (63.6%). The mean dose of valproate for stopping seizures was 27.1 ± 1.4 mg/kg/day.

Children whose seizures were controlled by sodium valproate were older than non - responsive children (mean ± SD: 4.8 ± 1.2 years vs. 3.1 ± 0.43 years, p = 0.03) and they also had shorter ICU stay days (mean ± SD: 2.6 ± 1.4 days vs. 5.6 ± 2.8 days, p= 0.01).

Two children had mild and transient nausea and vomiting. None of them had cardiopulmonary or severe paraclinical side effects.

Conclusion

Intravenous sodium valproate may be used as an effective and safe third-line antiepileptic drug in the treatment of pediatric generalized convulsive status epilepticus.

Keywords: Status epilepticus; Refractory status epilepticus; Intravenous sodium valproate; Children

Introduction

Status epilepticus (SE), which is defined as a seizure that persists more than 30 min or two or more sequential seizures without recovery of consciousness between them, is the most common pediatric neurology emergency (1).

Generalized convulsive SE is the most common type that has a significant morbidity and mortality (2) which is directly dependent on immediate and appropriate medical

therapy. The correct management strategy involves initial stabilization of airways, breathing and circulation, prompt control of seizures, evaluation and treatment of the underlying etiology (1, 3,4).

Refractory status epilepticus (RSE) is defined as ongoing seizures despite the use of two first-line drugs, usually a benzodiazepine plus either phenytoin or phenobarbital, or which continues for more than 60 minutes in spite of adequate treatment (3,5). All these patients must be managed in a pediatric intensive care unit (ICU) with aggressive monitoring of their hemodynamic and respiratory status. There is no consensus on the choice among available options for treatment of RSE in children and the drug of choice in its treatment often depends on the experience of a specific center (3).

If cessation of the seizures cannot be achieved, other therapeutic strategies such as thiopental, pentobarbital, propofol, midazolam drip, intravenous valproate, ketogenic diet, lacosamide and intravenous levetiracetam may have to be used (1-3, 6-9).

Valproate is a simple branched-chain carboxylic acid with a chemical structure very similar to that of short-chain fatty acids. Its mechanism of action is not fully determined, but it is thought to increase both synthesis and release of the inhibitory neurotransmitter of gamma amino butyric acid. Usage of valproate in the treatment of status epilepticus was approved by the Food and Drug Administration in 1997. If seizures do not respond to two conventional first-line drugs, intravenous valproate may be useful and efficient, especially when the setting of intubation and artificial ventilation are not available (1, 10 -12).

Although intravenous valproate may be used as a second-line antiepileptic drugs in treatment of pediatric status epilepticus (2, 13-15).

Less than three-year-old children are at a considerably increased risk of developing lethal hepatotoxicity, especially in those who have a history of hepatic disease, taken polytherapy of antiepileptic drugs, or with severe seizure disorders accompanied by mental retardation (16).

The purpose of this study was to investigate the clinical efficacy and safety of intravenous sodium valproate as a third-line drug in the treatment of children's refractory generalized convulsive status epilepticus in Shahid Sadoughi Hospital,Yazd, Iran.

Materials & Methods

In a retrospective study with a non-random census sampling method, medical records of all children with generalized convulsive status epilepticus who were admitted to ICU of Shahid Sadoughi Hospital, Yazd, Iran from 2009 to 2011 and were treated with intravenous sodium valproate, were evaluated.

Care was taken to select patients with the below mentioned criteria:

1. No history of urea cycle disorder, hepatic diseases or kidney dysfunction (either past or present) based on history and physical exam, hypotension and electrolyte abnormality
2. First time occurrence of status epilepticus
3. BUN, Cr, sodium, potassium, total calcium, and glucose in normal limits to exclude electrolyte abnormalities and hypoglycemia as the cause of seizure
4. Admission to the ICU for aggressive cardiac monitoring
5. Seizures not responding to benzodiazepines plus either phenytoin and phenobarbital and therefore, sodium valproate used as a third-line drug

The risk of developing lethal hepatotoxicity is high in less than three-year-old children (16); therefore, in our department, sodium valproate treatment is used in older than three-year-old children and its protocol in SE was as follows:

An initial dose of 15 mg/kg was given intravenously at the rate of 3 mg/kg/min and followed by continuous infusion of 20 mg/kg/day. If no response was seen or seizures recurred, the dose of the drug was increased up to 30/mg/kg/day. If the drug was effective in the control of seizures, it would be infused with the same dose for 12 hours and then tapered and ceased during the next 12 hours.

Treatment was considered to be effective when intravenous sodium valproate stopped clinical seizures.

Blood pressure, electrocardiography, respiratory rate and oxygen saturation were continuously monitored to detect cardiopulmonary complications. Liver function tests, complete blood count and ammonia level were measured daily. Measurement of serum sodium valproate level

and video electroencephalography monitoring were not available in our hospital.

If seizures were not stopped with the maximum dose of sodium valproate infusion drip, it was regarded to be unsuccessful, so the drug use was discontinued and benzodiazepines or pentobarbital drip was introduced.

The data were gathered from the patient's medical records in pediatric ICU. Variables such as age, sex, neuroimaging and EEG findings, neurodevelopmental delay, seizure control, adverse effects (hypotension, respiratory depression needing intubation and mechanical ventilation, gastrointestinal upset, dizziness, headache, hepatotoxicity, hyperammonemia and thrombocytopenia) and days of stay in the ICU were carefully recorded. Informed consent was obtained from the subjects' parents.

Results

Eleven children including six girls (54.5 %) and five boys (45.5%) with the mean age of 5.12 ± 1.2 years (range: 3 - 9.6 years), were evaluated.

From the viewpoint of etiologic classification of status epilepticus, eight (72.7%) were symptomatic, two (18.2%) idiopathic and one (9.1%) was febrile status epilepticus. Symptomatic etiologies included inborn error of metabolism in four (50%), encephalitis in two (25%), each of poisoning and hypoxic ischemic encephalopathy in one child (12.5%).

The seizure type was generalized tonic- clonic in seven (63.6%), generalized clonic in three (27.3%) and generalized tonic in one (9.1%) patient.

Intravenous valproate was effective for cessation of seizures in seven patients (63.6 %) and the mean dose of valproate for stopping of seizures was 27.1 ± 1.4 mg/kg/day.

Comparison of some clinical and paraclinical characteristics of patients based on seizure control are presented in Table I which indicates that the mean age of patients whose seizures were controlled by sodium valproate was more than non- responsive children and the patients whose seizures did not stop by sodium valproate had a prolonger ICU stay.

Two children had mild and transient nausea and vomiting. None of them had cardiopulmonary complications or severe clinical and paraclinical side effects such as hepatotoxicity, thrombocytopenia with abnormal bleeding and severe hyperammonemia.

Discussion

Intravenous valproate can be used as an alternative to phenobarbital and phenytoin in the treatment of seizures and epileptic syndromes, especially in allergic patients and in progressive myoclonus epilepsy. Lack of life threatening cardiovascular, neurological, or local adverse effects supported its use in emergency conditions as well (9).

A few researches have been carried out regarding the use of intravenous valproate in pediatric SE.

In the present study, intravenous valproate as a third-line drug was effective in controlling generalized seizures that were refractory to benzodiazepine and phenytoin or phenobarbital in 63.6% of children and this efficacy rate is similar to 63.3% in another study (17,18).

Other studies of valproate effectiveness for seizure control in pediatric SE showed a response rate ranging from 58 to 100% (9, 12, 17-24). Possible explanations for these discrepancies are differences in race, sample size, patient age and drug dosage.

In a systematic review, Sofou et al. concluded that intravenous valproate as a third-line drug was effective and safe in children's convulsive status epilepticus which was refractory to diazepam and phenytoin (11). On the other hand, in a study in Taiwan, Chang et al. concluded that intravenous valproate can be used as the first choice in the treatment of SE and acute repetitive seizures in children (9).

In a randomized unblinded study, Misra et al.'s study found that in the treatment of SE, valproate was superior both as a first-line (66% vs. 42%) and second-line (79% vs. 25%) drug (15).

In the present study, the mean dose of valproate for stopping seizures was 27.1 ± 1.4 mg/kg/day which is lower than the study in Taiwan (31.2 ± 26.45 mg/kg/day) (9). Sodium valproate is often used in a dosage of 20-30 mg/kg at a rate of about 3 mg/kg/min and it may also be administered as a rapid intravenous infusion for up to 6 mg/kg/min to a maximum dose of 45 mg/kg (16).

The results of this study also indicate that undesirable side effects were not seen in valproate use. Safety results of this study support other ones (9, 19-24). None of

the patients in the present study required ventilation or developed hypotension. Cardiovascular side effects such as hypotension or arrhythmia and respiratory depression are rare in administration of intravenous valproate even in high doses and rapid infusions (25) and since the drug showed no hemodynamic adverse effects, it can be useful in SE of children and elderly patients with cardiovascular instability who may be at increased risk for adverse reactions due to phenytoin/fosphenytoin (21,26,27).

The incidence of side effects in patients taking intravenous valproate is low (less than 10%). These side effects are mainly hypotension, dizziness and thrombocytopenia (17) and the drug seems to be well tolerated in patients with SE (27). Valproate hepatotoxicity which has been explained as four distinct subtypes; namely, a transient elevation of liver enzymes, hyperammonemia, toxic hepatitis and a Reye-like syndrome (26) are rare above the age of three and in monotherapy (16).

Based on results of the present study, intravenous valproate use is cost-effective considering no respiratory depression and also no need for ventilator support coincided with short stay days in the ICU.

The limitations of this study were lack of video-EEG monitoring and its inability to recognize electrographic seizure cessation and the small number of our patients. Therefore, it is necessary to conduct randomized clinical trials to evaluate and compare the efficacy of intravenous valproate and other antiepileptic drugs in the treatment of pediatric refractory status epilepticus.

We conclude that intravenous valproate can be used as a safe and effective third-line, antiepileptic drug in children's status epilepticus.

If patients have chronic respiratory disease or severe disability and respiratory impairment or wherever management of respiratory depression (intubation and artificial ventilation) is not available, intravenous valproate might be used as the first choice in the treatment of convulsive status epilepticus.

Table 1. Comparison of Children's Characteristics Based on Seizure Control

Data \ Control of Seizures		Yes	No	P Value
Age in year (Mean ± SD)		4.8 ± 1.2	3.1 ± 0.43	0.03
Stay days in ICU (Mean ± SD)		2.6 ± 1.4	5.6 ± 2.8	0.01
Gender	Girl	3	3	0.1
	Boy	4	1	
Etiologic Classification	Idiopathic	1	1	0.3
	Symptomatic	5	3	
	Febrile	1	0	
Type of Seizure	Generalized tonic-clonic	4	3	0.7
	Generalized clonic	2	1	
	Generalized tonic	1	0	
Developmental Status	Normal	4	2	0.6
	Delay	3	2	
EEG Result	Normal	2	1	0.4
	Abnormal	6	2	
Neuroimaging Finding	Normal	3	2	0.5
	Abnormal	4	2	

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