Clinical Features And Prognostic Factors For Status Epilepticus In The Pediatric Emergency Department: A Retrospective Study

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Abstract

Background: Uncontrolled status epilepticus (SE) causes damage to all organs, especially the brain. Although there are guidelines regarding the management of convulsive SE, the timing for administering first-line rescue medications (RMeds) remains unclear. Therefore, we analyzed patients with persistent SE lasting for >30 min, who visited the pediatric emergency department (pED), to determine clinical features and risk factors and provide directions for management on arrival to the pED.

Methods: This study was conducted by retrospectively reviewing medical charts of patients aged 0–19 years diagnosed with SE and accompanying motor seizures, who visited the pED between January 2010 and December 2019. After arrival at the pED, patients were divided into two groups, namely ≥30 min (n = 12) and <30 min (n = 13), according to the additional seizure time and administration of the first dose of RMeds before and after 5 min.

Results: Seizures lasting for <30 min were mainly belonged to idiopathic SE in the pED. Among four SE patients who needed intensive care unit (ICU) management, three had delayed administration of RMeds of >5 min, which was statistically significant; hence, more hospitalizations in the ICU were observed when RMed administration was delayed (p = 0.047). In acute symptomatic SE such as encephalitis, more than three doses of RMeds were needed to control seizures.

Conclusions: Patients with convulsive SE should arrive at the pED as soon as possible and immediately receive RMeds after arrival at the pED for good outcomes.

Background

Status epilepticus (SE) is a life-threatening neurological problem and is one of the most critical issues that needs to be controlled in the pediatric emergency department (pED). SE in pediatric patients is accompanied by neurodevelopmental sequelae as observed in both survivors and non-survivors [1–5]. In 2015, the International League Against Epilepsy (ILAE) provided a new definition for SE; however, it is generally referred to as involving seizures lasting for more than 30 min, which supports the possibility of irreversible nerve damage after 30 min of sustained seizure activity [6–8].

There are two treatment guidelines for SE involving motor seizures: one proposed by the Neurocritical Care Society (NCS) in 2012 and the other proposed by the American Epilepsy Society (AES) in 2016. The two guidelines are similar and the only main difference is the timing for administering first-line rescue medications (RMeds) such as benzodiazepine (BZD) [9, 10].

Seizure duration can change the systemic physiology and metabolism in the brain. If the seizure is prolonged, then compensatory mechanisms may not respond appropriately, possibly leading to brain damage and organ failure [11–13]. Moreover, as the seizure persists, response to RMeds decreases [14–16]. Therefore, it is important to arrive at a medical institution as soon as possible to receive treatment when seizures begin.

In this study, we aimed to analyze patients with convulsive SE lasting for > 30 min and who visited the pED to determine clinical features and risk factors that cause seizures to persist and provide directions for management after arriving at the pED.

Methods

Ethics statement

The research was approved by the institutional review board (approval no. 4-2020-1224) of the Yonsei University Health System. The need for informed consent was waived because of the retrospective nature of the study.

Patients and study design

This study was conducted by retrospectively reviewing medical charts of 164 patients aged 0–19 years who were diagnosed with SE for the first time accompanied by focal or general motor seizures and who visited the pED at Severance Hospital in Seoul, Korea, between January 2010 and December 2019. To analyze persistent SE cases accompanied by motor seizures lasting for > 30 minutes (min) after the onset of motor seizures, we excluded patients who did not meet the criteria for SE (n = 102). The definition for SE used in this study was that proposed by the ILAE in 2015 [6]. We also excluded 37 patients who were transferred to the pED for further evaluation and management after achieving control of SE in other hospitals (Fig. 1). Henceforth, continuous SE cases accompanying motor seizures will be referred to as SE for convenience.

We analyzed the patient groups as 1) motor seizure time after arrival at the pED (< 30 min vs ≥ 30 min), and 2) at the time of first RMeds administration after arrival (≤5 min vs > 5 min), and 3) etiology type. The etiology has been classified into idiopathic SE and acute symptomatic SE, which develops acutely, such as infection related to the central nervous system. Finally, chronic symptomatic SE is related to congenital abnormalities such as genetic abnormalities and brain damage in the neonatal period. The outcomes were analyzed by dividing them into 1) required endotracheal intubation, 2) required intensive care unit (ICU) care, or 3) expired cases.

Statistical analysis

Descriptive statistics are expressed as the median value and the interquartile range (IQR) and as frequency and percentage for continuous and categorical variables, respectively. Logistic regression analysis was used to compare the categorical and continuous variables. A p-value < 0.05 was considered statistically significant. We rounded off the fourth decimal place and presented the values as numbers up to the third decimal place. All statistical analyses were performed using SAS, version 9.3 (SAS Institute, Cary, NC, USA).

Results

This study enrolled 25 patients who had persistent SE lasting for > 30 min. Table 1 shows detailed information of the demographic and clinical characteristics of the patients. Eleven patients (44%) were male and 14 (56%) were female. Their median age was 39 (IQR: 24.0–84.0) months, and the average time to arrive at the pED was 40 (IQR: 30.0–60.0) min. The first-line RMed administered to the patients was BZD. The generalized type of motor seizures was noted in 80% of the patients, and the focal type was observed in 20%. Etiologically, 28% of the cases were idiopathic, and 28% were accompanied by acute symptomatic disorders such as encephalitis. Finally, 44% of the cases were accompanied by chronic symptomatic conditions such as neonatal brain injury.

Table 1
Demographic and clinical characteristics of the study patients with status epilepticus according to the duration of motor seizures after arrival at the pediatric emergency department.

Variable	Total (n = 25)	mSZ duration of < 30 min (n = 13)	mSZ duration of ≥ 30 min (n = 12)	*p*
[a]Age (mo)	39.0 (24.0–84.0)	39.0 (30.0–84.0)	36.0 (21.2–71.5)	0.855
[a]Sex (male)	11 (44)	6 (46.2)	5 (41.7)	0.842
[a]Time to arrival to the pED (min)	40.0 (30.0–60.0)	40.0 (30.0–40.0)	60.0 (56.2–112.5)	0.051
[a]Time to the first dose of rescue medication (min)	1.0 (1.0–5.0)	3.0 (1.0–5.0)	1.0 (1.0–4.2)	0.984
[b]Type of motor seizure				0.551
General/Focal	20 (80)/5 (20)	11 (84.6)/ 2 (15.4)	9 (75)/ 3 (25)	
[b]Etiology				0.842
Idiopathic	7 (28)	5 (38.5)	2 (16.7)	
Acute symptomatic	7 (28)	3 (23.1)	4 (33.3)	
Encephalitis	4 (16)	1 (7.7)	3 (25)	
PRESS	1 (4)	1 (7.7)	0	
Complex febrile seizure	1 (4)	1 (7.7)	0	
Brain tumor	1 (4)	0	1 (8.3)	
Chronic symptomatic	11 (44)	5 (38.5)	6 (50)	
Neonatal brain injury	7 (28)	5 (38.5)	2 (16.7)	
Congenital brain AbNL	4 (16)	0	4 (33.4)	
[b]First rescue medication				1.000

[a]Data are expressed as the median (interquartile range).

[b]Data are expressed as n (%)

mSZ: motor seizure; pED: Pediatric emergency department; PRESS: Posterior reversible encephalopathy syndrome; AbNL: Abnormality; DZP: Diazepam; LZP: Lorazepam; MDZ: Midazolam

Variable	Total (n = 25)	mSZ duration of < 30 min (n = 13)	mSZ duration of ≥ 30 min (n = 12)	*p*
DZP	6 (24)	3 (23.1)	3 (25)	
LZP	18 (72)	9 (69.2)	9 (75)	
MDZ	1 (4)	1 (7.7)	0 (0)	
[a]Data are expressed as the median (interquartile range).				
[b]Data are expressed as n (%)				
mSZ: motor seizure; pED: Pediatric emergency department; PRESS: Posterior reversible encephalopathy syndrome; AbNL: Abnormality; DZP: Diazepam; LZP: Lorazepam; MDZ: Midazolam				

When the two groups depending on the seizure duration after admission to the pED (seizures lasting < 30 min (n = 13) or those lasting > 30 min (n = 12) in the pED) were compared, there was no significant between-group difference. The average time taken for administering the first-line RMed was 1 (IQR: 1–5) min in all cases. Furthermore, the average time taken for RMed administration was 3 min and 1 min for patients with seizures lasting for < 30 min and ≥ 30 min, respectively; however, there was no statistically significant difference. More generalized types of seizures were also observed in addition to focal-type seizures in both groups.

We examined patients based on the time taken for administering first-line RMeds after arrival at the pED (Table 2). When the first-line RMed was administered ≤ 5 min, the median time of persistent motor seizures observed in pED was 10 (IQR: 3.2–27.7) min. However, when the time is taken to administer RMed was > 5 min, the seizures could be observed for 18 (IQR: 6.5–39.0) min after admission to the pED, which is not statistically significant. ICU care was required in 42.9% of the cases in which RMed was administered > 5 min after arrival at the pED ($p = 0.047$).

Table 2
Comparison between groups with regard to first-line rescue medication administered < 5 min or ≥ 5 min after arrival at the pediatric emergency department

Variable	Total (n = 25)	≤5 min (n = 18)	> 5 min (n = 7)	*p*
[a]mSZ duration after arrival at pED	10.0 (5.0–30.0)	10 (3.2–27.7)	18.0 (6.5–39.0)	0.696
Endotracheal intubation	3 (12%)	1 (5.6%)	2 (28.6%)	0.148
ICU care	4 (16%)	1 (5.6%)	3 (42.9%)	0.047
Expire	2 (8%)	1 (5.6%)	1 (14.3%)	0.485
[a]The data unit is min, which is expressed as the median (interquartile range).				
mSZ: motor seizure; pED: pediatric emergency department; ICU: intensive care unit				

We also analyzed the relationship between the etiology and the frequency of RMed administration. In the idiopathic group, seizures were controlled after the first- or second-line RMed administration in 28.6% of the patients. Among patients with chronic problems, such as brain injury in the neonatal period, seizures were controlled in seven (63.7%) patients after the administration of first- and second-line RMeds, and four patients (36.4%) needed more than three doses to achieve seizure control. However, in acute symptomatic SE (n = 7), such as encephalitis, five patients (71.4%) needed three or more doses of RMeds to achieve seizure control (Fig. 2).

Discussion

In the early stage of SE, seizures can be easily controlled by drugs that reduce excitement or enhance inhibition. However, the effectiveness of gamma aminobutyric acid (GABA)-ergic drugs such as BZD decreases over time [14–16], because repetitive seizures reduce the number of functional GABA receptors through the inactivation process that converts GABA receptors into vesicles and transfers them to lysosomes or the Golgi apparatus [16, 17]. Therefore, rapid administration of RMeds is an essential part of SE management [18]. SE is considered to pose a potential threat to the human brain, leading to damage, when it occurs for over 30 min [6,8,11–13,19,20]. In our study, we examined patients who had motor seizures lasting for 30 min accompanied by potential brain damage, and they were considered to show poor response to GABAergic drugs. We determined whether the prognosis of these patients was different after arriving at the emergency room according to the clinical characteristics that cause long-term seizures and the administration time of RMed.

More than three doses of RMed were required to control convulsive SE in 71.4% of acute symptomatic cases. On the other hand, in 42.9% and 36.4% of idiopathic and chronic symptomatic convulsive SE cases, respectively, more than three doses were required. It is thought that detailed medical history-taking in the pED can provide clinicians with important data for predicting the prognosis of SE. Additionally, if multiple medications are required to stop seizures, then, brain imaging and cerebrospinal fluid testing

should focus on identifying diseases such as encephalitis, which can be affected by cognitive dysfunction and life-threatening conditions if proper treatment is not provided.

If SE with motor seizures persists for > 30 min, then, homeostatic failure may set in and instability of vital signs may occur [11–13]. Therefore, if the duration of motor seizures is not precise, according to the physician's judgement, endotracheal intubation can be performed before other treatments such as immediate administration of first-line RMed. In this study, only three patients required endotracheal intubation, and two patients required the use of inotropes owing to hypotension. When RMed administration was > 5 min, a trend of requiring ICU treatment was observed, which was statistically significant. Thus, the rapid control of seizures is considered important, and we emphasize on educating caregivers regarding the impact of seizure duration on prognosis and consider approving the administration of prehospital drugs (e.g., DZP rectal gel) in prehospital emergency medical services. It is necessary to establish a system that allows quick transfer of patients to the pED on arrival.

This study had some limitations. For example, this study was performed with a small number of enrolled patients recruited from a single institution. Primary data collection was performed retrospectively, which could be inaccurate. Moreover, there could be selection bias.

In the future, based on the research finding that the number of functional N-methyl-D-aspartate receptors and the number of functional GABA receptors at synapses may change as SE progresses [16, 17], further studies are needed regarding first- and second-line RMeds used in pEDs. Further research on the prevention of brain damage caused by persistent SE and the postictal phase management should also be conducted.

Conclusions

Achieving seizure control in persistent SE is challenging and if inadequately managed, it can lead to organ failure such as brain damage. Convulsive SE with chronic symptomatic disorder, such as neonatal brain injury, shows a longer duration than other etiologies; however, in acute symptomatic cases, more than three doses of RMeds are frequently required. For good outcomes in convulsive SE patients, patients should reach pED as soon as possible after the onset of seizures, and RMeds should be rapidly administered after arrival at the pED.

Abbreviations

AbNL: Abnormality; AES: American Epilepsy Society; BZD: Benzodiazepine; DZP: Diazepam; GABA: Gamma aminobutyric acid; ICU: Intensive care unit; ILAE: International League Against Epilepsy; IQR: the interquartile range; LZP: Lorazepam; MDZ: Midazolam; mSZ: motor seizure; NCS: Neurocritical Care Society; pED: pediatric emergency department; PRESS: Posterior reversible encephalopathy syndrome; RMeds: rescue medications; SE: Status epilepticus

Declarations

Ethics approval

This study was approved by the Institutional Review Board at Severance Hospital (4-2020-1224).

Consent to participate

Written consent was not necessary for this study because of the retrospective design.

Consent for publication

All authors provide permission for publication.

Availability of data and materials

The datasets analyzed in this study are available from the author on request.

Conflicts of interest/Competing interests

The authors have no relevant financial or non-financial interests to disclose.

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Authors' contributions

KCM and ESH designed the study. ESH collected and analyzed the study data. KCM supervised the data collection and conduct of the study. ESH wrote the original draft. KCM and KHE reviewed and edited the manuscript. All authors contributed equally to data interpretation and literature search.

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Not applicable

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Figures

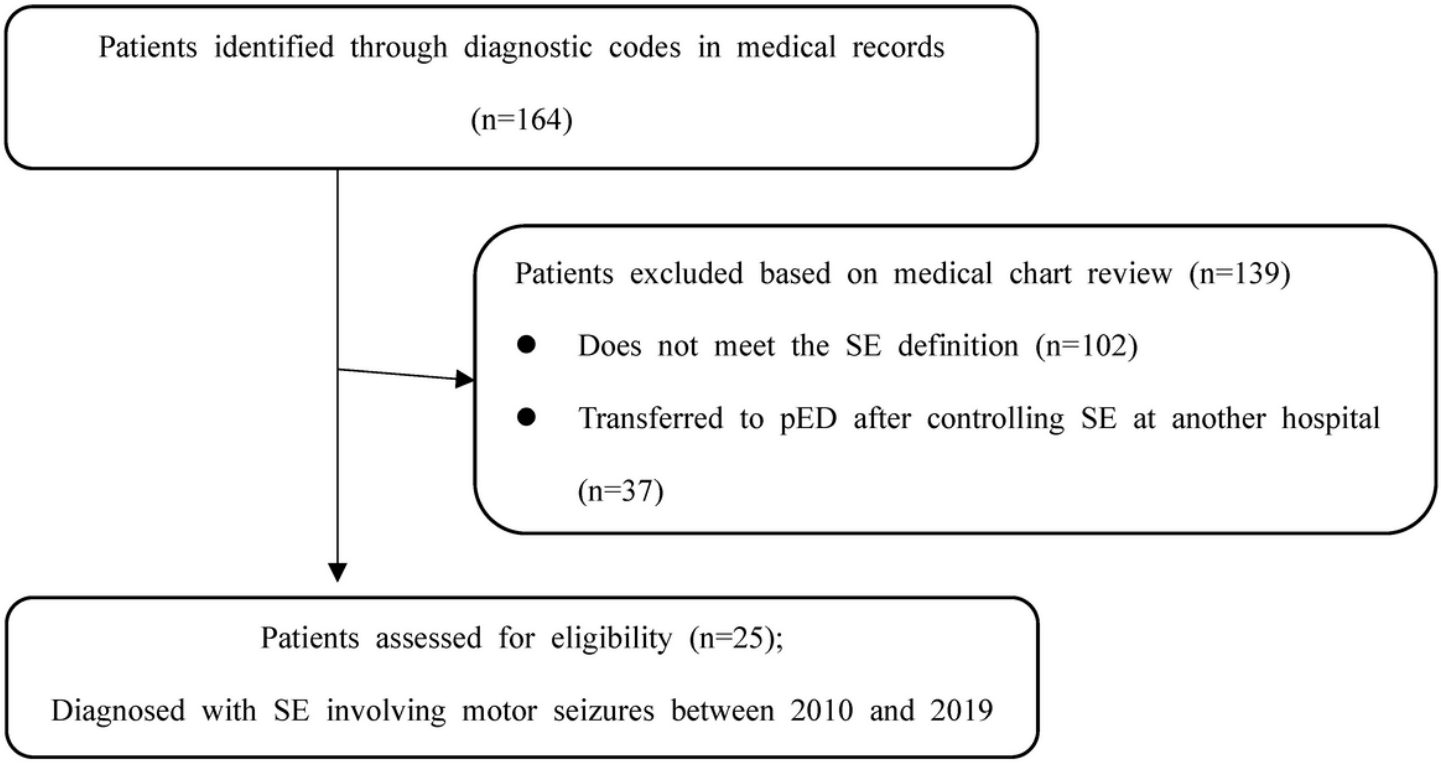

Figure 1

Flowchart of the protocol for the selection of study participants

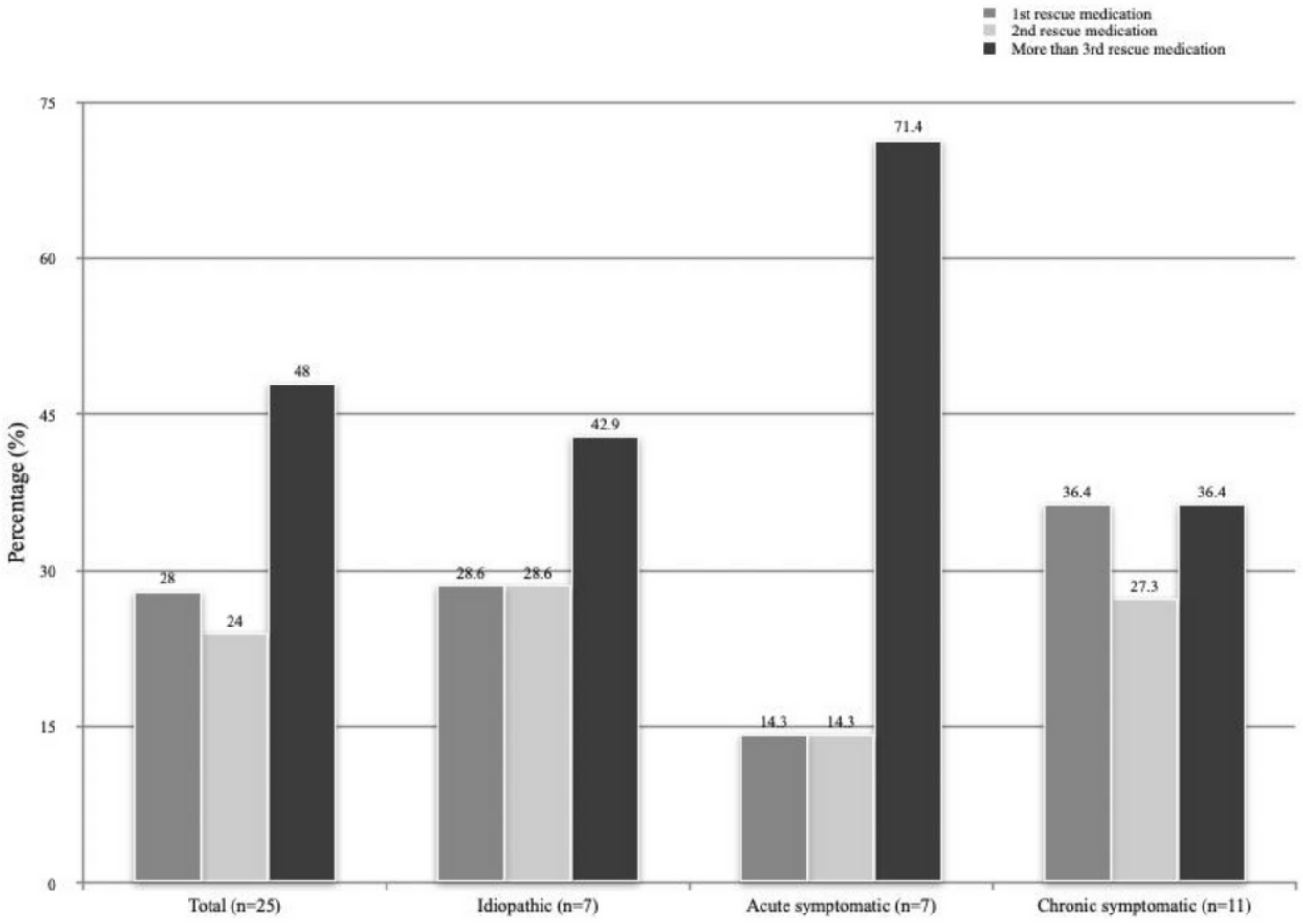

Figure 2

Bar graph of the frequency of the administration of rescue medication for achieving seizure control