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Original article

Fosphenytoin vs. continuous midazolam for pediatric febrile status epilepticus

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Abstract

Background: Fosphenytoin (fPHT) and continuous intravenous midazolam (cMDL) had commonly been used as second-line treatments for pediatric status epilepticus (SE) in Japan. However, there is no comparative study of these two treatments.

Methods: We included consecutive children who 1) were admitted to Kobe Children's Hospital because of convulsion with fever and 2) were treated with either fPHT or cMDL as second-line treatment for convulsive SE lasting for longer than 30 min. We compared, between the fPHT and cMDL groups, the proportion of barbiturate coma therapy (BCT), incomplete recovery of consciousness, mechanical ventilation, and inotropic agents.

Results: The proportion of BCT was not significantly different between the two groups (48.7% [20/41] in fPHT and 35.3% [29/82] in cMDL, $p = 0.17$). The prevalence of incomplete recovery of consciousness, mechanical ventilation, and inotropic agents was not different between the two groups. After excluding 49 patients treated with BCT, incomplete recovery of consciousness 6 h and 12 h after onset was more frequent in the cMDL group than in the fPHT group (71.7% vs. 33.3%, $p < 0.01$; 56.6% vs. 14.2%, $p < 0.01$; respectively). Mechanical ventilation was more frequent in the cMDL group than in the fPHT group (32.0% vs. 4.7%, $p = 0.01$).

Conclusions: Our results suggest that 1) the efficacy of fPHT and cMDL is similar, although cMDL may prevent the need for BCT compared with fPHT, and 2) fPHT is relatively safe as a second-line treatment for pediatric SE in patients who do not require BCT.

Keywords: Status epilepticus; Fosphenytoin; Midazolam; Acute encephalopathy; Safety; Second-line treatment; Consciousness; Respiratory depression

1. Introduction

Convulsive status epilepticus (CSE) is one of the most common neurologic emergencies in children [1]. CSE has

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an estimated incidence of 10–38 per 100,000/year, a mortality rate of 2.7–5.2%, and a morbidity rate of 0–30% [1,2]. Benzodiazepines were established as the initial therapy of choice for CSE in evidence-based guidelines [3]. However, high-level evidence is not available for second-line treatment, although several drugs, such as intravenous fosphenytoin (fPHT), phenytoin (PHT), valproic acid (VPA), levetiracetam (LEV), and phenobarbital (PB) are used [3–5]. In addition, continuous intravenous midazolam (cMDL) had commonly been used as second-line treatment for pediatric status epilepticus in Japan [6,7]. The efficacies of fPHT and cMDL have been reported in several previous studies [7–9]. However, reports on the adverse effects of these therapies, specifically central nervous system (CNS) depression, are limited [7]. To best of our knowledge, there is no comparative study of fPHT and cMDL for the treatment of CSE as second-line agents. The objective of the present study was to investigate the efficacy and adverse effects of fPHT and cMDL as second-line treatments in children with febrile CSE.

2. Subjects and methods

This study was approved by the local ethical committee of Kobe Children's Hospital, which stated that no patient consent was needed due to the nature of the observational design of this study. A flowchart describing the subjects in the study is shown in Fig. 1. We created a database of children admitted to the pediatric intensive care unit at Kobe Children's Hospital, which is a tertiary referral hospital, due to convulsions or impaired consciousness with fever between October 2002 and November 2015. Our cohort consisted of patients with intrinsic neurological disease and did not include those with traumatic injury or cardiopulmonary arrest. Of the original cohort, 430 patients with convulsive status epilepticus, which is defined as a convulsive seizure or a sequence of intermittent seizures lasting for 30 min or longer without the patient fully regaining consciousness, were identified. Of the 430 patients, we included 145 patients who had been treated with either fPHT or cMDL after benzodiazepine administration. Six patients without complete data regarding the level of consciousness 6 h or 12 h after onset and 16 patients who were treated with 2 or more second-line treatments, including fPHT, cMDL, PHT, and PB, were excluded. We did not consider VPA and LEV, as these drugs were not available for intravenous use before 2016. One hundred and twenty-three patients were thus included (Cohort A, Fig. 1). Additionally, after excluding 49 patients treated with barbiturate coma therapy (BCT), we conducted a subgroup analysis (Cohort B, Fig. 1). We conducted subgroup analysis because BCT depresses consciousness and requires mechanical ventilation and inotropic agents, which comprised one of the endpoints of the current study.

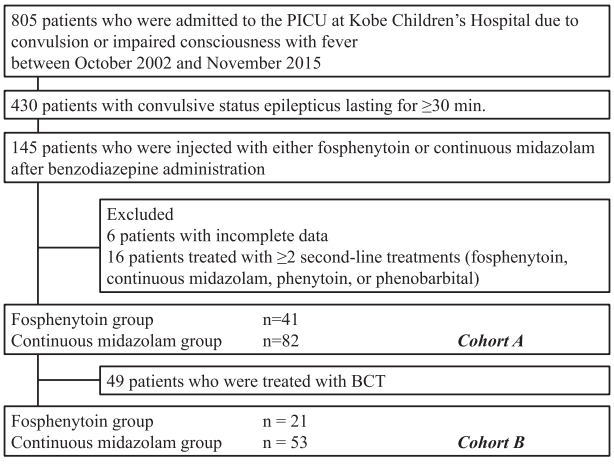

Fig. 1. Flow chart describing the subjects. PICU: pediatric intensive care unit; BCT: barbiturate coma therapy.

The primary endpoint of the study was the BCT induction, which represents failure of second-line treatment. The endpoints for adverse effects were 1) prevalence of incomplete recovery of consciousness 6 h and 12 h after onset, which represented CNS depression; 2) use of mechanical ventilation, which represented respiratory failure; and 3) use of inotropic agents, which represented circulatory failure. The proportion of patients treated with BCT was analyzed in Cohort A and endpoints for adverse effects were analyzed in both Cohort A and Cohort B. Seizure onset was defined as the beginning of any neurological symptoms, including convulsion. Convulsion was preceded by a non-convulsive seizure in some patients, although all subjects had a convulsive seizure or a sequence of intermittent seizures lasting for 30 min. Convulsion duration was defined as the time between beginning and final cessation of convulsion. Incomplete recovery of consciousness was defined as a score of <15 on the Glasgow Coma Scale. Other clinical variables that were assessed included age, sex, neurological medical history, baseline neurological functional state using the Pediatric Cerebral Performance Category (PCPC) scale, body temperature on admission, convulsion duration, first-line treatment, duration of hospital stay, mortality, final diagnosis, and prevalence of poor outcome defined as higher PCPC score at discharge than at baseline. The PCPC is an established scale wherein a score of 1 represents normal performance, a score of 2 represents mild disability, a score of 3 represents moderate disability, a score of 4 represents severe disability, a score of 5 represents a persistent vegetative state, and a score of 6 represents death (Supplementary Table 1) [10].

Our protocol for the treatment of status epilepticus begins with benzodiazepine administration. For example, a patient may first be treated with 0.3–0.5 mg/kg

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