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Original article

Efficacy and safety of intravenous sodium valproate versus phenobarbital in controlling convulsive status epilepticus and acute prolonged convulsive seizures in children: A randomised trial

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ABSTRACT

Status epilepticus and acute prolonged seizures are the most commonly occurring neurological emergencies in children. Such events have high morbidity and mortality rates along with poor long-term outcomes, depending on their duration and causes. Therefore, such seizures warrant urgent treatment using appropriate doses of anticonvulsants. Benzodiazepines, phenobarbital, and phenytoin are the most commonly used anticonvulsants for controlling status epilepticus and acute prolonged seizures. However, these medications have several well-known adverse effects. Previous studies on both adults and children have shown the efficacy and safety of rapid infusion of valproate in controlling status epilepticus. However, few well-designed randomised trials have been carried out in children, and there remains a paucity of data regarding intravenous sodium valproate use in children. Therefore, our aim was to compare the efficacy and safety of rapid loading of valproate with those of intravenous phenobarbital in children with status epilepticus and acute prolonged seizures. Sixty children (30 in each group) with convulsive status epilepticus and acute prolonged seizures were enrolled and randomly assigned to receive either valproate or phenobarbital. The main outcome variable was termination of all convulsive activity within 20 min of starting anticonvulsant infusion. Intravenous rapid loading of valproate was successful in seizure termination in (27/30, 90%) of patients compared to phenobarbital (23/30, 77%) ($p = 0.189$). Clinically significant adverse effects occurred in 74% patients of the phenobarbital group and 24% patients of the valproate group ($p < 0.001$). In conclusion, rapid loading of valproate is effective and safe in controlling convulsive status epilepticus and acute prolonged convulsive seizures in

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children. Intravenous valproate should be considered as a suitable choice for terminating status epilepticus and acute prolonged seizures in children.

1. Introduction

Status epilepticus and acute prolonged seizures are the most commonly occurring neurological emergencies in children. Unlike brief seizures, such events have high morbidity and mortality rates, along with poor long-term outcomes depending on their duration, causes, and co-morbidities. Therefore, such seizures warrant urgent treatment using appropriate doses of rapidly acting anticonvulsants. An ideal anticonvulsant for treating status epilepticus should be effective, reach the brain rapidly, lack serious adverse effects, and should have a formulation appropriate for rapid administration to a patient experiencing convulsions.[1–3]

Traditionally, benzodiazepines administered via the rectal, buccal, and intravenous routes have been relied upon as the first line of treatment by emergency room physicians. Caregivers at home generally prefer to administer rectal, nasal, and buccal benzodiazepines as seizure-aborting agents.[1] When benzodiazepines, particularly intravenous forms, either fail to terminate the convulsion or successfully stop the convulsion, a long-acting anticonvulsant should be administered, the selection of which depends on the circumstances specific to each case. Such long-acting anticonvulsants include phenytoin or phenobarbital.[2,3] In our country and most other developing countries, phenobarbital and phenytoin are the most commonly used second-line anticonvulsants for controlling status epilepticus and acute prolonged seizures. However, these medications have several well-known and potentially serious adverse effects. Respiratory depression, sedation, and hypotension are the primary adverse effects resulting from phenobarbital rapid infusion, especially when the patient has previously received a high dose of intravenous benzodiazepine as the first-line treatment. Cardiac dysrhythmias and hypotension have frequently been reported following rapid infusion of phenytoin; local irritation, phlebitis, and dizziness are also commonly observed adverse effects.[4]

Recently, an intravenous formulation of sodium valproate has become available in our country. The pharmacokinetics of intravenous valproate have been elucidated in both adults and children,[5–8] with several studies on adults and a small number on children demonstrating the efficacy and safety of rapid infusion of sodium valproate in controlling status epilepticus and acute prolonged seizures.[9–29] However, most of these studies have used relatively small sample sizes or have major methodological shortcomings. Besides, very few well-designed randomised trials have been conducted in children specifically, and there remains a paucity of data regarding intravenous sodium valproate use in children at standard or rapid infusion rates.[5,20] To the best of our knowledge, no study has been performed to compare the efficacy of rapid loading of sodium valproate versus phenobarbital in children with status epilepticus and acute prolonged seizures. Therefore, we carried out a randomised controlled trial with the aim of comparing the efficacy and safety of rapid infusion of intravenous sodium valproate with those of intravenous phenobarbital in children with convulsive status epilepticus and acute prolonged convulsive seizures.

2. Materials and methods

2.1. Study location, sample, and design

Our study was conducted between May 2008 and May 2010 in 2 major university paediatric hospitals in Tehran, Iran. We enrolled children aged 2 years and older presenting with convulsive status epilepticus or acute prolonged convulsive seizures.

Our definition of status epilepticus was based on the practical definition of status epilepticus proposed by Lowenstein et al., who defined status epilepticus as a continuous, generalised, convulsive seizure lasting longer than 5 min[9,30] Based on this definition, we enrolled all children who were experiencing convulsions while attending emergency rooms and whose seizures were not controlled by a bolus of intravenous diazepam (0.2 mg/kg) within 5 min. We excluded children with a history of adverse reactions to sodium valproate or similar drugs, a history of uncontrolled bleeding, thrombocytopaenia, active hepatic disease, cardiac rhythm disturbances, orthostatic hypotension, or syncope, and children who had received high doses of lamotrigine (more than 200 mg/day).

Consecutive patients were enrolled and randomised in quaternary blocks to receive either intravenous sodium valproate rapid loading or intravenous phenobarbital. We used a random number table for randomisation. Skilled staff, who administered the treatments, and patients alike were blinded to the medication packages, and after random allocation of patients to blocks, each patient received the medication package designed for that block. Phenobarbital was given at loading dose of 20 mg/kg via an infusion pump at a rate not faster than 60–100 mg/min. Sodium valproate was given at loading dose of 20 mg/kg, diluted in 20 ml saline, at a maximum rate of 5–6 mg/kg per minute over 5–10 min via an infusion pump. We used Depakine sodium valproate that was provided by a Sanofi company representative in Iran.

2.2. Response assessment and monitoring adverse effects

The main outcome variable was termination of all convulsive activity, which should be achieved within 20 min of starting anticonvulsant infusion, without respiratory depression or hypotension and without another convulsion within 1 h. Otherwise, the treatment was considered a failure, and the