A Comparative Assessment the Efficacy of Intravenous Infusion of Sodium Valproate and Phenytion in the Treatment of Status Epilepticus

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Date of Submission: Feb 24, 2013

Date of Acceptance: Mar 11, 2013

How to cite this article: Chitsaz A, Mehvari J, Salari M, Gholami F, Najafi MR. A comparative assessment the efficacy of intravenous infusion of sodium valproate and phenytion in the treatment of status epilepticus. Int J Prev Med 2013;Suppl 2: S216-21.

Original Article

ABSTRACT

Background: Status epilepticus (SE) is a type of persistent lasting seizure with high mortality and morbidity. Numerous medications are suggested for the treatment of SE, two of which are sodium valproate and phenytoin. The purpose of this study is to conduct a comparison between the effi ciencies of intravenous sodium valproate and phenytoin in the treatment of this type of epilepsy. **Methods:** This is a clinical trial study conducted on SE-suffering patients admitted to the emergency departments of Al-Zahra and Ayatollah Kashani Medical Centers of Isfahan in 2009 and 2010. The patients were randomly assigned into two groups and taken under treatment, separately by intravenous infusion sodium valproate and phenytoin. **Results**: No significant difference was observed between the two groups (at $P = 0.06$). In terms of incidence of the clinical complications, the incidence of clinical complications in the two groups was significantly different (at $P = 0.03$). **Conclusions:** Based on the findings the efficiency of sodium valproate is larger than that of the phenytoin, and thus, the treatment by sodium valproate is preferred over the treatment by phenytoin.

Keywords: Intractable epilepsy, phenytoin, sodium valproate, status epilepticus

INTRODUCTION

Status epilepticus (SE) is a type of seizure, which is characterized by either of the following conditions:

- It should last for about 5-20 min or more; or
- It should occur for an adequate number of times, provided that no intervals of consciousness would be evident in between the seizures

The amount of mortality associated with SE has considerably reduced during the recent decade, with a mortality spectrum that falls in the range of 3% up to 20%.[1] Concerning SE, longer seizures are associated with a higher level of morbidity, which may be resulted by complications such as acidemia, hypoglycemia, or hypotension. On the other hand, controlled SE can be associated with mental, cognitive, and movement disorders in children and

adults in long-term, without taking into account any underlying neurological disorders. The sooner and quicker the treatment of SE begins, the better the prognosis will be; and the less the complications such as metabolic acidosis, respiratory arrest, aspiration pneumonia, neurogenic pulmonary edema, and lactic acidosis will occur.[2]

The mortality in tonic–clonic type of SE is about 20%, and the incidence of permanent neurological complications falls in the range of 10-30%.[3-5] If the SE is not controlled in the early stages, its mortality can surpass 85% in individuals over 70 years of age.[6-8] Generalized tonic–clonic SE is a medical emergency, and the patients must be immediately evaluated and the appropriate therapy should be initiated without delay. Furthermore, parallel to these procedures, the cause of the seizure must be determined to prevent any recurrence of it, and treat any underlying complications.[3-5,9]

Today, the initial treatment of SE after the primary procedures, includes prescription of Airway Breathing Circulation (ABC) transporters, glucose transporters, and vitamins; alongside with seizure control with diazepam or lorazepam. Next, conservative treatment in early stages includes, phenytoin, and phenobarbital (in case phenytoin does not control the condition) and in later stages midazolam, pentobarbital, and propofol. It should be noted that these drugs are used when the initial treatment does not succeed with drugs such as diazepam and lorazepam, or phenytoin and phenobarbital.[1,2]

Most of the existing medications are associated with several disadvantages and unfavorable side-effects. For instance, phenobarbital can cause severe drowsiness, developmental respiratory problems such as apnea, and an increased risk of infection. Intravenous phenytoin is highly alkaline, and is merely associated with pain and tissue irritation, thus, it involves placing a large intravenous line, and the drug should be injected very slowly. Simultaneously, 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 arrhythmias.[6-8] Although, new drug compounds such as Fosphenytion are soluble in the injection solvent, and do not bring about complications in the site of injection (as phenytoin does), their effectiveness is limited in the control of myoclonic, atonic, and absence seizures;[6] plus this product is not available in the pharmaceutical market of Iran.

In the control of seizures, there are a few cases when the application of an intravenous form of the anti-seizure medication is necessary; because in these cases, the patient is not able to receive the oral form of the anti-epileptic drug, or there is a need for an urgent loading. SE is the most urgent type of these cases.[8] In SE cases, two criteria should be considered for an intravenous anti-seizure drug to be useful:

- The intravenous drug would be able to reach high therapeutic levels by means of a single load dose; and
- The rapid administration of intravenous infusion would be possible without any health risks.

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 on several types of partial epilepsy. Its effect mechanism is to prevent depolarization and blockade of sodium-dependent channels, alongside with enhancing the effects of gamma-aminobutyric acid (GABA). Intravenous sodium valproate is a convenient loading dose method, and an anti-seizure drug for the treatment of SE, with no effect of drowsiness.

A number of studies conducted in 1995, 1997, and 2000, have demonstrated the effectiveness and safety of intravenous sodium valproate in the treatment of seizures in the form of rapid infusion and loading dose.[10-12]

Peters *et al*. examined the effect of sodium valproate in 102 adult patients, and inferred that the seizures were controlled in 85.6% of the patients with no serious side-effects.[8] The intravenous application of sodium valproate was legalized in 1997, by America's Food and Drug Administration.[13] Another study published in 2003, showed the effectiveness and safety of intravenous sodium valproate in the treatment of SE in children.[13]

In general, the body of research in this area since 1997, suggests the wide range of intravenous sodium valproate application and its safety in controlling the life-threatening seizures of SE;[13-16] and also the empirical results confirm the quick

and direct anti-seizure effects of sodium valproate on SE cases. Nevertheless in Iran, intravenous phenytoin is the most common medication used to control the SE seizures as the first step in conservative treatment. The purpose of the present study is to compare the efficiency of intravenous infusion of sodium valproate and phenytoin in the treatment of SE in terms of controlling the seizures, meaning that the clinical cessation of the seizures would occur within less than 1 h after the after the beginning of the treatment; and as a second objective, no clinical recurrence of the seizures would be observed within the next 12 h.[17]

METHODS

This is a clinical trial study, conducted on SE-suffering patients admitted to the emergency departments of Al-Zahra Medical Center and the emergency Departments of Ayatollah Kashani Medical Center of Isfahan during the years 2009 and 2010.

The conditions for entering the study population included the diagnosis of SE by the neurology resident through obtaining the patient's history from the companions and clinical examination based on the mentioned criteria, the minimum age of 10, and the maximum age of 70, lack of evidence on substance abuse and addiction, no history of any cardiac, renal, or hepatic disorders, no history of absence, myoclonic, atonic, or non-convulsive seizures (according to the history obtained from the companions), no history of metabolic disorders causing seizures, no history of allergy to phenytoin and sodium valproate, no history of cardiac arrhythmias, no evidence of pregnancy, and no history of phenytoin consumption in the individuals whose treatment had been began with sodium valproate. The exclusion criteria of the study included not receiving the full dose of medication for any reason, and the existence of metabolic disorders causing seizures during the diagnostic evaluation.

All patients underwent routine laboratory tests such as electrolytes, Cell Blood Count (CBC) analysis, liver enzyme tests, and kidney function tests, so that the patient with metabolic disorders would not be included in the research project.

In the first phase of SE, diazepam ampoule was administered at a dosage of 0.15 mg/kg and at a rate of 5 mg/min. In case the seizure remained uncontrolled within 1 min after the infusion, the diazepam ampoule was administered once more. After this phase, the patients who met the conditions for inclusion in the study were randomly assigned into two groups, and the treatment process continued with intravenous phenytoin for one group, and intravenous sodium valproate for the other. The patients in the first group received intravenous sodium valproate. The initial bolus dosage of 20 mg/kg was infused within 10 min; and half an hour after this loading, continuous infusion at a rate of 1 mg/kg/h was administered as the maintenance dose within 24 h.

The patients in the second group were infused phenytoin intravenously at a dosage of 20 mg/kg and at a rate of 50 mg/min (25 mg/min for older patients) as the loading; and also a supplementary loading dose of 10 mg/kg was considered. Then, the maintenance dose of 4.5 mg/kg/day was administered for the next 24 h. The next group of drugs was used in case of seizure recurrence after loading with each of the mentioned drugs. During the intravenous infusion of both drugs, all patients underwent electrocardiogram monitoring, and the heart rate and the blood pressure were measured before and after the infusion. The IV site was controlled for erythema and tenderness during the infusion, once in the first 10 min, and once more after 12 h. All examinations were performed by one physician, and all serological tests were conducted in a single laboratory.

The rate of response to treatment, and also the side-effects of treatment were recorded in the checklist: And finally, all collected data were entered in to computer, and analyzed using SPSS ver. 16 software. The study was conducted after obtaining approval from the education department of the relevant hospitals, and coordination with the representatives of the emergency medical services system.

FINDINGS AND RESULTS

For the purpose of this study, 30 patients suffering from intractable epilepsy with an average age of 46.5 ± 18.7 years, and within the age range of 14-73 years were selected, randomly assigned into two groups of 15 persons. The average age of the patients in the group under treatment with sodium valproate and the group under treatment with phenytoin were respectively 47.4 ± 14 years and

45.5 ± 20.4 years. According to the *t*-test results, there was no significant difference between the average ages of the two groups (at $P = 0.2$). In terms of gender distribution, there were five and seven female subjects (33.3% vs. 46.7%) in the sodium valproate group and the phenytoin group respectively; and the rest were male. Based on the Chi-squared test, the gender distribution of the patients was not significantly different as well (at $P = 0.3$).

Table 1 illustrates the distribution of the studied variables in the two groups. According to this table, in the two groups under treatment with sodium valproate and phenytoin, respectively 40% and 46.7% of the subjects had a history of seizures, and according to the results of the Chi-squared test, no significant difference was evident in the two groups in this regard (at $P = 0.5$).

Moreover, according to this table, the rate of response to treatment within the first 12 h in the two groups under treatment with sodium valproate and phenytoin was respectively 73.3% and 60%, and according to the Chi-squared test, there was no significant difference between the two groups (at $P = 0.06$).

Figure 1 shows the rate of response to treatment in terms of the previous history of seizures, separately for the two groups. The Chi-square test was carried out on the mentioned data, and its results showed that the previous history of seizures has had no significant effect on the rate of response to treatment in neither of the two groups.

In terms of incidence of the clinical complications, no complications were observed in the group under sodium valproate treatment; whereas in the group under treatment with phenytoin, 4 patients (26.7%) were diagnosed with side effect complications. The type of complication in all 4 patients was erythema at the injection site, and according to the Fisher's exact test, the incidence of clinical complications in the two groups was significantly different (at $P = 0.03$).

Table 1: Distribution of demographic variable between the two groups

Variable	Group of treated level	Variables sodium valproate	Phenytoin	*P*
Age	Year	47.4±14	45.5±20.4	0.2
Gender	Male	5	7	0.3
	Female	10	8	
Past history of seizure	No	9 (60)	8 (53.3)	0.5
	Yes	6 (40)	7 (46.7)	
Response at first 12 h	Yes	11 (73.3)	9 (60)	0.06
	No	4 (26.7)	6 (40)	
Complication after treatment	Yes	0 (0)	4 (26.6)	0.03
	No	15 (100)	11 (73.4)	

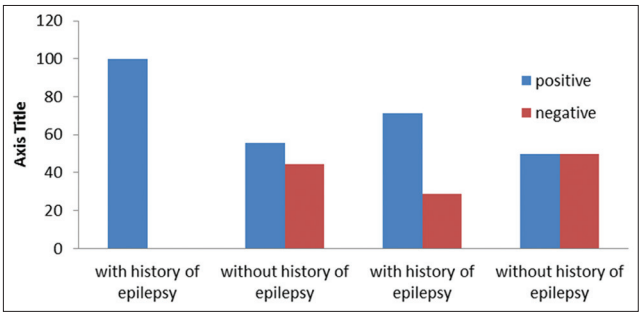

Figure 1: The frequency response based on previous history of seizures in two groups

DISCUSSION

The overall objective of this study was to determine the rate of clinical response to treatment for the intravenous infusion of sodium valproate, compared to phenytoin, in the treatment of SE patients.

In the present study, both the experimental and the control groups were identical in terms of factors such as age, gender, and also previous history of seizures. Therefore, these factors did not cause any bias in our study.

The findings of our study revealed that despite the apparent superiority of the response to treatment in the first 12 h, the group under treatment with sodium vawlproate had no statistically significant difference compared to the group under treatment with phenytoin. Our results also showed that no clinical complications have been observed in the group under treatment with sodium valproate; however, four cases of clinical complications have been evident in the group under treatment with phenytoin, all in the form of erythema at the injection site. Furthermore, the study of Misra *et al.* conducted in 2006 in order to compare the effects of intravenous sodium valproate and phenytoin in patients with SE, demonstrated the higher effectiveness of sodium valproate in comparison to phenytoin. In the aforementioned study, the effectiveness of sodium valproate and phenytoin have been calculated as equal to 79%

and 25%, respectively.[16] However, the study of Kanner *et al*. (2008) has obtained results similar to ours; and there has been no significant difference between the effectiveness of sodium valproate and phenytoin. Also, according to this study, no serious complications have been reported with either sodium valproate or phenytoin infusion.[18] Similarly, Agarwal *et al*. (2007) have reported that the effectiveness values for the sodium valproate and phenytoin are statistically equal. This study evaluates the effectiveness of sodium valproate and phenytoin as respectively equal to 88% and 84%. The treatment side effects in the two groups are not significantly different as well.[19] In the study of Yu *et al*. (2003) conducted on 40 patients with the diagnosis of SE and recurrent seizures, the treatment success of intravenous sodium valproate have been equal to 100% for the SE, and 95% for the recurrent seizures.[14] Shorvon (2003) has also shown that intravenous sodium valproate is preferred to intravenous phenytoin as the first-line therapy.[17]

Fallahi *et al*. (2011) examined the effectiveness of sodium valproate on 13 patients with intractable epilepsy in an age range of 4-12 years; and concluded that intravenous infusion of sodium valproate has led to cessation of the seizures in 63.3% of the patients.[20]

CONCLUSIONS

According to the findings of our study, and the other studies in this area, the efficiency of sodium valproate is larger than that of the phenytoin, and thus the treatment by sodium valproate is preferred over the treatment by phenytoin. Moreover, fewer side-effects are observed when using sodium valproate, and this fact supports the superiority of this medication over the use of phenytoin for treatment. Another important issue, is the higher cost of sodium valproate infusion compared to phenytoin infusion. This criterion (pharmaceutical costs) should be considered alongside with the relatively equivalent efficiency of the two drugs.

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Source of Support: Nil, **Conflict of Interest:** None declared.