Pediatric EM

Quality assurance evaluation of a simple linear protocol for the treatment of impending status epilepticus in a pediatric emergency department 2 years postimplementation

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ABSTRACT

Objective: To evaluate the efficacy and safety of a simple linear midazolam-based protocol for the management of impending status epilepticus in children up to 18 years of age.
Methods: This is a descriptive, quality assessment, retrospective chart review of children presenting with the chief complaint of seizure disorder in the emergency department (ED) of a tertiary care pediatric hospital and a triage category of resuscitation or urgent from April 1, 2009, to August 31, 2011. In children with at least one seizure episode in the ED treated according to the linear protocol, three main outcomes were assessed: compliance, effectiveness, and complications.
Results: Of the 128 children meeting the above study criteria, 68 had at least one seizure episode in the ED, and treatment was required to terminate at least one seizure episode in 46 of 68 patients (67.6%). Fifty-five seizure episodes were treated in the 46 patients: 51 of 55 seizure episodes were treated with midazolam (92.7%) and 4 of 55 with lorazepam or diazepam (7.3%). Of those treated with midazolam, 86.3% (44 of 51) were successfully treated with one or two doses of midazolam. The median seizure duration for all treated patients was 6 minutes. Of the 42 patients treated with midazolam, 7 required either continuous positive airway pressure or intubation, and two patients were treated for hypotension. One patient died of pneumococcal meningitis.
Conclusion: This simple linear protocol is an effective and safe regimen for the treatment of impending status epilepticus in children.

RÉSUMÉ

Objectif: L'étude visait à évaluer l'efficacité et l'innocuité d'un simple protocole linéaire, fondé sur le midazolam, pour le traitement d'un état de mal épileptique imminent, chez des enfants âgés de 18 ans et moins.

Méthode: Il s'agit d'un examen rétrospectif et descriptif, aux fins d'évaluation de la qualité, de dossiers médicaux d'enfants conduits au service des urgences (SU) d'un hôpital de soins pédiatriques tertiaires, du 1er avril 2009 au 31 août 2011, pour des crises épileptiques, et classés dans la catégorie Réanimation ou Urgent. Parmi les enfants qui ont fait au moins une crise épileptique au SU et qui ont été traités selon le protocole linéaire, trois critères ont été évalués, soit le respect, l'efficacité et les complications du plan d'intervention.
Résultats: Sur 128 enfants qui respectaient les critères de sélection décrits ci-dessus, 68 ont fait au moins une crise épileptique au SU, et il a fallu intervenir pour mettre fin à au moins une crise chez 46 d'entre eux (67.6%). Cinquante-cinq crises épileptiques ont été traitées chez ces 46 patients: 51, par le midazolam (92.7%) et 4, par le lorazépam ou le diazépam (7.3%). Le traitement par le midazolam s'est montré efficace après une ou deux doses de médicament chez 86.3% (44 sur 51) des enfants ainsi soignés. La durée médiane des crises épileptiques chez tous les patients traités était de 6 minutes. Sur les 42 malades ayant reçu le midazolam, 7 ont dû être soumis à la ventilation spontanée en pression positive continue ou être intubés, et 2 ont été traités pour de l'hypotension. Un patient est mort d'une méningite à pneumocoques.
Conclusion: Ce simple protocole linéaire s'est révélé une intervention sûre et efficace pour le traitement d'un état de mal épileptique imminent chez les enfants.

Keywords: midazolam, pediatric emergency, quality assurance, seizure protocol, status epilepticus

Status epilepticus (SE) is one of the most common serious medical emergencies in pediatrics. Although the definition of SE is traditionally a seizure lasting

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longer than 30 minutes, there is evidence that even 5 minutes of seizure is sufficient to cause neuronal injury and that seizures are unlikely to self-resolve after that duration of time has elapsed.[1] SE has a case-fatality rate of 3 to 11%.[2] The mortality rate is nearly 10 times higher for seizures longer than 30 minutes than for those 10 to 29 minutes.[3] Associated morbidity is also high; new neurologic disorders or sequelae occur in 15% of cases.[1] Given that prompt treatment is more likely to succeed, physicians recognize the need for early treatment.[4]

Initial treatment with benzodiazepines followed by phenytoin or phenobarbital is generally the method of treatment for SE. Many protocols are based on a combination of these medications.[2] Diazepam, lorazepam, and midazolam have been studied in randomized, controlled trials, confirming their efficacy in treating SE in children.[5–11] Most seizure protocols used in emergency departments (EDs) list all three benzodiazepines as possible choices. Midazolam is known for its better pharmacokinetic properties.[12] Multiple studies have proven that midazolam is at least as effective as diazepam in terms of safety and risk of recurrence, with the advantage of providing a faster initiation of treatment, leading to more rapid seizure cessation.[3,5,8,10,11,13–19] Midazolam has emerged as a highly efficacious drug in the treatment of impending SE, with several routes of administration exhibiting high bioavailability.[19] In a recent article proposing evidence-based and expert consensus practice guidelines, the Neurocritical Care Society lists midazolam as Class I, Level A for the emergent treatment of SE, as Class IIB, Level B for urgent treatment (continuous infusion), and as Class IIa, Level B for refractory treatment using the evidence rating system of the American Heart Association.[20]

The Canadian Pediatric Society (CPS 2011) and the Advanced Pediatric Life Support (APLS Australia Committee 2009) have proposed midazolam (intravenous [IV], intramuscular [IM], intraosseous [IO]) as a choice in their algorithms for the treatment of SE, but neither of these protocols has been studied.[21,22] Two midazolam-based protocols were studied in pediatric intensive care units (PICUs),[2,3] and one was studied in known epileptic patients who were admitted.[4] Midazolam was successful in these three studies. To our knowledge, this is the first study to evaluate a linear seizure protocol used in a pediatric ED proposing midazolam as the sole benzodiazepine. Our goal was to prove that this linear, single–agent, and standardized protocol was effective and safe in treating SE.

METHODS

This was a descriptive, retrospective, quality assessment study performed in the pediatric ED of a tertiary care hospital following approval by the Research Ethics Board, the director of professional services, and the Research Institute of the McGill University Health Centre. Nurses and physicians working in the ED developed a midazolam-based linear protocol for impending SE in children up to 18 years of age (Figure 1). The previous protocol published by the CPS in 1996 suggested lorazepam or diazepam as the initial treatment. The new protocol was created with the collaboration of the divisions of Pediatric Emergency Medicine, Neurology, and Intensive Care. Educational sessions (i.e., lectures, small-group training sessions, and individual consultations) were held prior to the protocol implementation on April 2009. The protocol was posted online on all ED computers and provided in paper format in acute patient care areas.

Patients eligible for chart review were identified in our ED database according to the following criteria: registration between April 1, 2009, and August 31, 2011; age 0 to 18 years; presenting complaint or discharge diagnosis of febrile convulsion; seizure disorder, epilepsy, seizure, convulsions, or SE; Canadian Pediatric Triage and Acuity Scale (CPTAS) of 1 or 2 on arrival; actively seizing in the ED; and necessitating abortive treatment.[23] Eligibility was verified subsequently by chart review.

Impending SE is defined as continuous generalized seizures for > 5 minutes, continuous focal seizures for > 15 minutes, or two seizures without full recovery between the two episodes.[1] In this study, any child with CPTAS 1 or 2 arriving seizing in the ED or who started seizing in the ED was considered as impending SE. The time of onset of a seizure was determined as time of arrival if the patient was actively seizing or the time of onset of a new seizure if the patient started seizing in the ED. The time of seizure control was defined as the time of cessation of seizure activity, subsequent improvement in conscious state, or no need for further acute therapy.

In the children treated with the protocol, patient characteristics, laboratory data (see Figure 1), compliance,

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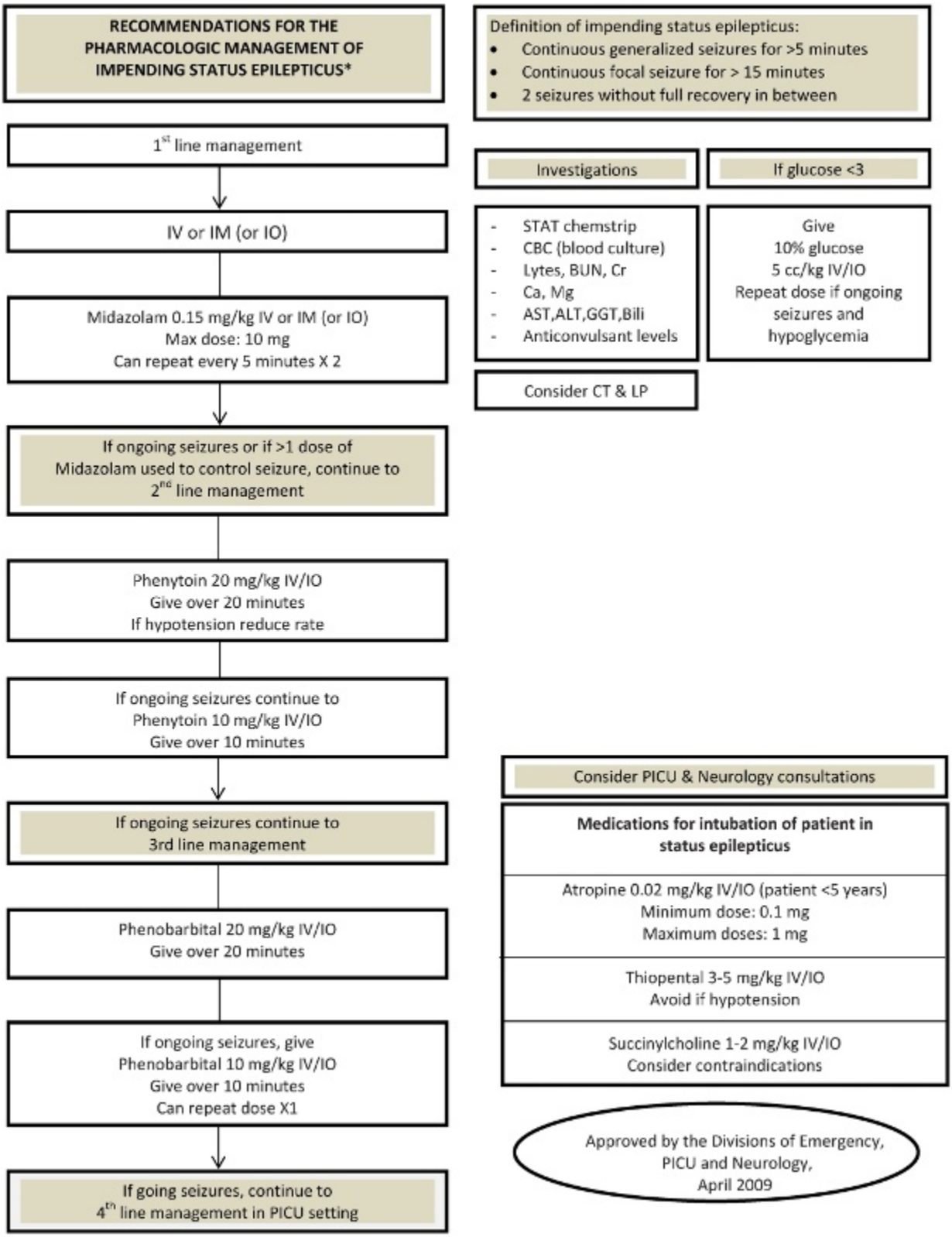

Figure 1. Proposed protocol. ALT = alanine aminotransferase; AST = aspartate aminotransferase; Bili = bilirubin; BUN = blood urea nitrogen; Ca = calcium; CBC = complete blood count; CT = computed tomography; Cr = creatinine; GGT = γ-glutamyl transpeptidase; IM = intramuscular; IO = intraosseous; IV = intravenous; LP = lumbar puncture; Mg = magnesium; PICU = pediatric intensive care unit.

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effectiveness, and complications were evaluated. The assessment of compliance and effectiveness was based on pre-existing and proposed quality assessment indicators for the treatment of pediatric SE that were discussed by experts at a Pediatric Emergency National Advisory Panel held in 2011 (Table 1).[24–32] Respiratory depression and hypotension, the two main serious adverse effects following the treatment of SE with benzodiazepines,[20] were used as the two safety outcomes. Respiratory depression was defined as any patient requiring bag/mask ventilation, continuous positive airway pressure (CPAP), or intubation. Hypotension was defined as a systolic blood pressure less than 90 mm Hg for children age 10 years and above and 70 mm Hg plus twice the age in years for children age 2 to 10 years.

Objective data were selected for extraction and included the following: sex, age, weight, vital signs (e.g., respiratory rate, oxygen saturation, blood pressure) at triage and after medication administration, times (e.g., arrival to ED, administration of medication, seizure onset and cessation), type of medications, dosage, number of doses, and laboratory results. Data were abstracted from the charts and *OACIS* (an electronic laboratory test result database) and entered in an *Excel* database at the time of chart review. Conflicting data were adjudicated between the first author and the supervising coauthor (D.M.). Unavailable data were coded as not available (e.g., time) or not done (e.g., laboratory results). Past medical history was determined by chart review of the current and past admissions and if not found was coded as no relevant previous medical conditions. We based our results only on available data; there were no estimates.

Table 1. Quality indicators for status epilepticus

Protocol for treatment of pediatric patients with status epilepticus
Availability of a pediatric neurologist for consultation
Treatment deviation from emergency department protocol
Timely treatment with antiepileptic drugs for patients in status epilepticus
Percentage of patients on antiepileptic drug prophylaxis with levels drawn
Percentage of patient with rapid bedside glucose documented
Percentage of patient with serum or ionized calcium measured
Percentage of patient with serum sodium measured
Percentage of patients in whom initial drug therapy in emergency department included a benzodiazepine
Time from emergency department arrival to seizure termination
Percentage of patients treated with benzodiazepine dose outside of suggested guideline dosage
Time from arrival to administration of first-, second-, or third-line anticonvulsants
Failure to achieve seizure control within 40–60 minutes of emergency department arrival
Percentage of patients requiring ventilator support

Adapted from Pediatric Emergency National Advisory Panel 2011 Submitted.

Testing of interrater agreement was performed for clinically important predefined effectiveness and safety variables. A second reviewer (the supervising coauthor, D.M.) independently reabstracted charts, and the results were compared to those of the first reviewer. Five items were tested for interrater reliability: total number of midazolam doses received, use of a second-line anticonvulsant, total number of seizures treated with midazolam in the ED, respiratory complications, and hypotension. We focused on the variables that would most likely have the greatest safety impact.

Data were analyzed in an *Excel* database. Descriptive statistics are presented per patient for patient characteristics, laboratory data, and complications and per seizure for compliance and effectiveness. Data are presented as means or medians for continuous variables and as proportions or percentages for categorical variables. Single-measure intraclass correlation coefficient (ICC), 95% confidence interval (CI) using a two-way mixed effects model, and type absolute agreement were computed to estimate the interrater reliability for continuous variables (total number of midazolam doses received, total number of seizures treated with midazolam in the ED). Kappa (κ) statistic was performed to determine interrater reliability for categorical variables (use of a second-line anticonvulsant, respiratory support, and hypotension). Interrater reliability was analyzed using *IBM SPSS Statistics* version 20 (IBM Corp., Somers, NY).

RESULTS

One hundred twenty-eight patients met the criteria for chart review, of whom 68 had at least one seizure in the ED (Figure 2). Forty-six patients required treatment with a benzodiazepine to terminate at least one seizure. These patients had a total of 55 seizures.

Compliance and effectiveness

Four patients with only one seizure were treated with either diazepam or lorazepam. The remaining 42 patients had 51 seizures, all treated with midazolam. Thus, 51 of 55 (92.7%) seizures were treated with

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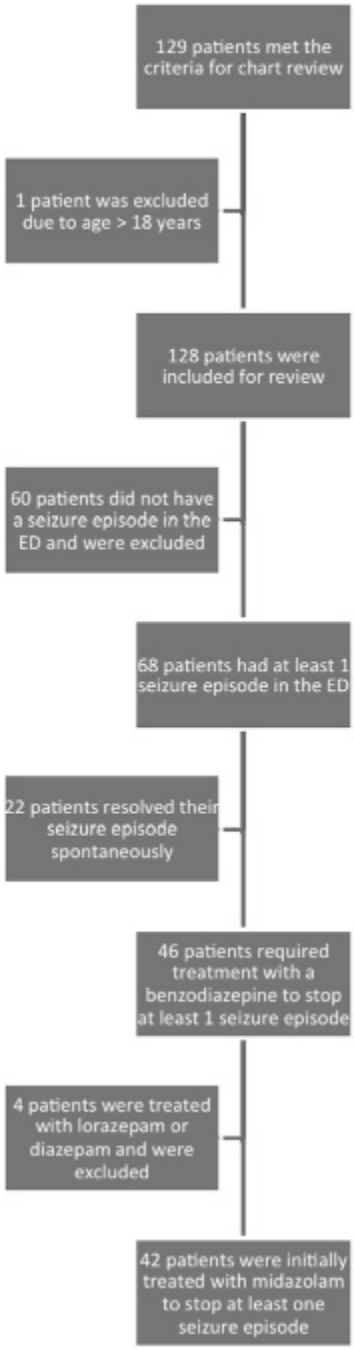

Figure 2. Flow diagram. ED = emergency department.

midazolam. These patients and seizure events underwent further analysis. The patient population is described in Table 2.

Study results are presented in Table 3. Midazolam (IV administration in 87.0% and IM in 13.0%) was the single drug used to abort 44 of 51 (86.3%) seizures. Seven seizures did not respond to midazolam alone (13.7%) and required a second-line anticonvulsant. Six were treated with phenytoin, and phenobarbital was used in one other seizure episode. All 51 seizures (100%) ceased with midazolam ± phenytoin or phenobarbital. No third-line anticonvulsants were required.

Seven seizures did not have times recorded. For the 44 remaining seizure episodes, midazolam was given within 15 minutes, with a median of 3 minutes and an average of 4 minutes. Seizure activity was controlled in all 44 seizures within 1 to 58 minutes; the median seizure duration was 6 minutes, with an average of 12 minutes. For the seizures requiring a second-line anticonvulsant, the medication was given within 20 minutes in 57.1%.

Complications

The most serious consequences included intubation and hypotension. Six patients required intubation and were admitted to the PICU for further management, including two patients intubated prior to transfer from a referring centre where they had been treated with lorazepam, phenytoin, and phenobarbital. One patient had seizures associated with pneumococcal meningitis and received one dose of midazolam for a recurrent seizure in our ED prior to PICU transfer, where he died of his disease. The other child was transferred with refractory SE and continued to have intractable seizures requiring a continuous infusion of midazolam in the PICU. He also required a bolus of fluid to treat hypotension. From the four patients intubated in our ED, one had a medication error where thiopental was given instead of phenobarbital. He recovered rapidly. Two patients had a history of seizure disorder and developmental delay, whereas the two other patients had no previous predisposing conditions. One patient known for lissencephaly, seizure disorder, and recurrent aspiration pneumonia required CPAP and went to the PICU. Seven patients required brief periods of bagging but did not require intubation.

Of the five patients with an episode of hypotension, three were mild and found only on one reading of blood pressure. They resolved spontaneously. Two patients were treated with a bolus of normal saline followed by rapid resolution for one and by admission to the PICU for the one intubated with refractory SE.

Interrater reliability

A moderate to high degree of reliability was identified between raters for effectiveness variables. Agreement

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Table 2. Patient population (*N* = 42)

Patient characteristic	*n* (%)
Age	
< 3 yr	16 (38.1)
≥ 3 yr	26 (61.9)
Range	11.2–178.9 mo
Median	57.9 mo
Sex	
Male	23 (54.8)
Female	19 (45.2)
Fever	23 (54.8)
Seizure disorder or predisposing condition (i.e., alternating hemiplegia of childhood, autism spectrum disorder, childhood disintegrative disorder, global developmental delay, hypoxic-ischemic encephalopathy, Rett disorder, transcobalamin deficiency, tuberous sclerosis)	32 (76.2)
Antiepileptic drug prophylaxis	20 (47.6)
On 1 antiepileptic drug	3 (7.1)
On 2 antiepileptic drugs	9 (21.4)
On 3 antiepileptic drugs	4 (9.5)
On 4 antiepileptic drugs	4 (9.5)
Electrolyte abnormality	
Hypoglycemia	1 (2.4)
Hyponatremia	3 (7.1)
Hypocalcemia	2 (4.8)
CNS infection	2 (4.8)

CNS = central nervous system.

was excellent for the total number of midazolam doses received (ICC = 0.893; 95% CI 0.809–0.941) and good for the total number of seizures treated with midazolam in the ED (ICC = 0.468; 95% CI 0.201–0.671). For use of a second-line anticonvulsant, the agreement between raters was found to be very good (κ = 0.699; 95% CI 0.517–0.881). A fair to moderate agreement was found between raters for safety variables. Agreement was moderate (κ = 0.590; 95% CI 0.406–0.774) for respiratory support and fair (κ = 0.234; 95% CI −0.218–0.686) for hypotension.

DISCUSSION

This linear protocol was proven successful in controlling impending SE in children. It was well accepted by the medical team who used it in 92.7% of the treated seizures after implementation. A standardized and simple seizure protocol is useful for preventing delays in treatment, avoiding medication errors, facilitating staff education, and promoting uniformity across management teams.[33] Our results are comparable to those previously achieved in three midazolam-based protocol studies in children with SE treated in a non-ED setting. The range of success in these studies was between 89 and 95%.[2–4] Our results are comparable to those reported in the literature assessing the use of midazolam for seizure control in the emergency setting and reporting success rates of 56 to 96.7%.[3,5,8,10,11,13–17] To our knowledge, there are no studies comparing IV midazolam to either lorazepam or diazepam IV in the ED setting. Silbergleit and colleagues published a double-blind, randomized, noninferiority trial comparing the efficacy of IM midazolam to that of IV lorazepam: IM midazolam was at least as safe and effective as IV lorazepam.[19] In 448 patients, 73.4% of seizures (95% CI 69.3–77.5) stopped with one dose of IM midazolam, whereas in 445 patients, 63.4% (95% CI 58.9–67.9) stopped with one dose of IV lorazepam. In our smaller study of 42 patients undergoing 51 seizures, 74.5% of seizures (95% CI 62.5–86.5) ceased with one dose of midazolam.

Noncompliance was noted in the management of some seizures. First, four seizures (7.3%) were treated with a benzodiazepine other than midazolam. These deviations occurred in the first 8 months of the study,

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Table 3. Outcome results for compliance, effectiveness, and complications

Outcome	*n* (%)
Midazolam given as first-line medication	51/55 (92.7)
Time of administration of midazolam ≤ 15 min (median: 3 min)	44/51 (86.3)
Correct dosage of midazolam used (0.15 mg/kg)	34/69 (49.3)
Seizures controlled with midazolam only	44/51 (86.3)
Number of doses of midazolam given	
1 dose given	38/51 (74.5)
2 doses given	9/51 (17.6)
3 doses given	3/51 (5.9)
4 doses given	1/51 (2.0)
Seizure controlled with second-line anticonvulsant	7/51 (13.7)
Time of administration of second line ≤ 20 min	4/7 (57.1)
Third-line anticonvulsant given	0/51 (0.0)
Time from ED arrival to seizure termination	
Seizure controlled ≤ 60 min (median: 6 min)	44/51 (86.3)
Seizure time unavailable	7/51 (13.7)
Laboratory data	
Antiepileptic drug levels drawn	14/20 (70.0)
Bedside glucose measured	32/42 (76.2)
Serum ionized calcium measured	21/42 (50.0)
Serum sodium measured	42/42 (100)
Adverse effect	18/42 (42.9)
Respiratory support needed	14/42 (33.3)
Intubation needed (including 2 patients already intubated)	6/42 (14.3)
Bag/mask ventilation	7/42 (16.7)
CPAP	1/42 (2.4)
Hypotension	5/42 (11.9)
Mortality	1/42 (2.4)
Outcome	
Discharged home	11/42 (26.2)
Admission	31/42 (73.8)
Pediatric intensive care unit admission	11/42 (26.2)

CPAP = continuous positive airway pressure; ED = emergency department.

suggesting a lack of protocol familiarity. Second, midazolam was often used outside the suggested dosage (50.7%). A lower dose than recommended was the main dosage deviation (49.3%). Possible reasons could include an inaccurate weight estimation or titration of the dose to effect as the seizure slowed down or stopped to prevent respiratory depression. Third, in eight episodes (15.7%), an additional anticonvulsant was not given despite having used more than one dose of midazolam, likely because the patient had stop seizing. We advocate loading the patient with phenytoin after two doses of midazolam have been used given that one dose is unlikely to cause complications. Judgmental decisions will always be made in the patient's apparent best interest, especially in more complex patients. A second-line anticonvulsant was given in eight seizures (15.7%) despite resolution after one dose of midazolam, perhaps for prevention. Fourth, phenobarbital was used once as the second-line anticonvulsant instead of phenytoin in a 7.8-year-old child; there is some limited evidence that phenobarbital may be more effective in the neonatal period.[34] Finally, the administration of a second-line anticonvulsant was delayed beyond 20 minutes of seizure activity in three of seven episodes (42.9%). Although midazolam offers many routes of administration, the IV, IM, and IO routes are readily accessible in the ED setting. Using the same dosage for both IV and IM routes makes the protocol easier to use. Despite the protocols written by Brevoord and colleagues, Papavasiliou and colleagues, and Friedman (CPS) recommending a lower dosage (0.1 mg/kg) for the IV

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route and a higher dosage (0.2 mg/kg) for the IM route,[2,4,21] we chose to follow the recommendations by Saz and colleagues and Babl and colleagues (APLS Australia Committee) proposing the use of the same dosage (0.15 mg/kg) for both routes.[3,22] We intend to emphasize the need for titrating the IV dose to effect to possibly prevent dose-related adverse effects in future versions.

This study's main limitation is that it was a retrospective study. For seven episodes, times were not documented, so we were unable to document the seizure duration and the timing of administration of medication. These patients received only one dose of midazolam and no second-line treatment, suggesting short seizure duration and no recurrence. In addition, there is no comparison group, which limits the conclusions of the study.

In a systematic review, Sofou and colleagues reported complication rates of up to 60% for respiratory depression, up to 50% for hypotension, and up to 38% for mortality in children treated for SE.[1] In comparison, our study found complication rates of 33.3% for respiratory support, 11.9% for hypotension, and 2.4% for mortality. As previously mentioned, it is well recognized that the most serious adverse effects of all benzodiazepines are respiratory depression and hypotension. In their study, Silbergleit and colleagues had an endotracheal intubation rate within 30 minutes of arrival of 14.1% for IM midazolam and 14.4% for IV lorazepam after one dose of medication.[19] In our study, the intubation rate was comparable at 14.3%. In their study, the rate of treatable hypotension was 2.7% for IM midazolam and 2.9% for IV lorazepam compared to 4.7% in our study.

The six intubated patients presented in the Results section show a pattern of complex patient needs and, in some cases, significant treatment prior to their arrival and in our ED. These children were consequently very ill, and support was needed not just due to medications given as part of the protocol to stop the seizures but also due to the underlying pathology. For the two hypotensive patients treated with a bolus of fluid, the hypotension did not seem to correlate with the number or dosage of midazolam as they had only one dose of midazolam (one received 0.15 mg/kg and one received 0.1 mg/kg). All individuals using benzodiazepines for seizure control must have teaching related to the potential complications and be comfortable with resuscitative management skills. As in other studies, mortality was not attributable to SE itself; rather it was dependent on the underlying cause (pneumococcal meningitis).

Finally, the fair agreement found between raters for hypotension was discordant to the better agreement for the other four variables. In the initial chart review, five patients were identified as having hypotension, but only two patients were identified by the second reviewer, who was using a stricter definition for hypotension that took into account a need for a second confirming blood pressure. Although this issue needs to be discussed in the planning of future studies, we have used the original data collection and have reported five patients with hypotension.

CONCLUSION

This linear midazolam-based protocol is an effective and safe regimen for the treatment of children with impending SE, with 86.3% of the seizures controlled with midazolam alone and 100% with a combination of midazolam and phenytoin or phenobarbital. Based on this work, we will make two changes to the protocol: reinforce the need to titrate the dosage of IV midazolam to effect and recommend the early use of IM midazolam when the IV route is difficult.

The advantage of this linear protocol format is its simplicity, making it an educational guideline with the potential to speed up appropriate therapy, avoid confusion, and reduce medication errors. Given that this is the first study to evaluate a simple linear midazolam-based seizure protocol used in a pediatric ED, it would be important to have other centres evaluate our protocol.

Future studies used to evaluate ED protocols in a real-life setting might benefit from using audiotape and videotape recordings that could be reviewed postevent provided that there was agreement with the family, medical staff, and hospital administration.

Competing interests: None declared.

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