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Randomized study of intravenous valproate and phenytoin in status epilepticus

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Summary

Introduction: The evidence based data to guide management in patients of benzodiazepine refractory status epilepticus (SE) is still lacking. We conducted a randomized study to evaluate the comparative effect of intravenous (IV) phenytoin and intravenous valproate (IV VA) in patients of benzodiazepine refractory SE.
Background and methods: Hundred, age and sex matched, patients of benzodiazepine refractory SE were randomly divided into Group A (50 patients), treated with IV VA and Group B (50 patients) treated with IV phenytoin. Twelve patients, in whom SE was not controlled with a single drug, were switched over to the other group. Treatment was considered successful when all motor or EEG seizure activity ceased within 20 min after the beginning of the drug infusion and no return of seizure activity during the next 12 h. Secondary study end points were adverse events to treatment, in-hospital complications and the neurological outcome at discharge.
Results: In this study, IV VA was successful in 88% and IV phenytoin in 84% ($p > 0.05$) of patients of SE with a significantly better response in patients of SE <2 h ($p < 0.05$). The total number of adverse events did not differ significantly between the two groups ($p > 0.05$). There were no differences among the treatments with respect to recurrence after 12-h study period or the outcome at 7 days.
Conclusion: IV VA is as effective as IV phenytoin. It is easy to use, better tolerated and can be used as an alternative to IV phenytoin in patients of benzodiazepine refractory SE, especially in patients of cardio-respiratory disease. The better outcome in patients having shorter duration of SE (<2 h) suggests need of immediate treatment.

Introduction

Approximately 5% of adult and 10—25% of children with epilepsy have at least one episode of status

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epilepticus (SE) during the course of their disease.[1–3] SE is present in nearly all epileptic syndromes, even idiopathic ones, although it is more frequent in cryptogenic and symptomatic forms.[4] Phenobarbital,[5–7] phenytoin,[8–10] diazepam plus phenytoin[11,12]and lorazepam[13–15] have been advocated for the initial treatment of SE, and each is used by a substantial number of physicians. No randomized controlled data supporting phenytoin as a second line treatment are available, but one uncontrolled study suggested that 50% of patients not successfully treated with a benzodiazepine alone would respond to a second line treatment (usually phenytoin).[16] Traditionally, based on a long clinical experience, and case controlled studies, intravenous (IV) phenytoin has been used as the second drug.

Starting in the 1980s, the use of intravenous valproate (IV VA) has been reported in an increasing number of uncontrolled case series, indicating relative ease of use, relatively good tolerability and suggesting that it may be efficacious.[17] In one study, 20 adult patients in acute or static SE with generalized tonic–clonic seizures (GTCS) or simple partial motor seizures were administered IV valproic acid in a bolus dose of 15 mg/kg body weight and then as a continuous infusion of 1 mg/kg/h for 24 h safely. SE was interrupted in less than 30 min in 80% of cases.[18] Recently, there are other reports about successful use of IV VA in controlling SE[19,20] but there is no randomized comparative study to the best of our knowledge till now. Hence, we planned a randomized study to demonstrate the efficacy and safety of IV VA as the initial therapy for controlling seizures in patients of SE refractory to diazepam, and to compare it with IV phenytoin.

Materials and methods

This study was conducted on patients of status epilepticus refractory to IV diazepam admitted in emergency ward and intensive care unit from December 2004 to February 2006. The definition of SE is based on the clinical manifestations—a prolonged seizure or a series of seizures during which the patient has incomplete recovery of consciousness, and duration. The traditional definition of status has been 30 min, however, the duration parameter is highly controversial and has created a flux in our definition of SE. The operational definition of SE proposed by Lowenstein et al.[21] is a continuous, generalized, convulsive seizure lasting greater than 5 min, or two or more seizures during which the patient does not return to baseline consciousness. In our study patients of SE were defined as continuous or repeated seizure activity for more than 5 min without recovery of consciousness.[22] Pregnant women, children less than 2 years of age and patients of hepatic encephalopathy were excluded from the study. Patients with myoclonic status epilepticus, neurological emergency requiring immediate surgical intervention, or contraindication to therapy with hydantoin, benzodiazepine, or barbiturate drugs were also excluded. Only the first episode was included in the analysis if the patient was enrolled more than once by mistake. The intention to treat analysis was done and patients who left the treatment against medical advice were also included in the study.

Out of 3000 patients of epilepsy seen in outdoor and emergency ward, hundred patients were diagnosed as benzodiazepine resistant SE and included for the study after taking informed consent from conscious patients $\geq$18 years or from the parents in case of unconscious patients and patients under 18 years of age. These patients were randomly divided into groups A and B after matching for age and sex. Fifty patients in Group A received IV valproic acid in doses of 20 mg/kg (Limdi et al.[20]) as loading dose at rate of 40 mg/min[23–25] and 50 patients in Group B received IV phenytoin in the doses of 20 mg/kg (max. rate of 50 mg/min) after dilution with normal saline. All these patients were earlier given IV diazepam in doses of 0.2 mg/kg at 2 mg/min up to a maximum of 20 mg before labeling as refractory to diazepam.[22] We used commercially available intravenous valproate (Encorate®, Sun Pharmaceuticals Ind. Ltd., India).

Status epilepticus was considered to end at the time when convulsive seizure ceased and the patient subsequently regained consciousness. Status epilepticus was considered ongoing when seizures were clinically evident or when clinically seizures ended but the patient remained comatose and an electroencephalogram (EEG) indicated ongoing electrical seizure activity, or when the patient remained unconscious and subsequently had a convulsive seizure requiring treatment with an antiepileptic drug. We changed the therapy if life-threatening seizures were continued as per the standard protocol used in management of status epilepticus. All patients were monitored for the vitals viz. pulse, blood pressure, respiration, electrocardiogram (ECG), seizure activity, Glasgow coma scale (GCS), wherever required every 5 min for 2 h, then every 15 min for 12 h. All patients were followed for 7 days for seizure outcome and adverse events. EEG was done in all patients and repeated whenever required. Patients were followed up for 7 days to measure the outcome. All cases were investigated for complete blood count, blood sugar, serum electrolytes, blood urea, serum creatinine