Comparison of efficacy and safety of intravenous sodium valproate and phenytoin in the treatment of status epilepticus

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Abstract

Background: Sodium valproate is effective and safe in the treatment of status epilepticus (SE) and is not associated with serious side effects. The drug is cheap and easily available and is being increasingly used in therapeutic protocol; its efficacy in SE is to be formally characterized.

Objective: To see the safety and efficacy of intravenous sodium valproate in comparison to intravenous phenytoin in patients with SE.

Materials and Methods: The sample size for this randomized control trial was $N = 70$. The patients were divided into two groups. Patients in Group A ($n = 35$) received intravenous phenytoin 20 mg/kg diluted in normal saline @ 1 mg/kg/min. If the seizures still persisted, the patient was given phenytoin 10 mg/kg/min as per the standard treatment. Patients in Group B ($n = 35$) received intravenous sodium valproate 20 mg/kg diluted in normal saline @ 1 mg/kg/min.

Result: For patients in Group A (phenytoin) under parameter sodium (meq/L), the result obtained was $140.45 ± 3.5$ (before infusion) and $139.75 ± 4.5$ (after 12 h) at $>0.05$ level. For patients in Group B (valproate), the result was $139.65 ± 3.66$ (before infusion) and $141.22 ± 2.91$ (after 12 h) at $>0.05$ level. None of the patients showed any significant changes in parameter used in this study. No patient had changes in electrolytes levels and liver functions in either group.

Conclusion: Sodium valproate is a relatively safe drug for the treatment of patients of SE with no adverse effects when given in a bolus dose in emergency conditions. Although the drug undergoes significant hepatic metabolism, it does not produce any detectable side effects. It is also proven that the dose between 20 and 40 mg/kg bolus is the most effective and safe dose of intravenous sodium valproate in pediatric population.

KEY WORDS: Sodium valproate, phenytoin, epilepticus

Introduction

Status epilepticus (SE) is a serious, life-threatening neurological pediatric emergency characterized by prolonged seizure activity. Any type of epileptic seizure activity can develop into SE, but the most common associated type is tonic-clonic or convulsive SE. It is estimated that 16%–24% children with epilepsy and 5% with febrile seizures have at least one episode of SE.[¹]

Approximately 4.5 million cases of SE occur worldwide in pediatric age group. More than 40% pediatric SE occurs in children less than 2 years of age. Mortality from refractory SE is 20%–30% and over 50% survivors have neurological sequelae. Mortality rate is low in children and they are also more resistant to permanent neurological damage than adults but they have considerable complications after refractory seizure act.[²] Prolonged seizure activity itself produces irreversible cerebral damage independent of accompanying hypoxia acidosis and consequent biochemical derangements. In a study by Lowenstein,[³] treatment of prolonged seizures...
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within 30 min of onset was associated with an 80% response rate to first-line anticonvulsants compared with less than 40% response rate if seizure persisted for more than 2 h.

Early diagnosis and prompt initiation in treatment can directly shorten the duration of seizure with consequently minimizing the risk of minor and major neurological sequelae. Treatment of seizures in emergency department is an important practical issue. Benzodiazepines and phenytoin are the most commonly used drugs in the management of SE. Although phenytoin is an effective drug, it causes infusion-related hypotension and peripheral vascular injury. Also due to its unpredictable pharmacokinetics and side effects, search is on for a better drug.\(^4\)

Sodium valproate is effective and safe in the treatment of SE and is not associated with serious side effects. The drug is cheap and easily available and is being increasingly used in therapeutic protocol, but its efficacy in SE is to be formally characterized.\(^5\) Keeping in view of the above facts, the study was planned to see the safety and efficacy of intravenous sodium valproate in comparison to intravenous phenytoin in patients with SE.

Materials and Methods

The study was carried out in the Department of Pediatrics and Department of Biochemistry, Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana, India. Keeping in mind only large side effects to be significant, the sample size for this randomized control trial was kept at 70. The patients were divided into two groups. Patients of Group A (\(n = 35\)) received intravenous phenytoin 20 mg/kg diluted in normal saline @ 1 mg/kg/min. If the seizures still persisted, the patient was given phenytoin 10 mg/kg/min as per the standard treatment. Patients of Group B (\(n = 35\)) received intravenous sodium valproate 20 mg/kg diluted in normal saline @ 1 mg/kg/min. If the seizures still persisted, the patient was given sodium valproate 10 mg/kg/min as per the standard protocol. The investigations were performed immediately on admission and after 12 h. During the process of infusion, vital signs of the patient were monitored and the patient was neurologically examined. At the end of the study, the data were compiled and analyzed by using appropriate statistical method. The liver functions and electrolyte estimation was performed in the subjects to look for any liver damage or hypersensitivity to the drugs.

Results

The overall objective of this study was to assess the safety and efficacy of intravenous sodium valproate in comparison to intravenous phenytoin in patients with SE [Table 1].

On the basis of the procedure used, none of the patients showed any significant changes in earlier-mentioned parameters. No patient had changes in electrolyte levels and liver functions in either group.

Discussion

In reference to the results obtained in this study, Giroud et al.\(^6\) described successful termination of SE within 20 min in 19 of 23 patients. They used intravenous valproate as an initial loading dose of 15 mg/kg/h followed by continuous infusion of 1 mg/kg/h. No local pain or inflammation was noted at the site of intravenous catheter. No significant change in respiration or liver functions was noted.\(^6\) Devinsky et al.\(^7\) studied the safety of intravenous sodium valproate in SE. In a multicentric open trial of patients with epilepsy, 318 patients were included. In this study, the results showed no severe hematological and serum biochemistry abnormalities. It also showed that intravenous sodium valproate was well tolerated even in large number of doses.\(^7\)

Venkataraman and Wheless\(^8\) evaluated the safety of rapid intravenous infusion of sodium valproate electively in 21 patients with epilepsy. The target loading dose was 25 mg/kg. No significant changes were observed in lab parameters.\(^8\) Campistol et al.\(^9\) used intravenous sodium valproate in the management of SE in 19 pediatric patients with a loading dose of 20 mg/kg followed by infusion 1 mg/kg/h and reported control of SE in 58% patients with no adverse effects.

Uberrall et al.\(^10\) used intravenous sodium valproate in 41 children who were refractory to treatment with other group

### Table 1: Lab parameters of study population

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients</th>
<th>Before infusion (mean ± SD)</th>
<th>After 12 h (mean ± SD)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (meq/L)</td>
<td>Group A (phenytoin)</td>
<td>140.45 ± 3.5</td>
<td>138.75 ± 4.5</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td></td>
<td>Group B (valproate)</td>
<td>139.65 ± 3.66</td>
<td>141.22 ± 2.91</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Potassium (meq/L)</td>
<td>Group A (phenytoin)</td>
<td>4.15 ± 5.4</td>
<td>4.16 ± 5.2</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td></td>
<td>Group B (valproate)</td>
<td>4.13 ± 0.45</td>
<td>4.22 ± 4.3</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>SGOT (IU/L)</td>
<td>Group A (phenytoin)</td>
<td>32.34 ± 30.32</td>
<td>39.63 ± 30.32</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td></td>
<td>Group B (valproate)</td>
<td>46.22 ± 22.67</td>
<td>47.31 ± 21.54</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>SGPT (IU/L)</td>
<td>Group A (phenytoin)</td>
<td>26.17 ± 13.33</td>
<td>32.16 ± 17.3</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td></td>
<td>Group B (valproate)</td>
<td>31.33 ± 17.9</td>
<td>47.31 ± 21.9</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Serum Alkaline phosphatase</td>
<td>Group A (phenytoin)</td>
<td>91.46 ± 38.72</td>
<td>107.93 ± 54.32</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td></td>
<td>Group B (valproate)</td>
<td>246.74 ± 142.82</td>
<td>258.25 ± 139.68</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

SGOT: Serum Glutamic Oxaloacetic Transaminase; SGPT: Serum Glutamic-Pyruvic Transaminase
of antiepileptic drugs. These patients received intravenous valproate 20–40 mg/kg over 1–5 min followed by an infusion of 5 mg/kg/h. Of these, 75% patients responded with no adverse effects.[10] Ramsay et al.[8] evaluated the safety of multiple infusions of valproate. One hundred twelve subjects were treated for SE. The study concluded that valproate infusions up to 15 mg/kg and @ 1.5 and 3.0 mg/kg/min were well tolerated in this population.[8] Mehta et al.[11] in a study compared efficacy and safety of intravenous sodium valproate versus diazepam infusion for control of refractory SE. Forty children were randomized to receive either sodium valproate or diazepam infusion. The period required to control SE was shorter in valproate group as compared to diazepam group. No adverse effects on liver function were seen with valproate in this study.[11] Limdi et al.[12] conducted a study in which 40 patients received a valproate loading dose administered intravenously @ 6 or 10 mg/kg/min. They concluded that rapid administration of undiluted valproate is safe and well tolerated at infusion rate up to 10 mg/kg/min and doses up to 30 mg/kg. The lack of serious hepatic or local adverse effects supports the use of valproate in emergent situations.[12]

Conclusion

The sodium valproate is a relatively safe drug for the treatment of patients of SE with no adverse effects when given in a bolus dose in emergency conditions. Although the drug undergoes significant hepatic metabolism, it does not produce any detectable side effects. It is also proven that the dose between 20 and 40 mg/kg bolus is the most effective and safe dose of intravenous sodium valproate in pediatric population.

References


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