Clinical features and prognostic factors for status epilepticus in the pediatric emergency department: A retrospective study

Sohyun Eun

Severance Hospital, Severance Hospital <https://orcid.org/0000-0002-9598-7519>

Hye Eun Kwon

Kwandong University Medical Library: Catholic Kwandong University College of Medicine

Heung Jin Kim

Severance Hospital

Seo Hee Yoon

Severance Hospital

Moon Kyu Kim

Severance Hospital

Se Hee Kim

Severance Hospital

Joon Soo Lee

Severance Hospital

Heung Dong Kim

Severance Hospital

Hoon-Chul Kang

Severance Hospital

Chungmo koo (✉ CM0904@yuhs.ac)

Severance Children's Hospital, Yonsei University College of Medicine <https://orcid.org/0000-0003-1434-6988>

Original research

Keywords: Status epilepticus, Pediatric emergency department, Rescue medication, Prognostic factor

Posted Date: March 30th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-354750/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Loading [MathJax]/jax/output/CommonHTML/jax.js

Abstract

Background: Uncontrolled seizures cause damage to all organs, especially the brain. Although there are guidelines regarding the management of status epilepticus (SE) involving motor seizures, the timing for administering first-line rescue medications (RMeds) remains unclear. Therefore, we analyzed patients with persistent SE lasting for >30 min and 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 who were diagnosed with SE accompanying motor seizures and who visited the pED between January 2010 and December 2019. After pED arrival, patients were divided into two groups, namely ≥ 30 min ($n = 12$) and < 30 min ($n = 13$), according to the additional seizure time and receipt of the first dose of RMeds before and after 5 min.

Results: Seizures lasting for < 30 min were mainly observed for the etiology of idiopathic SE in the pED. Among four SE patients who needed intensive care unit (ICU) management, three had delayed administration of RMeds of more than 5 min, which was statistically significant because 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 stop seizures.

Conclusions: Patients with convulsive status epilepticus should receive RMeds after arrival at the pED.

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, International League Against Epilepsy (ILAE) reported a new definition for SE; however, it is generally referred to as involving seizures lasting for more than 30 min, which supported 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, but 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 gaining control of SE in other hospitals (Fig. 1). Henceforth, continuous SE cases accompanying motor seizures will be referred to as SE for convenience.

We have analyzed the patient group 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 the endotracheal intubation, 2) required the 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

Loading [MathJax]/jax/output/CommonHTML/jax.js

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 patients, and the focal type was observed in 20%. Etiologically, 28% of cases were idiopathic, and 28% of cases were accompanied by acute symptomatic disorders such as encephalitis. Finally, 44% of cases were accompanied by chronic symptomatic conditions such as neonatal brain injury.

When the patients were divided into 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. and compared, there was no significant difference among patients with seizures lasting for < 30 min compared to those with seizures lasting for $\geq$ 30 min in the pED. The average time taken for administering the first-line RMed was 1 (IQR: 1–5) min in all cases. However, when dividing the patients into two groups and comparing them, the average time taken for RMed administration was 3 min for patients with seizures lasting for < 30 min and 1 min for patients with seizures lasting for $\geq$ 30 min, but 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 $\leq$ 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. The ICU care was required in 42.9% of cases in which RMed was administered > 5 min after arrival at the pED ($p = 0.047$).

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

Discussion

In the early stage of SE, seizures can be easily stopped 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, the rapid administration of RMed 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 30 min [6, 8, 11–13, 19, 20]. The abovementioned information is reported in several studies. 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 3 doses of RMed were required to stop 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, they required more than three doses, respectively. Those could be thought 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 begin, and instability of vital signs may occur [11–13]. Therefore, if the duration of motor seizures is not precise and physicians judge that by admitting late at the pED, then endotracheal intubation can be easily determined 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., Diazepam rectal gel) in prehospital emergency medical services. It is necessary to establish a system that can be quickly transferred to the pED when a patient arrives.

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 RMed 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

Persistent SE makes it difficult to gain control and leads to organ failure such as brain damage. For good outcomes in convulsive SE patients, they should reach pED as soon as possible after the onset of

Loading [MathJax]/jax/output/CommonHTML/jax.js nistered after arrival at the pED.

List Of Abbreviations

SE: Status epilepticus; pED: pediatric emergency department; NCS: Neurocritical Care Society; AES: American Epilepsy Society; RMed: Rescue medication; BZD: Benzodiazepine; ICU: Intensive care unit

Declarations

Acknowledgements

Not applicable.

Funding

Not applicable.

Availability of data and materials

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

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.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board at Severance Hospital (4-2020-1224). Written consent was not necessary for this study because of the retrospective design.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

Please contact author for data requests.

References

1. Sánchez Fernández I, Jackson MC, Abend NS, Arya R, Brenton JN, Carpenter JL, et al. Refractory Loading [MathJax]/jax/output/CommonHTML/jax.js without prior epilepsy or status epilepticus. Neurology.

- 2017;88:386–94.
2. Chin RFM, Neville BGR, Peckham C, Bedford H, Wade A, Scott RC. Incidence, cause, and short-term outcome of convulsive status epilepticus in childhood: prospective population-based study. *Lancet*. 2006;368:222–9.
 3. Loddenkemper T, Syed TU, Ramgopal S, Gulati D, Thanaviratananich S, Kothare SV, et al. Risk factors associated with death in in-hospital pediatric convulsive status epilepticus. *PLoS One*. 2012;7:e47474.
 4. Maytal J, Shinnar S, Moshé SL, Alvarez LA. Low morbidity and mortality of status epilepticus in children. *Pediatrics*. 1989;83:323–31.
 5. Chin RFM, Neville BGR, Scott RC. A systematic review of the epidemiology of status epilepticus. *Eur J Neurol*. 2004;11:800–10.
 6. Trinka E, Cock H, Hesdorffer D, Rossetti AO, Scheffer IE, Shinnar S, et al. A definition and classification of status epilepticus - Report of the ILAE Task Force on Classification of Status Epilepticus. *Epilepsia*. 2015;56:1515–23.
 7. Treatment of Convulsive Status Epilepticus. Recommendations of the Epilepsy Foundation of America's Working Group on Status Epilepticus. *JAMA*. 1993;270:854–9.
 8. Guidelines for epidemiologic studies on epilepsy. Commission on Epidemiology and Prognosis, International League Against Epilepsy. *Epilepsia*. 1993;34:592–6.
 9. Brophy GM, Bell R, Claassen J, Alldredge B, Bleck TP, Glauser T, et al. Guidelines for the evaluation and management of status epilepticus. *Neurocrit Care*. 2012;17:3–23.
 10. Glauser T, Shinnar S, Gloss D, Alldredge B, Arya R, Bainbridge J, et al. Evidence-based guideline: Treatment of convulsive status epilepticus in children and adults: Report of the Guideline Committee of the American Epilepsy Society. *Epilepsy Curr*. 2016;16:48–61.
 11. Foreman B, Hirsch LJ. Epilepsy emergencies: diagnosis and management. *Neurol Clin*. 2012;30:11–41. vii.
 12. Fountain NB, Lothman EW. Pathophysiology of status epilepticus. *J Clin Neurophysiol*. 1995;12:326–42.
 13. Hirsch LJ, Gaspard N. Status epilepticus. *Continuum Lifelong Learn Neurol*. 2013;19:767–94.
 14. Wasterlain CG, Mazarati AM, Naylor D, Niquet J, Liu H, Suchomelova L, et al. Short-term plasticity of hippocampal neuropeptides and neuronal circuitry in experimental status epilepticus. *Epilepsia*. 2002;43:20–9.
 15. Krishnamurthy KB, Drislane FW. Relapse and survival after barbiturate anesthetic treatment of refractory status epilepticus. *Epilepsia*. 1996;37:863–7.
 16. Chen JWY, Wasterlain CG. Status epilepticus: pathophysiology and management in adults. *Lancet Neurol*. 2006;5:246–56.
 17. Naylor DE, Liu H, Wasterlain CG. Trafficking of GABAA receptors, loss of inhibition, and a mechanism for pharmacoresistance in status epilepticus. *J Neurosci*. 2005;25:7724–33.

18. Bank AM, Bazil CW. Emergency management of epilepsy and seizures. Semin Neurol. 2019;39:73–81.

19. Meldrum BS, Horton RW. Physiology of status epilepticus in primates. Arch Neurol. 1973;28:1–9.

20. Treatment of convulsive status epilepticus. Recommendations of the Epilepsy Foundation of America’s Working Group on Status Epilepticus. JAMA. 1993;270:854–9.

Tables

Table 1. Demographic and clinical characteristics of the study status epilepticus patients 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)	<i>p</i>
^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 AbNL	4 (16)	0	4 (33.4)	
^b First rescue medication				1.000
DZP	6 (24)	3 (23.1)	3 (25)	
LZP	18 (72)	9 (69.2)	9 (75)	
MDZ	1 (4)	1 (7.7)	0 (0)	

^aData are expressed as the median (interquartile range).

^bData are expressed as n (%)

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

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)	<i>p</i>
^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

^aThe data unit is min, which is expressed as the median (interquartile range).

mSZ: motor seizure; pED: pediatric emergency department; ICU: intensive care unit

Figures

Figure 1.

Figure 1

Flowchart of the protocol for the selection of study participants

Figure 2.

Figure 2

Bar graph of the number of times the rescue medication was administered for ceasing seizures