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Original Article

Management of Patients With Status Epilepticus Treated at a Pediatric Intensive Care Unit in Turkey

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ABSTRACT

We investigated the etiology, treatment, and prognosis of patients treated for status epilepticus at a pediatric intensive care unit. Medical records of 89 patients admitted to a pediatric intensive care unit with status epilepticus were reviewed retrospectively. Patients ranged in age from 2 months to 18 years (mean age ± S.D., 4.7 ± 3.8 years). Seizure etiologies comprised remote symptomatic in 47 (52.7%), febrile in 15 (16.9%), acute symptomatic in 12 (13.5%), and unknown in 15 (16.9%). Seizure durations ranged from 30-60 minutes in 58 patients, whereas 31 manifested refractory seizures longer than 60 minutes. Seizure control was achieved within 30 minutes in 55 patients, from 30-60 minutes in 19, and after 60 minutes in 15. Rectal diazepam was administered to 38 (42.7%) patients before admission to the hospital. Length of intensive care unit stay increased with increasing seizure duration ($P < 0.05$). The total mortality rate was 3.4%. This lower mortality rate may be considered evidence of the effectiveness and reliability of the status epilepticus treatment protocol in our pediatric intensive care unit. Prehospital rectal diazepam administration and the treatment of brain edema in the intensive care unit may be useful in the management of patients with status epilepticus.

Introduction

Status epilepticus is an acute neurologic condition that may be observed at any age, but more commonly occurs during childhood. In epidemiologic studies, the incidence of status epilepticus was reported at 17-23/100,000/year, varying by race and age [1-3]. Because status epilepticus is associated with high rates of morbidity and mortality, early diagnosis and proper treatment are of critical importance [4,5].

The International League Against Epilepsy defined status epilepticus as a seizure persisting for 30 minutes or longer, or two or more seizure activities between which patients do not fully regain consciousness [6]. In recent years, however, seizure durations of 5-10 minutes have been considered sufficient for a diagnosis of status epilepticus and the initiation of treatment [7]. In patients with status epilepticus, treatment before hospital admission has become increasingly important. An achievement in seizure control and a reduction in morbidity and mortality were demonstrated by early and effective treatment [3,8-11]. However, an ideal treatment protocol cannot be established because of the lack of large-scale comparative studies on pediatric status epilepticus. Thus, several treatment protocols varying according to different countries or regions have been used in recent years [1,2,12]. Despite advances in the intensive care of status epilepticus, rates of morbidity and mortality in childhood continue to be high.

The present study involved a retrospective evaluation of the etiology, treatment, and prognosis of patients treated for status epilepticus at a pediatric intensive care unit, and an assessment of the effectiveness of our treatment protocol.

Patients and Methods

The medical records of 89 patients with convulsive status epilepticus were retrospectively reviewed. Patients were diagnosed with status epilepticus according to the 2001 classification of the International League Against Epilepsy, and were treated at the Pediatric Intensive Care Unit of the Mersin University School of Medicine between January 2007 and December 2010. Data regarding age, sex, seizure duration, time to achieve seizure control, etiologic factors, medications used

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during treatment and their side effects, treatment duration, and prognoses (recurrent seizures as of 1 year follow-up and mortality) were evaluated. Patients with electric status epilepticus during slow wave sleep and nonconvulsive status epilepticus were excluded from the study.

Patients were allocated into four subgroups, according to etiology [1]: (1) cause unknown, i.e., status epilepticus without an acute cause and with normal findings of a neurologic examination; (2) remote symptomatic, i.e., status epilepticus occurring in the absence of any other acute cause in a child with a known neurologic disorder (e.g., cerebral palsy, developmental disorder of the central nervous system, hydrocephaly, and genetic disorders); (3) acute symptomatic, i.e., status epilepticus occurring during an acute disorder affecting the central nervous system (e.g., encephalitis, meningitis, hemorrhage, trauma, electrolyte imbalance, and hypoxia); and (4) prolonged febrile convulsions, i.e., status epilepticus occurring because of a febrile illness (axillary temperature, $\geq$38.3°C) other than a central nervous system infection in child without a previous history of afebrile seizures.

Patients were divided into two groups according to seizure duration: those with a seizure lasting between 30 and 60 minutes (initial status epilepticus), and those with a seizure lasting more than 60 minutes (refractory status epilepticus). Patients were divided into three groups according to their time to achieve seizure control: less than 30 minutes, between 30 and 60 minutes, and more than 60 minutes [1,7]. The cessation of status epilepticus was determined clinically and confirmed by an electroencephalogram. Seizure types were classified as primary or secondary generalized.

The treatment protocol at our center involved five procedures:

(1) In seizures lasting for 5 minutes, an intravenous bolus dose of 0.1 mg/kg midazolam was administered. If seizure control was not achieved within 5 minutes, the same dose of midazolam was repeated. If an intravenous route could not be obtained immediately, rectal diazepam was administered.
(2) If seizure control was not achieved within 15 minutes despite three intravenous bolus doses of midazolam, the loading of 20 mg/kg phenytoin (1 mg/kg/minute) was performed. In patients unresponsive to phenytoin loading, an additional 10 mg/kg phenytoin was loaded 10 minutes after the initial phenytoin loading. If the patient was receiving valproic acid (those more than 2 years of age and whose valproic acid blood level was low) because of previous seizures, valproic acid (30 mg/kg, intravenous) loading was initiated instead of a second phenytoin loading.
(3) In patients unresponsive to antiepileptic drug loading, an intravenous infusion of midazolam was initiated at a dose of 0.1 mg/kg/hour. The dose of midazolam was increased by 0.1 mg/kg/hour every 5 minutes until seizure control was achieved. The maximum dose of midazolam comprised 0.6 mg/kg/hour. After a seizure-free period of 24 hours, the infusion of midazolam was gradually reduced to 0.05-0.1 mg/kg/hour every 6 hours.
(4) Patients unresponsive to the maximum dose of midazolam infusion were intubated. An initial loading dose of 10 mg/kg intravenous thiopental was followed by a continuous intravenous maintenance infusion of 3-5 mg/kg/hour.
(5) In patients with evidence of brain edema on cranial imaging (computed tomography or magnetic resonance imaging), mannitol (0.5 g/kg, 30-minute infusion) and/or a 3% saline infusion (0.5-1 mL/kg/hour for 24-48 hours) was administered.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences, version 11.5 (SPSS, Inc., Chicago, IL). Age and length of stay in the pediatric intensive care unit were calculated as means $\pm$ standard deviations. Relationships between the data (e.g., etiology, seizure duration, time to achieve seizure control, and treatments before hospital admission) were evaluated using the χ^2 test. The Mann-Whitney U test was used for the comparison of seizure duration and status groups in terms of the duration of midazolam infusion and length of stay at the hospital, because the assumption of normality was not fulfilled. The Kruskal-Wallis test was used for the comparison of etiologic groups in terms of duration of midazolam infusion and length of stay in the hospital, because the assumption of normality was not fulfilled. The significance of individual differences was evaluated using the Dunn test if the Kruskal-Wallis test produced significant results. The probability of recurrent seizures in patients who did not receive treatment before hospital admission, compared with those who did, was expressed as an odds ratio. $P < 0.05$ was considered statistically significant.

Results

Eighty-nine patients (42 girls and 47 boys) with a mean age of 4.7 $\pm$ 3.8 years S.D. (range, 2 months to 18 years) were included. The mean length of stay in the pediatric intensive care unit was 5.0 $\pm$ 3.7 days S.D. Seizure durations ranged from 30-60 minutes in 58 (65.2%) patients, and longer than 60 minutes in 31 (34.8%) patients. Seizure control was achieved within 30 minutes in 55 (61.8%) patients, at 30-60 minutes in 19 (21.4%) patients, and after 60 minutes in 15 (16.8%) patients. Rectal diazepam was administered to 38 (42.7%) patients before hospital admission (at home or in the ambulance). Primary generalized seizures were observed in 64 (71.9%) patients, and secondary generalized seizures were observed in 25 (28.1%) patients. Seizure etiologies included remote symptomatic in 47 (52.7%), unknown cause in 15 (16.9%), febrile in 15 (16.9%), and acute symptomatic in 12 (13.5%) patients (Table 1). No electrolyte imbalance or metabolic problems were detected in any patients. Medical histories revealed at least one previous seizure in 68 (76.5%) patients, and epilepsy in 55 (61.8%) patients. The recurrence of epileptic seizures was observed in 71 (79.8%) patients, and the recurrence of status epilepticus was observed in 24 (27%) patients after an episode of status epilepticus during the 1-year follow-up.

All patients initially received three doses of 0.1 mg/kg intravenous midazolam. However, rectal diazepam was administered to three (3.4%) patients because of the failure of the intravenous route immediately. After three doses of midazolam, intravenous phenytoin loading was administered at a dose of 20 mg/kg. Seventy (78.6%) patients were resistant to treatment, and a third antiepileptic drug was initiated. Forty-eight (53.9%) patients required an additional phenytoin loading dose of 10 mg/kg. Among patients previously receiving valproate medication, intravenous valproate loading was performed in 22 (24.7%). An infusion of midazolam was performed in 65 (73%) patients. An infusion of thiopental was initiated in eight (9%) patients in whom seizure control could not be achieved despite the maximum dose (0.6 mg/kg/hour) of midazolam. Mannitol was administered in 39 (43.8%) patients in whom brain edema was detected with cerebral imaging. Hypertonic saline (3% NaCl) was also administered in addition to mannitol in nine of these 39 patients. Eight patients were treated with thiopental, and five of them were intubated. No severe adverse effects such as arrhythmia, respiratory arrest, or reduction in oxygen saturation occurred during treatment. Agitation was observed in two of 65 patients with an infusion of midazolam, and three of eight patients developed hypotension during thiopental infusion. Of 89 patients, three (3.4%) died during treatment (Fig 1). Two of these patients were referred from another center because of uncontrolled seizures, and they had been diagnosed with an acute symptomatic etiology (trauma and encephalitis). The other patient was admitted to our hospital with status epilepticus attributable to a remote symptomatic etiology (developmental anomaly of the central nervous system). All three patients died because of herniation secondary to severe brain edema.

Table 1. Demographic data and clinical findings of patients

	Remote Symptomatic (n)	Unknown Cause (n)	Febrile (n)	Acute Symptomatic (n)	*P*
Age (years)*	6.3 $\pm$ 4.2	4.7 $\pm$ 3.3	1.9 $\pm$ 0.9	5.5 $\pm$ 5.1	<0.05
Sex					
Girl	25	6	6	5	>0.05
Boy	22	9	9	7	
Seizure duration					
30-60 minutes	30	14	8	6	>0.05
>60 minutes	17	1	7	6	
Time to achieve seizure control					
<30 minutes	30	13	7	5	>0.05
30-60 minutes	9	1	5	4	
>60 minutes	8	1	3	3	
Prehospital treatment					
Yes	26	7	4	1	<0.05
No	21	8	11	11	

* Age provided as mean $\pm$ S.D.

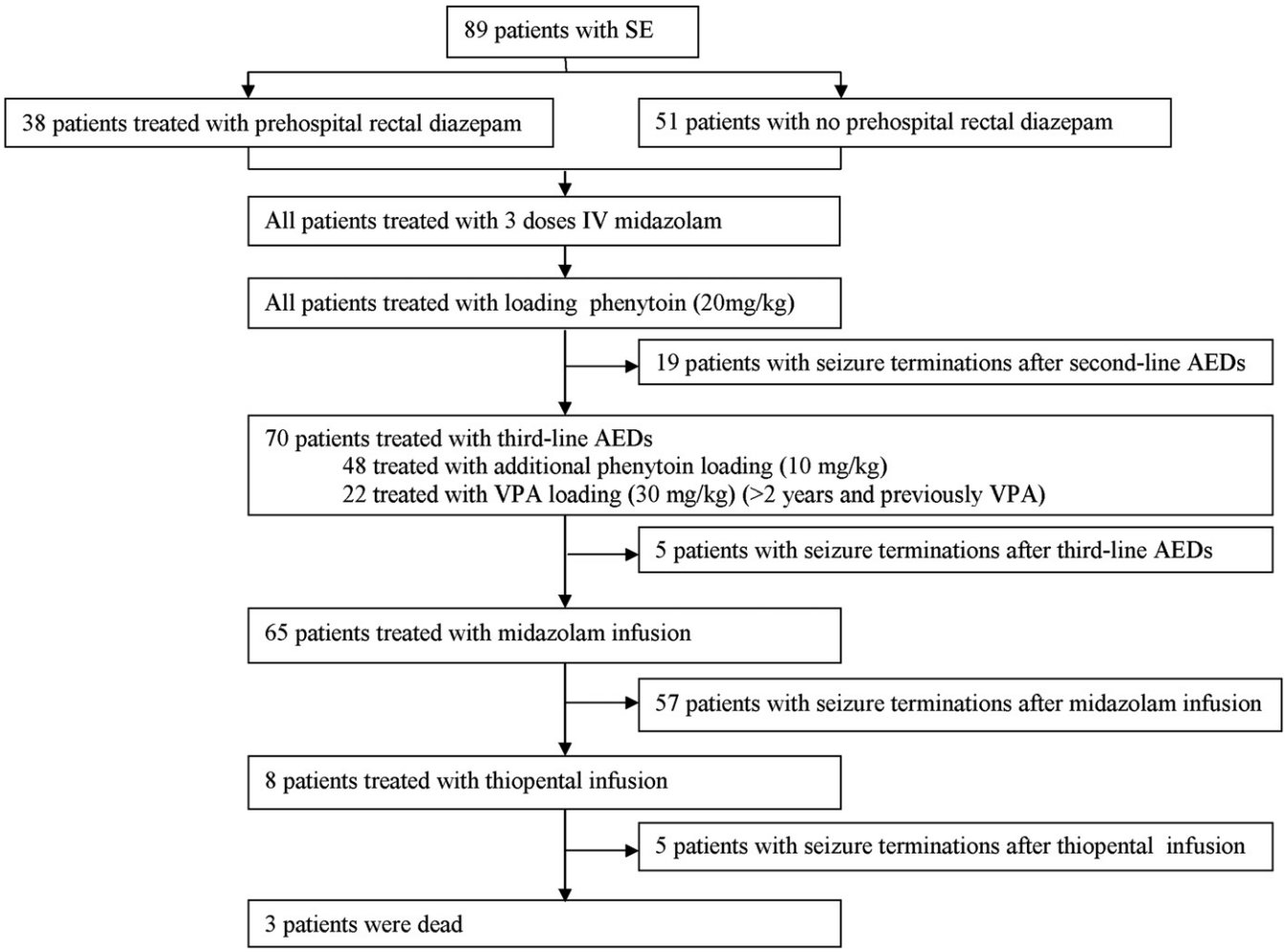

Figure 1. Study profile. AEDs, antiepileptic drugs; IV, intravenous; SE, status epilepticus; VPA, valproic acid.

Time to achieve seizure control, duration of midazolam infusion, and length of stay significantly increased with increasing duration of status epilepticus ($P < 0.05$). In patients who received rectal diazepam before hospital admission (Table 2), the duration of seizure and time to achieve seizure control were significantly shorter ($P < 0.05$ for each), and the requirement for a third antiepileptic drug and the need to treat brain edema were significantly less common ($P < 0.05$ for each). No significant difference was evident in terms of length of stay between patients who received rectal diazepam before hospital admission and those who did not receive rectal diazepam ($P > 0.05$). The probability of recurrent seizures in patients who did not receive treatment before hospital admission was determined to be 5.5 times higher than in those who received treatment before hospital admission (odds ratio, 5.5; 95% confidence interval, 2.72-10.31; $P < 0.05$).

The risk of recurrent seizures after status epilepticus was significantly higher in patients with a remote symptomatic etiology than in patients with other etiologies ($P < 0.05$). Moreover, the rate of previous history of status epilepticus and epilepsy was significantly higher in patients with a remote symptomatic etiology ($P < 0.05$). Length of stay at the pediatric intensive care unit was significantly longer in patients with additional neurologic problems, compared with those lacking any additional neurologic problems ($P < 0.05$). A significant association was evident between acute symptomatic etiology and refractory status epilepticus ($P < 0.05$).

The risk of recurrent seizures after status epilepticus was significantly higher for patients treated with an infusion of thiopental ($P < 0.05$).The risk of recurrent seizures increased when the length of stay at the pediatric intensive care unit was longer ($P < 0.05$). The length of stay at the pediatric intensive care unit was significantly longer for patients who received midazolam infusion ($P < 0.05$).

Discussion

Status epilepticus is an emergent neurologic condition that can occur because of different etiologies, and most patients have a favorable prognosis with successful treatment. Etiologies, risk factors, and prognoses vary depending on several factors, including age, sex, and socioeconomic status. In epidemiologic studies, the incidence of pediatric status epilepticus in developed countries was reported to be 17-23/100,000/year, whereas higher rates were reported in developing countries. This difference has been attributed to infection, trauma, and low socioeconomic status [1-4].

Studies on the etiology of status epilepticus have revealed differing results. Saz et al. reported that infections of the central nervous system comprised the most common cause of status epilepticus in patients admitted to the emergency room [13]. On the other hand, Valencia et al. reported that remote symptomatic etiologies comprised the most frequent cause of status epilepticus in

Table 2. Outcomes of patients with and without prehospital treatment

	With Prehospital Treatment (n)	Without Prehospital Treatment (n)	*P*
Seizure duration (minutes)			
30-60	31	27	<0.05
>60	7	24	
Time to achieve seizure control (minutes)			
<30	31	24	<0.05
30-60	4	15	
>60	3	12	
Third antiepileptic drug			
Administered	26	36	<0.05
Not administered	12	15	
Treatment for brain edema			
Administered	29	21	<0.05
Not administered	9	30	

the pediatric intensive care unit [4]. Chin et al. reported that the most frequent cause of status epilepticus in a series of 176 patients involved prolonged febrile seizures [1]. Similar to the results of Valencia et al. [4], we observed that the most common cause of status epilepticus involved a remote symptomatic etiology (in 52.8% of patients) at our pediatric intensive care unit.

Patients with epilepsy demonstrate a 10-20% risk of developing status epilepticus within the first few years after diagnosis [7,12]. Status epilepticus is more common in patients with a history of epilepsy. Status epilepticus can also be observed as the first seizure in childhood epilepsy. Although 5% of febrile convulsions manifest as status epilepticus, many acute symptomatic patients (with trauma and infection of the central nervous system) have no history of seizures before status epilepticus. Although Besli et al. [14] reported a history of epilepsy or seizure before status epilepticus in 55.4% of their patients, Asadi-Pooya and Poordast [15] reported a rate of 28% in their patients. In the present study, 76.5% of patients had a previous history of epilepsy or at least one seizure. The higher rate of epilepsy history in our study may be attributed to the fact that 52.8% of our patients had a remote symptomatic etiology, and that our hospital is a tertiary care center in the region.

Differing rates of the risk for recurrent status epilepticus were reported in previous studies [1,3,14,16]. Chin et al. reported a recurrence rate of 16% at 1-year follow-up after status epilepticus [1]. Lin et al. reported a recurrence rate of 8.5% after status epilepticus at 1-year follow-up [17]. An association between the risk of recurrent status epilepticus and etiology was suggested in previous studies [1,14,16]. The risk of recurrence in patients with a remote symptomatic etiology and progressive neurologic disorders was determined to be 3-23 times higher than in patients with status epilepticus exhibiting normal neurologic development [1,3,14,16]. In the present study, the recurrence rate of status epilepticus was 27% during the 1-year follow-up period. The higher rate of recurrence observed in the present study may be attributed to our higher rate of patients with a remote symptomatic etiology. Moreover, similar to the data in the literature, we observed a significant association between remote symptomatic etiology and the recurrence of status epilepticus ($P < 0.05$).

Seizures lasting longer than 60 minutes are defined as refractory status epilepticus. The rates for refractory status epilepticus were reported to range from 24.8-33% [13,15,17,18]. In the present study, the rate of refractory status epilepticus was 34.8%. The higher rate of refractory status epilepticus observed in our study may be attributed to the inclusion of patients from the pediatric intensive care unit. A significant association between refractory status epilepticus and acute symptomatic etiology was determined in studies by Lin et al. [17] and Maytal et al. [18]. Similarly, we observed a significant association between status epilepticus attributable to an acute symptomatic etiology and refractory status epilepticus ($P < 0.05$).

Treatment protocols for status epilepticus generally include medications and interventions performed in the hospital setting. More than 75% of status epilepticus cases have been determined to involve community-onset status epilepticus [1,3,9]. Early and effective treatment before hospital admission in patients with community-onset status epilepticus was reported to be of importance for seizure control and the reduction of morbidity and mortality [3,8-11]. However, the rate of prehospital treatment was reported to be insufficient, especially in patients with first-time seizures and status epilepticus attributable to an acute symptomatic etiology [1,9]. Chin et al. reported that rectal diazepam was administered in two thirds of 182 patients before hospital admission, and none of those patients developed refractory status epilepticus [9]. Vignatelli et al. attributed the high mortality rate (39%) in their patients with status epilepticus to the low rate (17%) of prehospital treatment [8]. Although rectal diazepam and nasal or buccal midazolam have been recommended by various centers as antiepileptic drug alternatives outside the hospital, rectal diazepam is the single choice of treatment in Turkey, because nasal midazolam is not available. In the present study, we documented that rectal diazepam was administered in 38 (42.7%) of 89 patients before admission to our hospital. In patients who received rectal diazepam before hospital admission, seizure duration and time to achieve seizure control were shorter ($P < 0.05$ for each), and the need for a third antiepileptic drug or treatment for brain edema ($P < 0.05$ for each) were less common, compared with those who had not received rectal diazepam before hospital admission. The most important and well-known adverse effect of rectal diazepam has been reported to be respiratory depression [9,11]. In the present study, respiratory depression attributable to rectal diazepam before hospital admission was not observed in any patients.

Although lorazepam and midazolam comprise the most frequently preferred antiepileptic drugs during treatment in the hospital setting, lorazepam is not available in Turkey. Because it consists of a water-soluble molecule with a short half-life, a rapid onset of action, and an inactive metabolite, midazolam is used as a first-line benzodiazepine that can be administered via nasal, buccal, intraosseous, intramuscular, and intravenous routes. All of our patients were treated with three doses of midazolam intravenously. If seizure control could not be achieved with this treatment, an additional antiepileptic drug (phenytoin or valproic acid) was loaded in our patients. Valproic acid was administered to patients receiving valproic acid treatment previously with low blood levels. If seizure control could not be achieved by antiepileptic drug loading, midazolam infusion was initiated. In our study, the efficacy of midazolam infusion in seizure control was measured at 87.7% (57/65). Hayashi et al. reported that midazolam infusion was effective for seizure control in 88% of their patients with status epilepticus [19]. Saz et al. reported that rate to be 95% [13]. In previous studies of status epilepticus, various rates of seizure control with midazolam infusion, ranging from 75-100%, were reported [19-21]. Our results were similar to those previously reported rates.

The mortality rate of patients with status epilepticus varies depending on etiology, age, seizure duration, and time of treatment initiation. The short-term (30-60 day) mortality rate after status epilepticus was reported at between 2.7% and 5.7% [1,2,12,14,18]. However, this rate was reported at between 5% and 9.3% in patients admitted to pediatric intensive care units [5,10,12,22]. The short-term mortality rate of our patients after status epilepticus (3.4%) was lower than previously reported mortality rates in pediatric intensive care units. This lower mortality rate may be considered evidence of the success of our treatment protocol.

The role of treatment for brain edema in the management of status epilepticus remains controversial. Status epilepticus may induce brain edema, but no data have established the benefits of antiedema treatment during status epilepticus [22-24]. Edema attributable to neuronal membrane injury caused by hypoxia and ischemia leads to an increase in intracranial pressure. The administration of mannitol and 3% saline solution was recommended to induce osmotic diuresis for the treatment of increased intracranial pressure attributable to hypoxia. The most frequent cause of status epilepticus-related mortality comprises herniation caused by increased intracranial pressure secondary to hypoxia because of prolonged seizures. Herniation especially develops secondary to refractory status epilepticus. Brain edema was observed on imaging studies in 39 (43.8%) of our 89 patients. Only mannitol was administered in 30 of these patients, whereas mannitol plus 3% saline infusion was administered in nine patients. Of patients who received treatment for brain edema, 22 manifested refractory seizures. A statistically significant association was evident between prolonged duration of seizures and treatment for brain edema ($P < 0.05$). In an animal study, Dudek et al. [25] reported that epileptiform activity was suppressed by mannitol and furosemide. The suppression of epileptiform activity by mannitol in patients with epilepsy was also described by Haglund and Hochman [26] in 2005. Because the patient profile in the present study was similar to that in previous studies, the lower mortality rate determined in the present study may be associated with the additional effectiveness of antiedema treatment.

In conclusion, because of a lack of large-scale, randomized, controlled trials on childhood status epilepticus, an optimal treatment protocol has not yet been established. When compared with mortality rates in the literature, the lower mortality rate in the present study may be considered evidence of the effectiveness and reliability of the status epilepticus treatment protocol in our department. We also suggest that prehospital rectal diazepam plays an important role, and that the treatment of brain edema in the intensive care unit may be useful, in the management of patients with refractory status epilepticus. Future large-scale, randomized, controlled trials studies are necessary to evaluate the effectiveness of prehospital treatment and the treatment of brain edema in the management of status epilepticus.

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