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The effect of early midazolam infusion on the duration of pediatric status epilepticus patients

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ABSTRACT

Purpose: Status epilepticus is one of the most common neurological emergencies in pediatric emergency departments. Although there are different approaches to treatment in the literature, early control of seizure activity is the most important factor determining prognosis. The purpose of this study was to evaluate the effect of early midazolam infusion on seizure duration.

Method: This retrospective study included 150 episodes of 135 patients aged one month to 18 years old with status epilepticus. All patients were treated according to the local hospital protocol for SE, which included early midazolam infusion. Demographic data, medical history, applied treatments during SE, and seizure durations were recorded.

Results: The median age of the patients (58.7% male) was 2.7 years (1.0–6.0 years). The most common identified etiologies were remote symptomatic etiologies, and generalized tonic-clonic seizure was the most common seizure type. The pediatricians had selected intravenous midazolam for 130 patients (86.7%) as the first-line therapy in emergency services. In 55 patients given continuous midazolam infusion, the cumulative bolus of midazolam was 0.5 mg/kg (0.4–0.7 mg/kg), and the median peak rate of midazolam infusion was 0.2 mg/kg/h (0.2–0.4 mg/kg/h). The median duration between the start of midazolam infusion and the complete cessation of SE was 15.0 min (9.0–25.0 min). The early-midazolam infusion group had shorter seizure duration after initiation of midazolam infusion ($p = 0.020$).

Conclusion: The current study shows that aggressive management of SE with early initiation of midazolam infusion was associated with a shorter seizure duration in SE patients.

1. Introduction

Status epilepticus (SE) is a serious and often life-threatening neurological emergency condition requiring prompt management, and it is related to high morbidity and mortality in the pediatric age group. The annual incidence of childhood SE is between 17 and 23 episodes per 100,000 children [1,2], but the highest incidence is in the first year of life.

Although SE is defined as continuous seizures or seizures in which consciousness is not regained between ictal events, the timing used in the definition has varied over the years and, in 2015, the International League Against Epilepsy (ILAE) defined two operational dimensions: time t1 is the point after which the seizure should be considered to constitute “continuous seizure activity,” and t2 is the time period of seizure activity that may lead to long-term consequences [3]; t1 was defined as 5 min (min) for generalized convulsive SE and 10 min for focal SE with impaired consciousness. Most seizures stop spontaneously, but the t1 time is important because it indicates the failure of the mechanisms responsible for seizure cessation or the initiation of such mechanisms, leading to prolonged seizures [3]. Normally, the predominant inhibitory mechanism of SE is the interactions between γ-aminobutyric acid (GABA) and GABA-A receptors. Benzodiazepines (BDZs), which are the first-line drugs in the treatment of SE because they control seizures rapidly, enhance the action of GABA on GABA-A receptors in the central nervous system and thereby induce seizure suppression [4]. When a seizure persists for a longer period of time, resistance to antiepileptic drugs (AEDs) occurs. Because some pathophysiological changes at the cellular level begin to emerge [5,6], inhibitory mechanisms begin to be ineffective and excitation mechanisms begin to be excessive, with receptor trafficking and neuropeptide

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expression occurring within minutes. Endocytosis of synaptic GABA-A receptors, called internalization, leads to a loss of potency of BDZ and other GABAergic drugs as SE proceeds. These receptors may be recycled to the synaptic membrane through the Golgi apparatus, but they may also be destroyed in lysosomes. Longer duration of a seizure and delay in treatment results in refractory SE (RSE) [7,8], also worsening the outcome [5,6]. Lorazepam, midazolam, or diazepam can not only be used as first-line therapy but also, after a failure of first and second-line treatments, midazolam can be given as an infusion in RSE. Because of the time-dependent internalization of synaptic GABA-A receptors, early treatment with a BDZ is crucial for terminating the seizure activity promptly.

In the literature, there are many national and regional guidelines for SE [9]. Although after initial stabilization, the first phase of therapy is the administration of BDZ in all guidelines, the choice of drugs for a second or third phase of therapies and the timing of the general anesthetic drugs for RSE are challenging in pediatric patients. In the current study, we aimed to evaluate the effect of early midazolam infusion on the duration of seizure activity in patients diagnosed with SE and present the data in accordance with the new definitions of the ILAE.

2. Materials and methods

2.1. Study population and protocol

This study was planned as a cross-sectional study. Data was retrieved retrospectively in the pediatric emergency department of the Dokuz Eylul University Faculty of Medicine. The electronic health records, written database records, and discharge summaries of 1832 patients admitted with febrile convulsion, convulsion, seizure, epilepsy, and SE were examined. A total of 150 episodes of 135 patients aged between one month and 18 years old diagnosed with focal or generalized convulsive SE were evaluated between January 2012 and December 2016. Generalized convulsive SE was defined as seizures lasting more than 5 min and focal SE with impaired consciousness was defined as lasting more than 10 min [3]. The zero time was defined as the onset of a seizure. Seizures persisting after 60 min despite the administration of appropriate first-line and second-line therapy were considered RSE. The duration of a seizure out of the hospital was based on information from the family notes and records of the emergency transportation services. The response time of early midazolam infusion was considered as the duration from initiation of midazolam infusion to the seizure cessation in hospital.

The clinical presentation, demographic data, history of seizure and SE, AED usage, previous electroencephalography (EEG) findings and results of cranial imaging methods, risk factors, etiological factors, underlying diseases, SE types, intensive care needs, and treatments were recorded. We used the risk factors in the literature [10,11]. Seizure type was classified according to clinical history and physical examination. The etiology of SE was divided into the following categories: known (i.e., symptomatic) (subdivided as follows: acute, remote, progressive, and SE in defined electroclinical syndromes) and unknown (i.e., cryptogenic). The prehospital duration of SE was based on the history from the patients' attendants and the physicians' notes from the emergency medical transport service. The time for each drug application, duration of total seizure activity in hospital, and seizure activity after midazolam infusion were recorded from electronic medical records and nursing records for all patients.

All patients were treated according to the local hospital protocol for SE, as shown in Table 1. The initial treatment included BDZ (midazolam or diazepam) followed by an intravenous second-line AED. If the patient was using an AED that could be given by intravenous (IV) route, the drug was chosen for second-line therapy; for the other patients, phenytoin or levetiracetam was chosen by the clinician. Midazolam infusion at 0.1 mg/kg/h was started at the 15th minute of total seizure duration and increased by 0.1 mg/kg/h with 0.1–0.2 mg/kg as a bolus every 5 min until complete control of seizures was achieved. If the seizure persisted despite finishing the second-line therapy, the other second-line therapy was administered. Pyridoxine was also administered to all cryptogenic SE patients younger than two years of age.

Table 1
Hospital protocol for status epilepticus treatment in children.

0–5 min	Airway - Breathing - Circulation Monitor vital signs Establish IV/IO access Obtain capillary blood glucose level (if hypoglycemic, 10% dextrose, 2 mL/kg) Obtain laboratory analyses and AED levels Midazolam, 0.1–0.2 mg/kg IV bolus (2 min) If IV access not available: midazolam, 0.2 mg/kg IM or diazepam, 0.5 mg/kg rectal - max: 10 mg
10 min	Midazolam, 0.1–0.2 mg/kg IV bolus or Diazepam, 0.3 mg/kg (max: 10 mg) IV bolus
15 min	Phenytoin, 20 mg/kg IV infusion (max: 1 mg/kg/min or 50 mg/min) or Levetiracetam, 30 mg/kg IV, 20 min inf. and Midazolam, 0.2 mg/kg IV bolus and 0.1–0.2 mg/kg/h IV infusion If < 2 years old, 100 mg pyridoxine
15–60 min	Midazolam increase of 0.1 mg/kg/h IV every 5 min and Add another second-line AED (after the first second-line therapy is finished)
> 60 min	Intensive care unit Intubation EEG monitoring Midazolam infusion, 0.1–1.9 mg/kg/h Thiopental, 3 mg/kg IV bolus and 1–5 mg/kg/h IV infusion

The results of biochemical analyses were recorded to exclude metabolic and electrolyte disturbances. The blood levels of phenobarbital, carbamazepine, and valproic acid, which could be measured in our center, were evaluated.

EEG could not be used for continuous monitoring, but it was used to confirm that ictal discharge compatible with SE was not present when convulsive seizure activity ceased. Control of SE was defined as the cessation of clinical seizure activity and absence of ictal discharge compatible with SE on EEG. The adverse effects of midazolam infusion and needs for intubation were recorded. Patients with absence of SE or myoclonic SE were excluded from data analysis.

Outcome measures included the length of seizure duration, the success rate for seizure cessation, adverse events, need for intubation, and mortality.

In this study, articles were selected to compare seizure duration. Published articles were included when they met the following criteria: [1] pediatric SE patients [2], midazolam infusion for SE treatment, and [3] information about the duration between the initiation of midazolam infusion and the complete cessation of SE.

2.2. Ethical approval

The study was approved by the Ethics Committee of the Dokuz Eylul University Faculty of Medicine and conducted in accordance with the latest version of the Declaration of Helsinki.

2.3. Statistical analysis

Statistical analysis was performed using SPSS 23.0 (IBM Corp., Armonk, NY, USA) for all analyses. Histograms were used to assess the normality of sample distributions. Data was presented with descriptive statistics (median with 25th–75th percentiles for continuous variables; frequency and percentage for categorical variables). The chi-square test for categorical variables was used to examine differences in

Table 2
Medical histories of all patients.

	n = 150 (%)	Results
Previous epilepsy	84 (56.0)	
History of SE	26 (17.3)	
AED usage	81 (54.0)	Monotherapy in 40 (49.4%) Multiple drugs in 41 (50.6%)
History	72 (48.0)	Motor/mental retardation in 48 (66.6%) Prematurity in 10 (13.8%) Congenital heart disease in 6 (8.3%) Malignancy in 5 (6.9%) Metabolic disease in 4 (5.5%) Sturge-Weber syndrome in 3 (4.1%)
Previous cranial imaging	86 (57.3)	Pathological findings in 50 (58.1%)
Previous EEG results	79 (52.6)	Normal in 30 (37.9%) Focal interictal discharges in 16 (20.2%) Generalized interictal discharges in 33 (41.7%)

demographic characteristics. The duration between seizure onset and the initiation of midazolam infusion, and seizure duration after midazolam infusion between the patients with seizure onset in and out of the hospital were assessed using the Mann-Whitney U test. The repeated measures ANOVA controlled for between subject effect and interaction effect was used with multivariate model. Statistical significance was set at $p < 0.05$. We hypothesized that early midazolam infusion provides shorter seizure duration. The post-hoc power analysis showed a power of 0.99 with a 5% level of significance and a 1.84 effect size.

3. Results

In the pediatric emergency department, 150 episodes (58.7% male patients) of focal or generalized SE in five years were evaluated. The median age of the patients was 2.7 years (25th–75th percentiles: 1.0–6.0 years). The medical histories of all patients are given in Table 2.

Remote symptomatic etiologies (53 patients, 35.3%) and unknown etiologies (49 patients, 32.6%) were the most commonly identified etiologies. Most of the patients had risk factors of SE, and although 63 (55.7%) patients had only one risk factor, 50 (44.3%) patients had multiple risk factors (Table 3). Seizure onset occurred out of the hospital in 81 patients (54%) and 25 of them (30.8%) received the first AED (intravenous midazolam for six patients, rectal diazepam for five patients, and intravenous diazepam for 14 patients) prior to arrival at the pediatric emergency department. Generalized tonic-clonic seizure was the most common seizure type (Table 3).

Only one patient had hyponatremia (129 mmol/L); two patients had hypoglycemia (57 mg/dL and 40 mg/dL). Hypomagnesemia was not observed. Fifty-five patients were using phenobarbital, carbamazepine, or valproic acid prior to SE. The levels of these drugs were evaluated in 46 patients (83.6%), and 27 of them (58.7%) had low blood levels of AEDs.

Table 3
Clinical features of the patients.

		n (%)
Risk factors of SE* (n = 113)	Young age (1 year or less) at onset	40 (35.3)
	Focal background EEG findings	36 (31.8)
	Generalized abnormalities on neuroimaging	35 (30.9)
	History of SE	26 (23.0)
	Symptomatic etiology of epilepsy	18 (15.9)
	Focal to bilateral tonic-clonic seizure	12 (10.6)
	Occurrence of SE as the first seizure	6 (5.3)
	Febrile plus generalized epilepsy	3 (2.6)
Seizure type (n = 150)	Generalized tonic-clonic seizure	53 (35.4)
	Generalized tonic seizure	31 (20.7)
	Generalized clonic seizure	11 (7.3)
	Focal to bilateral tonic-clonic seizure	24 (16.0)
	Focal tonic seizure	14 (9.3)
	Focal clonic seizure	

* References: [10,11].

The pediatricians had chosen IV midazolam for 130 patients (86.7%), IV diazepam for 16 patients (10.7%), and rectal diazepam for four patients (2.7%) as first-line therapy in emergency services. The patients who did not respond to BDZs received second-line therapy (117 patients, 78.0%), with phenytoin the most preferred drug for 96 patients (82.0%), and multiple second-line therapies were administered to 33 patients (28.2%). Forty-four patients using AEDs that could be given by IV were evaluated, and 28 patients (63.6%) received their own AEDs as second-line therapy.

Midazolam infusion was started in 55 patients (36.7%). There was no significant difference between the patients who received midazolam and the others, according to age [2.0 years (1.0–4.0 years) and 3.0 years (1.0–7.0 years), respectively ($p = 0.206$)]. Forty-two patients who had seizure activity at hospital admission had received midazolam infusion ($p < 0.001$). We found no significant differences according to the history of SE, previous epilepsy diagnosis, pathological findings in cranial imaging, or interictal discharges on previous EEG results ($p = 0.835$, $p = 0.339$, $p = 0.528$, and $p = 0.388$, respectively). In 55 patients given continuous midazolam infusion, the cumulative bolus of midazolam was 0.5 mg/kg (0.4–0.7 mg/kg; max: 1.2 mg/kg/h), and the median peak rate of midazolam infusion was 0.2 mg/kg/h (0.2–0.4 mg/kg/h; max: 0.9 mg/kg/h).

The median duration of SE from onset was 20.0 min (10.7–38.0 min) in all patients and 41.0 min (30.0–59.0 min) in patients treated with midazolam infusion. The median duration between the initiation of midazolam infusion and the complete cessation of SE was 15.0 min (9.0–25.0 min). The duration between seizure onset and the initiation of midazolam infusion was shorter in patients with seizure onset in the hospital ($p < 0.001$). This group (seizure onset in the hospital) had also shorter seizure duration after initiation of midazolam infusion than the patients with late initiation did (seizure onset out of the hospital) ($p = 0.020$) (Table 4).

Within the entire SE group, 13 patients (8.6%) had episodes of SE lasting longer than 60 min. None of the patients with seizure duration lasting longer than 60 min received any AED prior to arrival to the pediatric emergency department. We performed EEG for 99 patients after cessation of clinical seizure activity and none of those patients had ictal discharge compatible with SE. Generalized interictal discharges were observed in 21 patients, and focal interictal discharges were observed in 33 patients. The institutional treatment protocol controlled seizures in 148 of all patients with a 98.0% success rate and in 53 of the patients who received midazolam infusion with 96.3% success rate. The seizures of two patients could not be controlled with midazolam infusion and the administration of thiopental was required. We did not observe serious adverse effects associated with the administration of midazolam infusion. Only three patients had hypotension responsive to fluid therapy. The reasons for intubation in all 22 intubated patients were independent of midazolam infusion, and 27 patients were observed in the intensive care unit. The mortality rate was 2% and dependent on the underlying cause; two of these were cases of a metabolic disease with pneumonia and one was HELLP syndrome.

4. Discussion

SE is the most common neurological emergency of childhood and requires the appropriate administration of AEDs for prompt control. The findings of this retrospective study are important by demonstrating that convulsive SE duration was shortened with early midazolam infusion compared to the literature and by giving information about the etiology and characteristics of SE in the pediatric age group in accordance with the new definitions of the ILAE.

Table 4
Seizure durations of the patients who received midazolam infusion.

	Seizure onset		*p*
	In the hospital (n = 13)	Out of the hospital (n = 42)	
The duration between seizure onset and the initiation of midazolam infusion (min)	15.0 (15.0–16.0)	27.0 (18.0–32.0)	< 0.001
Seizure duration after midazolam infusion (min)	9.0 (1.0–18.5)	16.0 (10.0–25.5)	0.020
$p1 = 0.049$, $p2 = 0.049$, $p3 = 0.020$			

All data are presented as median (IQR).
p1; p value for multivariate.
p2; p value for within subjects.
p3; p value for between subjects.

SE can be seen as the initial seizure in patients with newly diagnosed epilepsy. In the current study, 56% of the patients had previous epilepsy and SE was the first presentation of epilepsy in 44%. However, it is well known that if a patient has a history of SE or epilepsy, that will be a good predictor for a subsequent SE episode [10]. We have shown that 17.3% of the patients had a previous episode of convulsive SE and approximately half of the patients had a previous diagnosis of epilepsy. Haut et al. showed that 28% of the patients who had epilepsy had at least one episode of convulsive SE [12]. In another study, 16% of children with convulsive SE had a recurrence within one year [1]. Berg et al. also showed that 32.1% of patients with previous SE had at least one further SE episode [10].

Different results are presented in the literature about the etiology of SE, according to age groups, the origin of the reports, and the classification of etiology [13]. Tully et al. showed that prolonged febrile seizure was most common at 1–5 years, and remote symptomatic seizure was most common at 5–10 years [14]. In other studies, whereas febrile or acute symptomatic causes were frequently seen under two years of age, remote symptomatic seizures were more common in children two years and older [1,15]. We have shown that remote symptomatic and unknown etiologies were the most common etiologies in our patients. In a review evaluating the etiology of SE, remote symptomatic or acute symptomatic etiologies were found to be the most frequent etiological factors in the pediatric age group [13].

Risk factors of SE are well defined and, in accordance with our results, most SE patients are known to have some risk factors [10]. SE in the first year of life was the most common risk factor in all patients (35.3%), and other common risk factors were focal background EEG findings and generalized abnormalities in cranial imaging. Novak et al. showed that focal background abnormalities on EEG and generalized abnormalities in neuroimaging were independent risk factors of SE, in accordance with our results [11].

In this descriptive study, we observed that the most common type of SE was generalized tonic-clonic seizure, as in the literature [16], and that SE activity began out of the hospital in approximately half of the patients, with 30.8% of them receiving the first AED before arrival at the hospital. Although prehospital treatment reduces the seizure activity [17], a prospective cohort study showed that more than half of the patients did not receive any AEDs before hospital admission [7]. Other studies also showed that most SE patients with or without prior epilepsy did not receive AEDs out of the hospital [18]. This study has shown that the patients with seizures that lasted longer 60 min did not receive any AED prior to arrival to the hospital. In the literature, a study that included 182 pediatric patients showed that for each minute of delay from seizure onset to arrival at the hospital, there was a 5% cumulative increase in the risk of SE lasting more than 60 min [19]. Although most seizures terminate spontaneously within several minutes, health practitioners must consider treatment during prehospital transport. In SE, the preferred choice of first-line therapy is a parenteral BDZ, particularly lorazepam. We used IV midazolam for most patients with IV access because lorazepam is not available in Turkey.

In the current study, our reason for choosing the patient's own AED that could be given by IV for second-line therapy was the low level of AEDs in one-third of patients with a previous diagnosis of epilepsy presenting with SE [20]. We have also shown that approximately half of our patients who received phenobarbital, carbamazepine, and valproic acid had low levels of AEDs. Abrupt discontinuation with a missed dose or recent alterations of AED usage may worsen the seizure frequency and cause SE [20]. If a patient with existing epilepsy has SE, the previous AED should be given first. However, the other patients received phenytoin as the most preferred second-line therapy because of its long-acting effects according to the literature [9], and there is no clear evidence that any one of these drugs is better than the others.

Although some guidelines recommend repeating another second-line therapy, most guidelines advocate the use of an intravenous anesthetic agent such as midazolam, thiopental, propofol, or pentobarbital with a different start time for RSE [9]. There are no clear recommendations for selection between these anesthetic agents, and most of the guidelines recommend starting a new drug after a previous AED has failed, although midazolam is the most preferred agent for RSE [21]. Rivera et al. [22] initially showed the efficacy of midazolam infusion treatment for RSE in the pediatric age group, and following studies supported their results with high rates of successful control of seizures. Most of the studies showed that midazolam infusion was begun if the seizures continued despite at least two doses of BDZ in succession followed by second-line therapy [9,22–29]. However, the guidelines of the Canadian Paediatric Society Acute Care Committee recommend another second-line therapy if there is no response to the first second-line therapy after 5 min [30]. Italian and Indian guidelines recommend similar drug choices according to intubation difficulty or intensive-care beds [31,32]. In addition to the initiation time of midazolam infusion, there are different applications for bolus doses and dose increase rates and intervals in different protocols [21]. Clinicians have used the range of 0.1–0.5 mg/kg for bolus doses of midazolam [21]. Although there is no definitive suggestion about the rate of increase in infusion, in some studies, the increase of infusion rate was performed at intervals of 5, 10, and 15 min [22–29,33]. The literature demonstrated that aggressive increments in the rate of BDZ infusion shortened the duration of seizure termination after midazolam infusion, in accordance with our results [27,29].

The initiation time of midazolam infusion treatment, which is considered the third phase of treatment in the literature, is approximately 40 min due to waiting for a response to at least two doses of BDZs and a second phase of therapy such as phenytoin or phenobarbital; this sequential polytherapy takes time [9]. However, it is known that within minutes to hours after seizure onset, molecular and cellular changes involving the internalization of GABA-A receptors begin to appear, and a 20-fold decrease in response to BDZs in seizure

Table 5
Midazolam for RSE.

	Midazolam infusion					Seizure control				
	Patient no.	Initial time for midazolam infusion	Bolus (mg/kg)	Initial rate (mg/kg/h)	Interval for increase (min)	Mean-median rate (mg/kg/h)	Maximum rate (mg/kg/h)	Time after infusion (min)	Success rate (%)
Rivera et al. (22)	24	–	0.15	0.06	15	0.138	1.08	46.8	100
Koul et al. (24)	20	2 doses of BDZ and second AED	0.15	0.06	15	0.126	0.3	54	95.0
Koul et al. (25)	51	2 doses of BDZ and second AED	0.15	0.06	15	0.112	0.42	31.1	98.0
Iguarta et al. (26)	8	–	0.15	0.06-0.12	15	0.84	1.44	78 h	88.0
Singhi et al. (27)	21	2 doses of BDZ and second AED	0.2	0.12	5	0.318	0.6	16	85.7
Ozdemir et al. (28)	27	2 doses of BDZ and second AED	0.2	0.06	15	0.186	0.3	65	96.0
Morrison et al. (29)	17	30 min	0.5	0.12	5	0.636	1.92	18	88.0
Current study	55	15 min	01–0.2	0.10	5	0.2	0.9	15	96.3

activity lasting longer than 30 min is observed [4]. The reason we want to start early midazolam infusion in this protocol is explained by the delay in seizure management predisposing to RSE. In the current study, midazolam infusion was started in the 15th minute of treatment, without waiting for the end of the second phase of treatment, and we have shown the shortest seizure duration after initiation of midazolam infusion in pediatric SE patients compared with the previous studies (Table 5).

One of the most important results of this study was that the seizure duration after initiation of midazolam infusion was longer in the patients who had late treatment because of the seizure onset out of the hospital. The early initiation of midazolam infusion in the SE period shortened the duration of seizures. Thus, the findings of this retrospective study show quick control of seizure activity with the early initiation of midazolam instead of waiting for a drug's failure to start polytherapy with a different AED (Table 5).

Although there are different definitions of RSE based on responses to first-line and second-line therapy or seizure duration, RSE occurs in about 25%–45% of children with SE [34]. In this study, the rate of RSE was found to be 8.6%. Our study included SE cases with durations of 5 min and longer, and this rate can be interpreted as relatively low because SE cases of over 30 min are included in studies in the literature in which RSE rates are given. However, it can be assumed that some of the seizures that were controlled in a short time with this protocol could have transformed into RSE if the early initiation protocol had not been implemented.

Midazolam infusion is a safe treatment method for SE because it has a short elimination half-life, rapid penetration into the central nervous system, a broad therapeutic index, little accumulation, and relatively fast recovery time. In the literature, 2.3% of patients had adverse effects such as hypotension and cardiovascular effects with high doses of midazolam [21]. Morrison et al. used the highest maximum dose of midazolam infusion with a dose increase every 5 min and showed that it could be given safely in high doses for RSE [29]. In the current study, a substantial proportion of children had no serious adverse reaction to treatment. In the study by Iguarta et al., which used a high dose of midazolam infusion, no patients had significant hemodynamic instability [26].

There are some limitations to this study. First, this study was retrospective and conducted in only one center. Second, we could not use continuous EEG monitoring. Third, the drug choice for second-line therapy could not be standardized. Further prospective controlled and multicenter studies are needed to clarify the effectiveness of this protocol.

5. Conclusion

The findings of this retrospective study demonstrate that aggressive management of SE with early initiation midazolam infusion is a safe and efficient treatment protocol with quick control of seizure activity in SE patients.

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Declarations of interest

None.

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