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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 minutes. 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 hours and 12 hours 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

INTRODUCTION

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

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 Figure 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 minutes 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 hours or 12 hours 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, Figure 1). Additionally, after excluding 49 patients treated with barbiturate coma therapy (BCT), we conducted a subgroup analysis (Cohort B, Figure 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.

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 hours and 12 hours 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 minutes. 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 intravenous diazepam and/or 0.1–0.3 mg/kg intravenous midazolam. This may then be followed by a choice of

second-line treatment, such as cMDL at 0.1–0.5 mg/kg/h, PHT at 20 mg/kg, fPHT at 22.5 mg/kg, or PB at 20 mg/kg (Supplementary Figure 1). When convulsive seizures persist, we induce BCT using 5 mg/kg intravenous thiamylal followed by continuous intravenous thiamylal at 1–5 mg/kg/h. Additionally, we repeatedly administer 1-2 mg/kg intravenous thiamylal until we observe burst-suppression by electroencephalography. Intubation, mechanical ventilation, and inotropic agents are used concurrently with BCT. Our protocol for second-line treatment has changed over time. In particular, we used cMDL between 2002 and 2009 and fPHT between 2013 and 2015. We usually used PB between 2010 and 2012.

All analyses were performed using JMP (version 11.0) statistical software (SAS Inc., Japan). The numerical data from the fPHT and cMDL groups were compared using Mann-Whitney U tests and categorical data were compared using Fisher exact tests or Pearson's chi-square tests. All results were considered significant at p values <0.05. We performed eight tests for the endpoints for adverse effects; thus, fewer than one test would be expected to have a significant result ($p < 0.05$) on the basis of chance alone.

RESULTS

Cohort A

The numbers of patients in the fPHT and cMDL groups were 41 and 82, respectively. Background variables, such as age, sex, neurological medical history of epilepsy, baseline

neurological functional status, and temperature on admission, were not statistically different between the fPHT group and the cMDL group (Table 1). Neurological medical history of febrile seizure was more common in the fPHT group. The median duration of convulsion was 115 minutes in the fPHT group and 119 minutes in the cMDL group. The two groups did not differ in terms of the use of diazepam or midazolam as first-line treatment, the duration of hospital stay, mortality, poor clinical outcomes, or final diagnoses. The proportion of patients treated with BCT was 48.7% in patients treated with fPHT and 35.3% in patients treated with cMDL (Table 2). Thus, there was no significant difference between the two groups in terms of BCT use ($p = 0.17$). Of the 49 patients who were treated with BCT, the median (range) of the duration between second-line treatment and third-line treatment was 210 (24–210) minutes in patients treated with BCT after fPHT and 240 (18–4,332) minutes in patients treated with BCT after cMDL, and there was no significant difference between the two groups ($p = 0.81$). Occurrence of incomplete recovery of consciousness 6 hours and 12 hours after onset, use of mechanical ventilation, and use of inotropic agents were also not different between the two groups.

Cohort B

The numbers of patients in the fPHT and cMDL groups were 21 and 53, respectively. Background variables, such as age, sex, neurological medical history, baseline neurological functional status, and temperature on admission, were not statistically different between the fPHT

group and the cMDL group (Table 3). The duration of convulsion, the use of first-line treatment, the duration of hospital stay, mortality, poor outcomes, or the proportions of final diagnoses were also not different between the two groups. Occurrence of incomplete recovery of consciousness 6 hours and 12 hours 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) (Table 4). Mechanical ventilation was conducted for only one patient (4.7%) in the fPHT group. In contrast, 17 patients (32.0%) in the cMDL group required mechanical ventilation. The proportion of patients requiring the use of inotropic agents was not different between the two groups.

DISCUSSION

There is no report comparing the efficacy and the adverse effects, including cardio-respiratory and CNS depression, of fPHT versus cMDL for the treatment of CSE as second-line agents. In this study, the proportion of BCT induction was 48% in patients treated with fPHT and 35% in those treated with cMDL. This indicated that the final effectiveness of fPHT was around 52% and that of cMDL was 65% when used as a second-line treatment. Although not statistically significant, cMDL treatment seemed to prevent BCT induction compared with fPHT. However, its retrospective design of this study limits the explanation. There are several reports regarding efficacy of fPHT or cMDL treatment [7-9, 11]. fPHT has been reported to be effective in a few retrospective studies [8, 9, 11]. The rate of seizure cessation following treatment with fPHT

was 65% in a study of pediatric patients with status epilepticus [8]. The rate of prevention of seizure recurrence following treatment with fPHT was reported to be 81% in adults after status epilepticus [11] and 87% in children with benign convulsions with mild gastroenteritis [9]. The rate of seizure cessation following treatment with cMDL as second-line therapy was reported to be 49% in pediatric patients with status epilepticus [7].

Regarding the endpoints for adverse effects, the proportion of patients who exhibited incomplete recovery of consciousness or required mechanical ventilation or inotropic agents did not differ between fPHT and cMDL groups in Cohort A. However, in the subgroup analysis (Cohort B), we found that the rate of incomplete recovery of consciousness, which represents CNS depression, was lower in children with CSE treated using fPHT than in those treated using cMDL. Moreover, mechanical ventilation, which represents respiratory depression, was rarely conducted for children treated using fPHT in Cohort B. These results suggest that fPHT was relatively safe as a second-line treatment for pediatric CSE in patients who did not need BCT. In contrast, the use of cMDL requires more attention to respiratory and CNS depression and indicates a need for intensive care even in the patients who did not need BCT. Several adverse effects involving the CNS, such as dizziness, ataxia, and somnolence, have been reported with the use of fPHT [12, 13]. However, in general, impaired consciousness was not a major adverse effect of fPHT [12, 13]. Although hypotension or cardiac arrhythmias have sometimes been reported with the use of fPHT [12, 13], a recent study of virus-associated acute encephalopathy in children revealed no obvious adverse

effects of this treatment, including cardiovascular effects and impaired consciousness [8]. In contrast, benzodiazepines such as midazolam often lead to cardio-respiratory depression and impaired consciousness [7, 12, 14]. These previous studies imply that respiratory and CNS depression is less frequent in patients treated using fPHT than in those treated using cMDL. However, they were not comparative in nature. To our knowledge, this is the first study to suggest that fPHT led to a lower incidence of respiratory and CNS depression than did cMDL.

Current guidelines for status epilepticus indicate that cMDL and barbiturates are used as pharmacologic coma medications [3, 5]. The use of cMDL as a second-line agent is unique and off-label. However, it had been the standard strategy for the treatment of status epilepticus in Japan until 2017 (new guideline for the treatment of SE was published in 2017 in Japanese) [6]. The dose of cMDL as a second-line agent (0.1-0.5 mg/kg/h) is lower than the dose required when used as an anesthetic agent (0.1-2.9 mg/kg/h) [6, 15]. Compared to its anesthetic use, which requires mechanical ventilation, the use of cMDL as a second-line agent causes respiratory depression less frequently [3, 5, 7]. Nevertheless, respiratory depression was detected in 19% of cases treated using ≤0.4 mg/kg/h of cMDL, although a causal relationship was present in only 6% of patients [7]. The efficacy of high-dose cMDL (median, 0.4 mg/kg/h; interquartile range [IQR], 0.2 to 1.0) has been compared to that of low-dose cMDL (median, 0.2 mg/kg/h; IQR, 0.1 to 0.3) in a previous study involving adults [16]. Seizure recurrence (15% vs. 64%) and mortality (40% vs. 62%) were less frequent in the high-dose cMDL group than in the low-dose cMDL group [16].

The etiology of pediatric CSE includes acute encephalopathy/encephalitis. This is especially the case in Taiwan and Japan, where more than 10% of the cases are due to encephalopathy or encephalitis [17-20]. The main symptoms used to distinguish virus-associated acute encephalopathy from prolonged febrile seizure is impaired consciousness. Therefore, anticonvulsants that lead to less CNS depression are desirable for treatment of febrile CSE [21]. Our results suggest the usefulness of fPHT when compared to cMDL as a second-line agent.

It is ideal and important to distinguish impaired consciousness from sedation, although this is very difficult, even in the intensive care unit (ICU) setting [22]. Moreover, there are considerable difficulties in assessing the level of consciousness in children [23, 24]. We have attempted to strictly evaluate these factors in the pediatric ICU. However, we were unable to distinguish unconsciousness due to the disease from that due to sedative use. This fact was one of the main limitations in this study. Although background characteristics were not significantly different between the two groups, there was a tendency for lower age and higher occurrence of acute encephalopathy/encephalitis in the cMDL group. These background characteristics may have affected the endpoints, including the level of consciousness.

This study has several other limitations. First, it was a retrospective study involving a single institution. In addition, the 2 groups were treated at different times. Moreover, the lower number of patients in the fPHT group may have limited potential comparisons. Second, we were unable to determine the exact dose and blood concentration of each anticonvulsant, although our

patients were strictly treated according to the protocol used at our institution. Finally, because we did not collect data regarding seizure cessation, we were unable to assess the rate of seizure cessation. A prospectively designed study will address these issues.

Although the data should be interpreted cautiously because of several important limitations, our findings suggest the following: The efficacy of fPHT and cMDL was not significantly different, although cMDL treatment could potentially prevent BCT induction compared with fPHT. On the other hand, fPHT is safer than cMDL as a second-line treatment for CSE in patients who do not require BCT, as it less likely to cause respiratory depression. Moreover, because fewer patients treated with fPHT showed CNS depression than did those treated with cMDL, fPHT seems to be safe for the treatment of CSE, especially when there is no continuous electroencephalogram monitoring.

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Figure legends

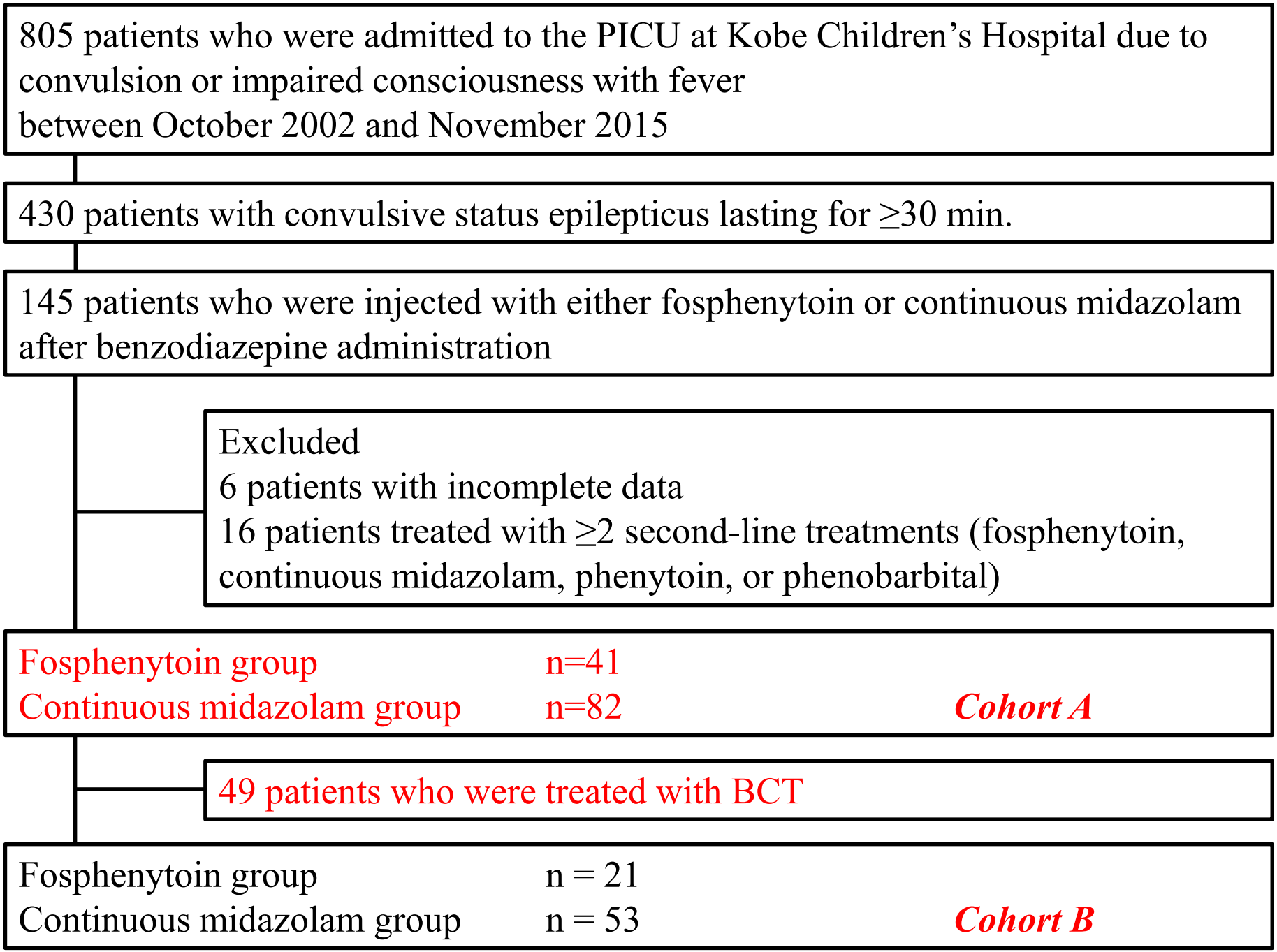
Figure 1. Flow chart describing the subjects

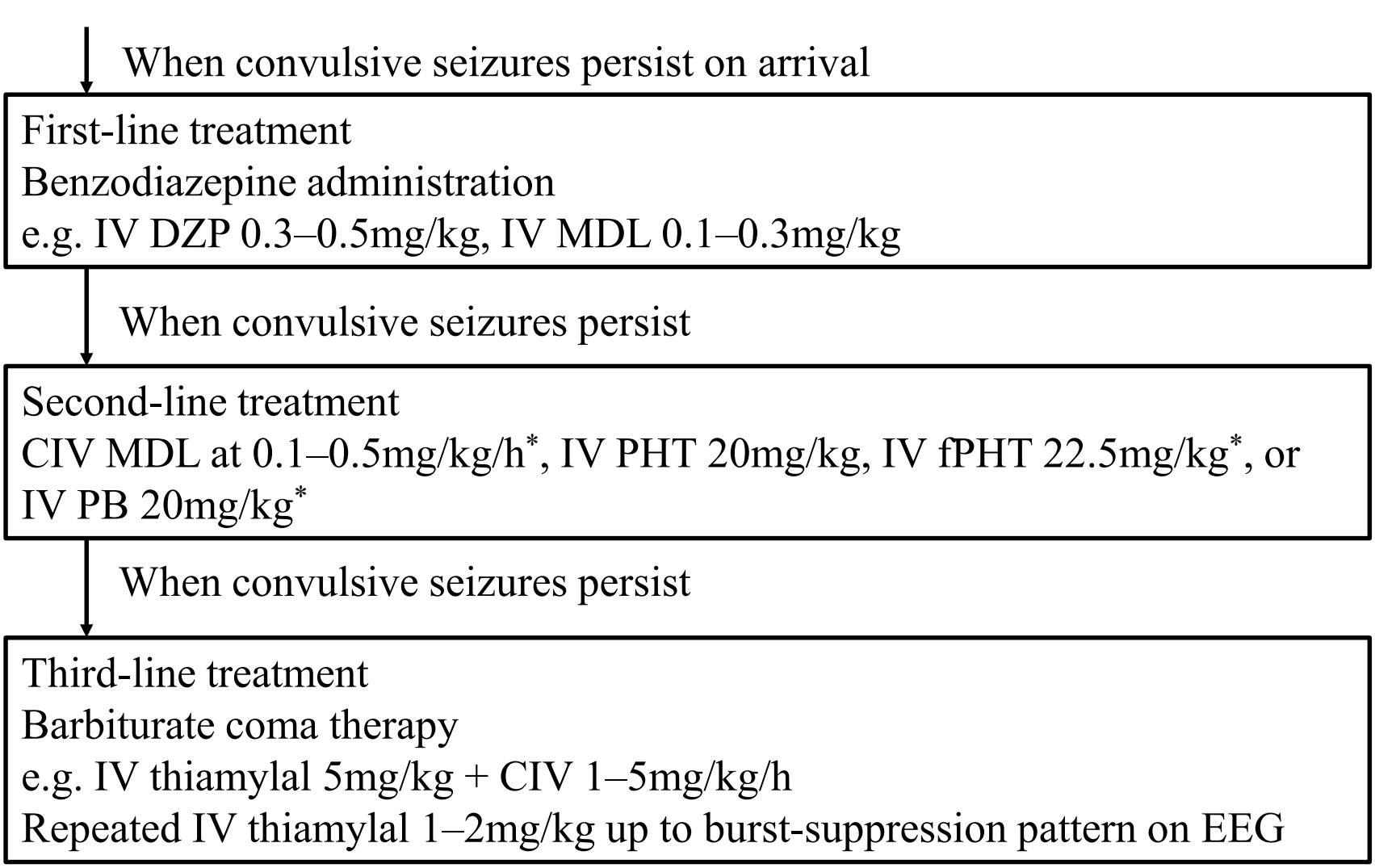
PICU: pediatric intensive care unit; BCT: barbiturate coma therapy

Supplementary Figure 1. Treatment protocol for status epilepticus used in the hospital

IV: intravenous; CIV: continuous intravenous; DZP: diazepam; MDL: midazolam; PHT: phenytoin;

fPHT: fosphenytoin; PB: phenobarbital; EEG: electroencephalogram


805 patients who were admitted to the PICU at Kobe Children's Hospital due to convulsion or impaired consciousness with fever between October 2002 and November 2015
430 patients with convulsive status epilepticus lasting for ≥30 min.
145 patients who were injected with either fosphenytoin or continuous midazolam after benzodiazepine administration
Excluded
6 patients with incomplete data
16 patients treated with ≥2 second-line treatments (fosphenytoin, continuous midazolam, phenytoin, or phenobarbital)
Fosphenytoin group n=41
Continuous midazolam group n=82
Cohort A
49 patients who were treated with BCT
Fosphenytoin group n = 21
Continuous midazolam group n = 53
Cohort B



*We basically select CIV MDL between 2002 and 2009 and IV fPHT between 2013 and 2015. We usually select PB between 2010 and 2012.

Table 1. Background of the subjects in Cohort A

	Fosphenytoin group n=41	Continuous midazolam group n=82	*P* value
Age, month	39 (9–149)	26 (1–180)	0.08
Sex, Male	22 (53.6)	47 (57.3)	0.70
Neurological medical history			
Epilepsy	11 (26.8)	14 (17.0)	0.23
Febrile seizure	21 (51.2)	22 (26.8)	<0.01
Baseline functional status			0.37
PCPC 1	24 (58.5)	57 (69.5)	
PCPC 2	4 (9.7)	10 (12.2)	
PCPC 3	7 (17.0)	8 (9.7)	
PCPC 4	5 (12.2)	7 (8.5)	
PCPC 5	1 (2.4)	0 (0.0)	
Temperature on admission, °C	38.7 (36.6–42.0)	38.8 (36.5–41.8)	0.74
Convulsion duration, minutes	115 (40–728)	119 (30–1995)	0.84
First-line treatment			
Diazepam i.v.	34 (82.9)	65 (79.3)	0.81
Midazolam i.v.	35 (85.4)	68 (82.9)	0.80
Duration of hospital stay, days	10 (2–23)	7 (1–237)	0.11
Mortality	1 (2.4)	2 (2.4)	1.00
Poor outcome	11 (26.8)	13 (15.8)	0.15
Final diagnosis			0.29
Acute encephalopathy/encephalitis	6 (14.6)	21 (25.6)	
Complex febrile seizure	25 (60.9)	46 (56.0)	
Epilepsy	10 (24.3)	13 (15.8)	
Others	0 (0.0)	2 (2.4)	

Data are shown as number of children (%) or median (range).

PCPC: Pediatric Cerebral Performance Category

Table 2. Outcome of the subjects in Cohort A

	Fosphenytoin group n=41	Continuous midazolam group n=82	*P* value
Barbiturate coma therapy	20 (48.7)	29 (35.3)	0.17
Level of consciousness			
Imcomplete recovery at 6 hours	27 (65.8)	66 (80.4)	0.11
Imcomplete recovery at 12 hours	23 (56.1)	58 (70.7)	0.11
Mechanical ventilation	21 (51.2)	43 (52.4)	1.00
Inotropic agents	20 (48.7)	32 (39.0)	0.33

Data are shown as number of children (%).

Table 3. Background of the subjects in Cohort B

	Fosphenytoin group n=21	Continuous midazolam group n=53	*P* value
Age, month	53 (14–149)	26 (9–180)	0.06
Sex, Male	12 (57.1)	30 (56.6)	1.00
Neurological medical history			
Epilepsy	9 (45.0)	11 (20.7)	0.08
Febrile seizure	11 (52.3)	16 (30.1)	0.10
Baseline functional status			0.24
PCPC 1	10 (47.6)	34 (64.1)	
PCPC 2	2 (9.5)	8 (15.0)	
PCPC 3	5 (23.8)	6 (11.3)	
PCPC 4	3 (14.2)	5 (9.4)	
PCPC 5	1 (4.7)	0 (0.0)	
Temperature on admission, °C	38.6 (37.0–40.4)	38.9 (37.0–41.8)	0.74
Convulsion duration, minutes	85 (40–298)	90 (30–670)	0.84
First-line treatment			
Diazepam i.v.	16 (76.2)	40 (75.4)	1.00
Midazolam i.v.	17 (81.0)	44 (83.0)	1.00
Duration of hospital stay, days	6 (2–16)	4 (1–52)	0.45
Mortality	1 (4.7)	2 (3.7)	1.00
Poor outcome	2 (9.5)	7 (13.2)	1.00
Final diagnosis			0.18
Acute encephalopathy/encephalitis	1 (4.7)	9 (16.9)	
Complex febrile seizure	12 (57.1)	32 (60.3)	
Epilepsy	8 (38.1)	10 (18.8)	
Others	0 (0.0)	2 (3.7)	

Data are shown as number of children (%) or median (range).

PCPC: Pediatric Cerebral Performance Category

Table 4. Outcome of the subjects in Cohort B

	Fosphenytoin group n=21	Continuous midazolam group n=53	*P* value
Level of consciousness			
Imcomplete recovery at 6 hours	7 (33.3)	38 (71.7)	<0.01
Imcomplete recovery at 12 hours	3 (14.2)	30 (56.6)	<0.01
Mechanical ventilation	1 (4.7)	17 (32.0)	0.01
Inotropic agents	1 (4.7)	8 (15.0)	0.43

Data are shown as number of children (%).

Supplementary Table 1. Pediatric Cerebral Performance Category scale

Score	Category	Description
1	Normal	Normal; at age-appropriate level; school-age child attending regular school classroom
2	Mild disability	Conscious, alert, and able to interact at age-appropriate level; school-age child attending regular school classroom but grade perhaps not appropriate for age; possibility of mild neurologic deficit
3	Moderate disability	Conscious; sufficient cerebral function for age-appropriate independent activities of daily life; school-age child attending special education classroom and/or learning deficit present
4	Severe disability	Conscious; dependent on others for daily support because of impaired brain function
5	Coma or vegetative state	Any degree of coma without the presence of all brain death criteria; unawareness, even if awake in appearance, without interaction with environment; cerebral unresponsiveness and no evidence of cortex function (not aroused by verbal stimuli); possibility of some reflexive response, spontaneous eye-opening, and sleep-wake cycles
6	Brain death	Apnea, areflexia, and/or electroencephalographic silence