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Original Article

Intramuscular Versus Buccal Midazolam for Pediatric Seizures: A Randomized Double-Blinded Trial

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ABSTRACT

Background: We compared the efficacy and safety of intramuscular with buccal midazolam as first-line treatment for active seizures in children brought to the emergency department.
Methods: In a double-blind, double-dummy randomized trial, patients with an active seizure lasting more than five minutes received blinded treatments on arrival. We employed deferred consent. The proportion of patients with cessation of seizure within five minutes of drug administration was the primary efficacy outcome; proportions needing additional medication to control seizure, duration of seizure activity, and side effects were secondary outcomes.
Results: We enrolled 150 children presenting with active seizure, age range 4.5 to 167.5 months. Cessation of seizure occurred in 61% of the intramuscular and 46% of the buccal treatment groups, ($P = 0.07$, difference 15.5%, 95% confidence interval for the difference −1.0 to 32.0%). Proportions requiring additional anti-seizure treatment were 39% in the intramuscular and 51% in the buccal groups. Mean duration of seizure activity after administration of study medication was 15.9 minutes (S.D. 28.7) in the intramuscular and 17.8 minutes (S.D. 27.5) in the buccal group. One patient in the intramuscular group developed respiratory depression and hypotension; there were no side effects attributed to investigational treatment in the buccal group.
Conclusions: Efficacy and safety of intramuscular midazolam as first-line treatment for pediatric seizures compare favorably to that of buccal midazolam.

Introduction

Seizures are among the most common pediatric presenting emergencies, accounting for 1% of all emergency room visits.[1] According to a literature review of relevant studies and meta-analyses febrile seizures affect 5% children younger than five years[2] and epilepsy in children has a prevalence of 0.5% in developed[3] and 4.4% in underdeveloped countries.[4] Increased excitability, a maturity imbalance between excitatory and inhibitory circuits, and brain immaturity are considered the main reasons behind seizures in children.[5]

International evidence-based guidelines for seizure management in children recommend benzodiazepines as first-line treatment for episodes lasting longer than five minutes.[6-8] Intravenous lorazepam, diazepam, or midazolam are the benzodiazepines commonly given when intravenous access is available.[8] However, in the prehospital and emergency department settings, when an

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intravenous line is not readily available, four commonly considered alternatives are potentially available: rectal diazepam, intranasal midazolam, buccal midazolam, and intramuscular midazolam. Rectal diazepam has a perceived psychological disadvantage, and intranasal midazolam requires a special atomizer and particular training.

Buccal midazolam is easy to administer and recommended in the National Institute for Health and Care Excellence guidelines as the first choice.[7] The efficacy of buccal midazolam for terminating clinical seizure activity within five to 10 minutes of administration ranged from 27% to 84% in previous reports.[9-14]

Intramuscular midazolam is easy to administer and was found to be a safe and effective alternative to intravenous lorazepam for active seizure treatment in the prehospital setting in a large double-blind noninferiority clinical trial. This study enrolled primarily adults with only 16% of patients aged less than 20 years of age.[15] The efficacy of intramuscular midazolam for terminating active seizures within five to 10 minutes ranged from 68% to 92% in previous studies.[12,16-20] As both buccal and intramuscular midazolam are the easiest to administer and there was limited evidence of intramuscular midazolam's effect in children, we sought to compare them as first-line seizure management in children presenting to the emergency department with an active convulsive seizure and no intravenous access.

Methods

Setting and participants

The study was conducted between September 2016 and November 2018 in the Pediatric Emergency Center of Hamad General Hospital, the only pediatric emergency facility in the State of Qatar at that time. The Center serves an average of 320,000 patients annually and manages three resuscitation, 25 treatment, and 42 observation beds. Patients admitted to the observation area are assessed at least every six hours by a pediatrician to determine readiness for discharge.

Children aged six months to 14 years presenting to the Center with active convulsive seizure lasting more than five minutes were eligible for the study if no intravenous access had been secured. Active convulsive seizure was considered present if there was abnormal motor activity with associated loss of consciousness on presentation. We defined status epilepticus as continuous or interrupted abnormal motor activity with loss of consciousness and no cessation of seizure activity for at least 30 minutes. Cessation of seizure activity was defined as physician-confirmed cessation of abnormal motor activity with at least partial recovery of consciousness.

Medication side effects in patients who required no further antiepileptic treatment after study medication administration were considered caused by the study medication. In patients who required further anti-seizure treatment, medication side effects reported within 15 minutes of study drug administration were considered related to the study medication, despite subsequent/intervening administration of the additional antiseizure treatment.

Patients were excluded for one or more of the following: cardiac arrest or hemodynamic instability at presentation, seizure activity associated with head trauma or drowning, subsequent confirmed diagnosis of bacterial meningitis or viral/bacterial encephalitis, significant hypoglycemia or electrolyte abnormalities before or on presentation to emergency, history of a diagnosis of congenital heart disease, inborn error of metabolism, or allergy to benzodiazepines.

Deferred consent was used in the study,[21] that is, consent was obtained after enrollment in the resuscitation area. After cessation of seizure activity and patient stabilization, written informed consent was then sought from one of the parents or legal guardians, which determined continuation of data collection or withdrawal from the study. Deferred consent was approved by the hospital institutional review board (study number 13290) and registered at www.clinicaltrials.gov (ID# NCT02897856).

Study procedures

Patients were placed in the resuscitation area of the center for the treatment of seizure activity. Those with active convulsive seizure more than five minutes were assessed for study eligibility immediately by the treating physician. The patients' weight was immediately measured using the resuscitation bed (Hill-Rom, Inc, Batesville, IN 47006, USA). Next, a previously computer-generated list of random numbers was used by the enrolling physicians in consecutive order to identify a sealed parcel, which was accessed and unsealed only by the resuscitation medication nurse. This contained two vials, one containing midazolam 15 mg/3 mL and the other containing normal saline. One, labeled for buccal administration at 0.06 mL/kg (maximum 2 mL), and the other, labeled for intramuscular administration in the thigh at 0.05 mL/kg (maximum 1.6 mL), were administered simultaneously by two different nurses. The slightly different dosages of midazolam were predefined based on reported bioavailability literature, indicating 90% by the intramuscular and 75% by the buccal route.[22,23] The vial-containing envelopes were prepared in advance by a study clinical pharmacist blinded to patient assignment using computer-generated block randomization. The randomization codes were only unblinded at the end of the study after enrollment of all study patients.

All patients were connected to a cardiac monitor and underwent bedside blood sugar measurement. After the study medication administration, serum electrolytes, complete blood count, other laboratory investigations were obtained at the discretion of the treating physician, and an intravenous line inserted. If the seizure continued for more than five minutes after administration of study medication, additional anti-seizure medications were added directed by the unit's seizure management guideline (Fig 1).

All patients stayed in the resuscitation bed with at least 1:1 nursing observation for more than one hour after arrival, and the exact time of seizure cessation or recurrence was monitored and documented. Patients who had refractory seizure activity and progressed to have status epilepticus were transferred to pediatric intensive care unit (PICU). Patients who stabilized in the resuscitation area and had complete cessation of seizure activity within less than 30 minutes were admitted to the observation area of the Centre or inpatient bed based on the anticipated course of treatment and bed availability. Patients were discharged when the treating physician determined that the patient was adequately treated for the underlying disease, did not need supplementary oxygen, was feeding adequately without intravenous fluids, and regained baseline level of consciousness with no more seizure activity during four hours of observation.

Study measurements and outcomes

The time to cessation of active convulsive seizure was documented for all patients. We selected cessation within five minutes after study drug administration as the primary efficacy outcome and compared the percentage of patients with cessation of seizure in each treatment group; this was based on the onset of action of midazolam in pediatric population.[23] Secondary outcomes selected were proportion of patients needing additional anti-seizure medication in each group, duration of seizure activity, proportion of patients with cessation of seizure within 10 minutes of study drug administration, proportion of patients who continued with active

seizure more than or equal to 30 minutes after arrival, recurrence of seizure activity within one hour of enrollment, length of hospital stay, proportion of patients requiring PICU admission, and reported side effects frequency for each treatment groups.

Statistical analysis

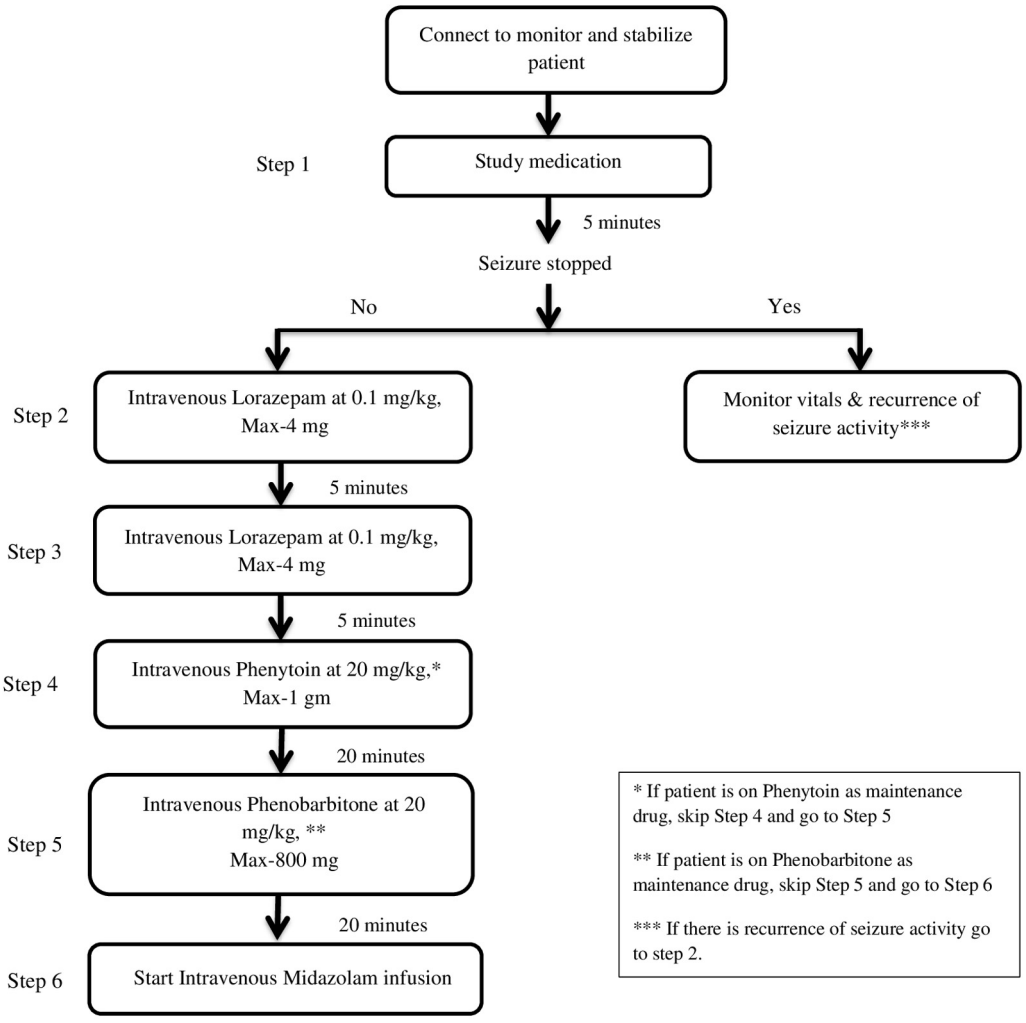
For sample size determination, based on previous studies, we estimated the proportion of patients whose seizures would successfully terminate within five minutes to be around 85% after intramuscular midazolam compared with 65% after buccal midazolam.[9,11,13,14,17,18,20] With these estimates, a study with sample size 73 patients in each arm was required for a superiority trial to show a 20% absolute difference between the two treatment groups with 80% power, two-tailed, and level of significance of 5%.

Categorical and continuous variables were expressed as frequency (percentage), mean, and standard deviation (S.D.). Medians and ranges were reported for skewed (non-normal) data. Descriptive statistics were used to summarize all baseline demographic and clinical characteristics of the patients. Quantitative data between the two intervention groups were analyzed using unpaired t or Mann-Whitney U test as appropriate. Associations between two or more qualitative variables were assessed using chi-square test. For small cell frequencies, chi-square test with continuity correction factor was used. Cox regression was used to estimate the proportion of patients with seizure activity in each group. Univariate Kaplan-Meier survival analysis was performed to estimate median duration (proportion of patients with seizure activity) in each group. The log-rank test was applied to determine any statistical difference in median seizure activity duration between these two groups. Statistically significant values were reported with their corresponding 95% confidence interval (CI) values. $P < 0.05$ was considered to signify a threshold for statistical significance. All statistical analyses were performed using statistical software package (SPSS version 22.0; SPSS Inc, Chicago, IL).

Results

One hundred fifty children presenting with acute convulsive seizure, median age 32 months (range, 4.5 to 167.5 months) were enrolled in the study between September 2016 and November 2018 (Fig 2).

Consecutive eligible patients were recruited, and informed consent was obtained from at least one parent after initial enrollment. No patients opted out from the study when consent was sought. Thirteen patients were excluded from the analysis: six had



Step 1 had buccal midazolam for the original Center seizure guidelines but was replaced with study medication for the study purpose.

FIGURE 1. Pediatric Emergency Center—Management of Seizure guideline.

inborn error of metabolism, three had viral encephalitis, three had bacterial meningitis, and one was aged less than six months on enrollment. Of the 137 children episodes remaining, 70 were randomized to receive buccal midazolam and 67 to receive intramuscular midazolam. Subjects' baseline characteristics were similar in the two treatment arms before enrollment (Table).

Efficacy

The number of patients with cessation of seizure activity within five minutes of study medication administration was 32 patients (46%, 95% CI, 33% to 57%) receiving buccal midazolam and 41 (61%, 95% CI, 49% to 73%) receiving intramuscular midazolam, absolute difference being 15.5% (95% CI −1.0 to 32.0%, $P = 0.07$). Time from administration of study medication until complete cessation of seizure activity was 17.8 minutes (S.D. 27.5) for the buccal midazolam and 15.9 minutes (S.D. 28.7) for the intramuscular midazolam groups, $P = 0.69$ (Fig 3).

The hazard ratio for cessation of seizure after study medication administration using Cox regression was 1.13 (95% CI, 0.80 to 1.58) for intramuscular midazolam and 0.89 (95% CI, 0.63 to 1.24) for buccal midazolam, showing a 13% shorter duration of seizure in intramuscular midazolam when compared with buccal midazolam groups, $P = 0.49$. Sixteen children in the buccal midazolam and 15 in the intramuscular midazolam progressed to status epilepticus after enrollment in the study. Need for further antiepileptic treatment, recurrence of seizure activity within the first hour after presentation, proportion with cessation by 10 minutes after drug administration, and length of hospital and PICU stay were similar in both arms. Outcome results are summarized in the online Supplementary Table.

Safety

One patient in the intramuscular midazolam and none in the buccal groups developed respiratory depression and hypotension three minutes after administration of study medication. Oral airway, ambu bag ventilation, and 20 mL/kg bolus of normal saline were required for stabilization. Ventilation and blood pressure recovered fully by 15 minutes after study drug administration.

Discussion

In our double-blind, double-dummy randomized trial, intramuscular midazolam compared favorably with buccal midazolam

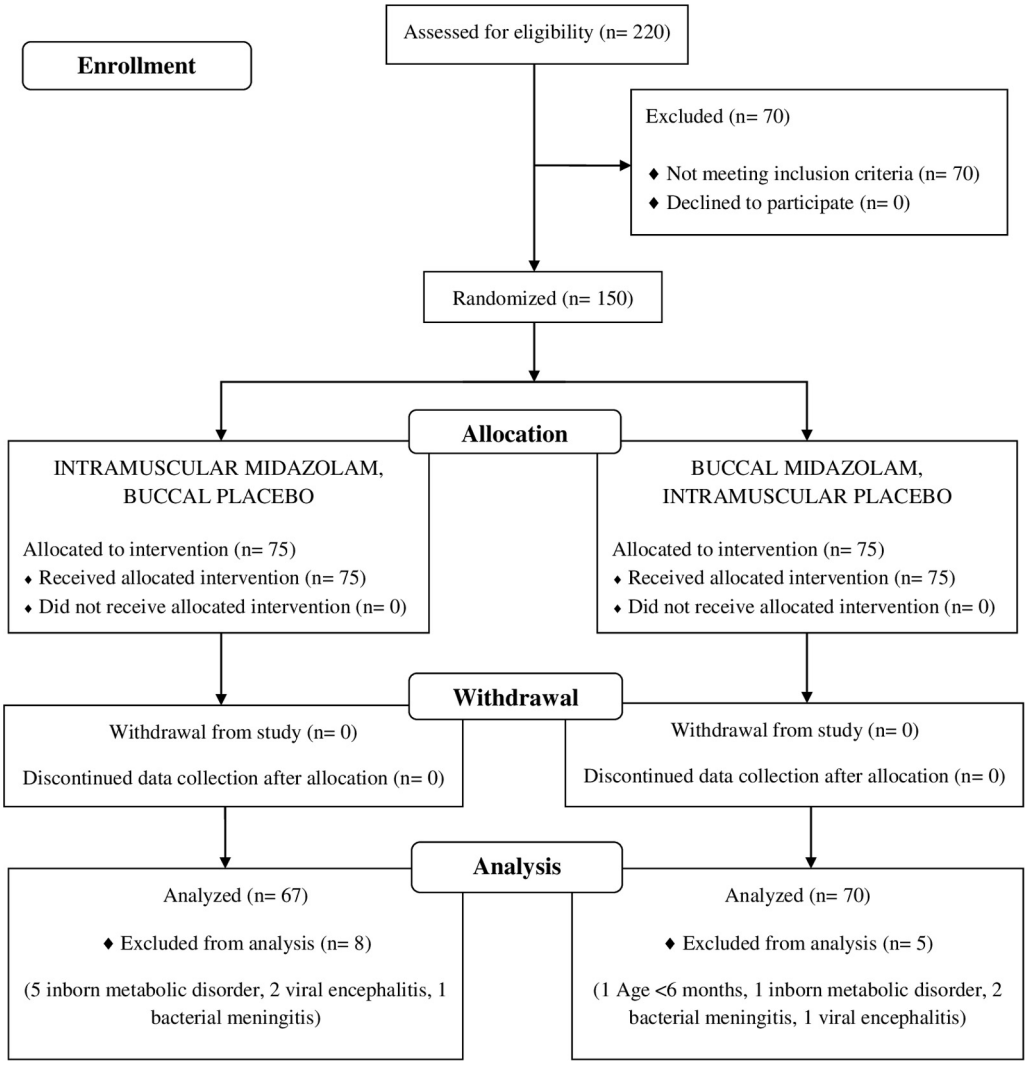


FIGURE 2. Study flowchart of enrolled patients.

for seizure cessation within five minutes, as well as time to seizure cessation, seizure control, and safety.

This is the first study with a moderate number of children to directly compare intramuscular and buccal midazolam in patients in the emergency department. There is one open-label 33-patient trial comparing midazolam by the buccal, intramuscular, and intravenous routes in African children with malaria. Successful termination of seizure within 10 minutes of drug administration was found in 100% in the intravenous, 75% in the intramuscular, and 63% in the buccal groups after 0.3 mg/kg of midazolam for seizure lasting more than five minutes duration. All enrolled patients had severe malaria, hence the application of the outcome of this study to other types of patients with epilepsy and/or febrile seizure is uncertain.[12] Other studies compared intramuscular midazolam in a mixed population of adults and children or a small number of children showed seizure termination rates similar to what we found: a seizure termination rate of 60% to 80% within five minutes and 90% within 10 minutes of administration[17,18,20] while, buccal midazolam had a seizure termination rate of 40% to 60% within five minutes and 60% to 80% within 10 minutes of administration.[9-11,13,14] While our studied population termination of seizure within five and 10 minutes for both routes are consistent with prior reports, our double-blind double-dummy method was intended to minimize observer bias in documenting time to cessation. The mean duration of seizure after study medication administration was variably defined in the literature and ranged from 1.5 to eight minutes for the intramuscular midazolam studies[15,17,18,20] and four to six minutes for the buccal midazolam studies.[10,14] Our study reported a mean duration of seizure postdrug administration of 15.9 minutes in intramuscular and 17.8 minutes in buccal routes. Because the time from seizure onset to emergency department arrival varies widely across individuals and across and within studies, and may affect the duration of seizure after drug administration, we must depend on randomization and larger numbers of children patients to estimate effects of different drug regimens. Time from arrival to resuscitation room until patient received study medication (both intramuscular and buccal) was slightly longer in our buccal midazolam group, 3.4 ± 1.9 minutes when compared with the intramuscular group, 2.7 ± 1.6 minutes, $P = 0.03$. This difference is likely a result of chance, but some effect of this difference on the outcome measured cannot be excluded.

We took care to apply a double-blinded randomization method to eliminate possible observer bias at different levels, whereas previous pediatric seizure trials comparing different routes of administration applied an open-label or single-blind method,[9-14,17-20] except for two.[15,16]

Deferred consent was selected in this randomized study to avoid delay in medical intervention and serve the purpose of enrollment in an emergency department trial; this was well accepted by 100% of the enrolled patients' guardians with no withdrawals. Our guardians' acceptance is consistent with the 95% to 97% success rate in deferred consent used in some previous pediatric seizure studies.[24,25]

The observed safety profiles for both treatments were similar, with a single adverse event in one patient; this mirrors the described low prevalence of side effects for both treatments in previous literature.[8]

Our study has some limitations. The trial was designed as a superiority trial based on the previously published efficacy of both

TABLE.
Baseline Characteristics of Enrolled Patients

Characteristics	Intramuscular Midazolam n = 75	Buccal Midazolam n = 75
Age, mean (S.D.), months	49 (46)	45 (37)
Male/female, n	41/34	33/42
Weight, mean (S.D.), kg	15.7 (9.2)	15.4 (8.6)
Seizure duration before arrival, mean (S.D.), minutes	23.8 (46.7)	16.6 (22.7)
Number of patients received rescue medication at home before arrival, n (%)	2 (3)	7 (9)
Medication received, n (%)		
Rectal diazepam	1 (1)	3 (4)
Buccal midazolam	1 (1)	4 (5)
Number of patients received rescue medication by Emergency Medical Service in route, n (%)	3 (4)	3 (4)
Medication received, n (%)		
Midazolam (Intranasal)	3 (4)	3 (4)
Number of patients who had seizure within 24 hours before presentation not related to index seizure, n (%)		
0 episode	56 (75)	54 (72)
1 episode	12 (16)	14 (19)
2 episodes	1 (1)	2 (3)
>2 episodes	6 (8)	5 (7)
Number of children presenting with seizure activity ≥30 minutes, n (%)	18 (24)	17 (23)
Patients presenting with fever, n (%)	48 (64)	48 (64)
Number of patients with past medical history of seizure, n (%)	42 (56)	54 (72)
Patients on antiepileptic treatment, n (%)	32 (43)	36 (48)
One drug	15 (20)	17 (23)
Two drugs	11 (15)	7 (9)
Three drugs	4 (5)	9 (12)
More than three drugs	2 (3)	2 (3)
Vagus nerve stimulation	0 (0)	0 (0)
Ketogenic diet	0 (0)	1 (1)
Prior seizure surgery	0 (0)	0 (0)
Comorbidities, n (%)		
Cerebral palsy/developmental delay	30 (40)	32 (43)
Prematurity	9 (12)	6 (8)
Ventriculoperitoneal shunt/hydrocephalus	0 (0)	1 (1)
Inborn metabolic disorder	5 (7)	1 (1)
Past medical history of febrile seizure, n (%)	11 (15)	23 (31)
Patients with prior PICU admission for prolonged seizure, n (%)	17 (23)	19 (25)
First blood sugar measured, mean (S.D.), mmol/L	6.9 (2)	7 (2)
Patients with electrolyte derangement (sodium, calcium, magnesium), n (%)	0 (0)	0 (0)

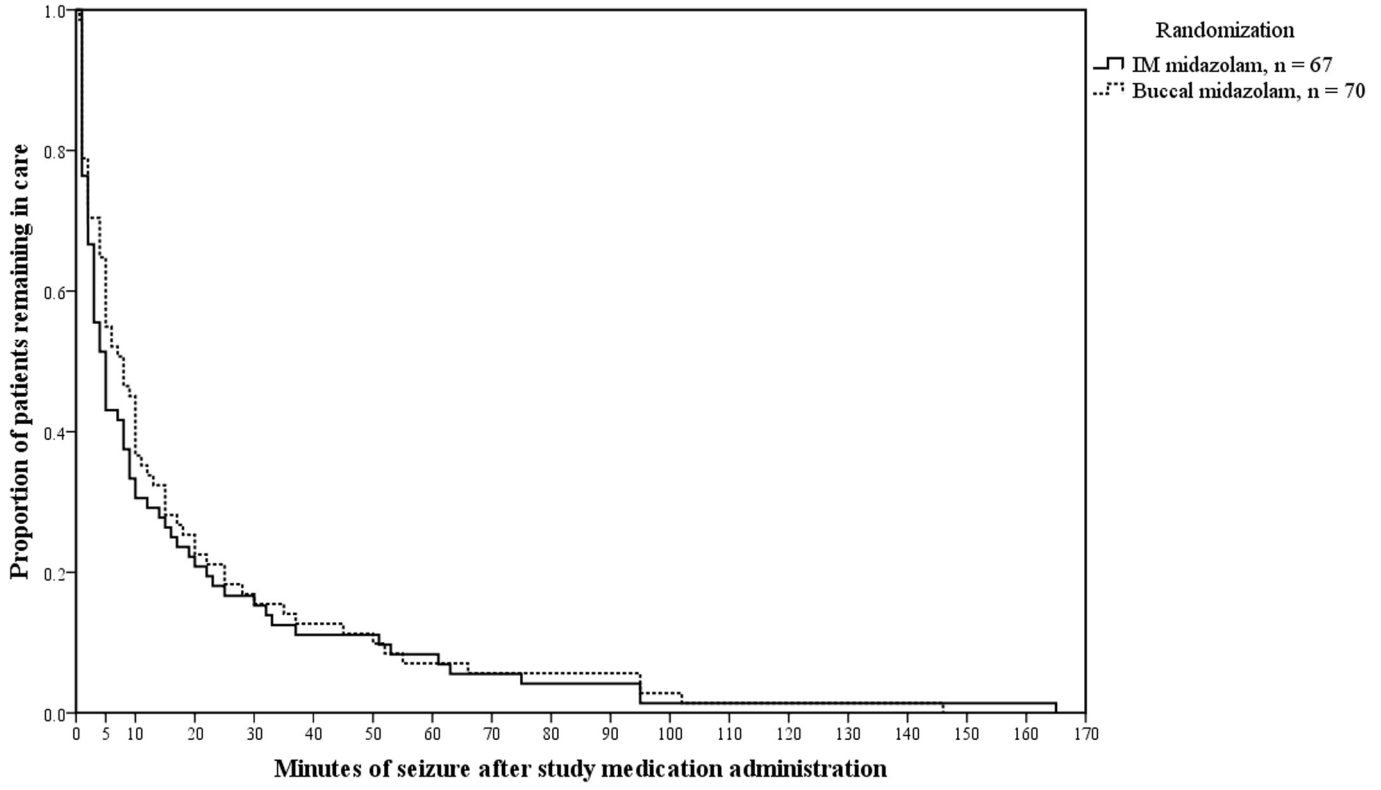


FIGURE 3. Kaplan-Meier curve for time to seizure cessation.

routes; failing to find a statistically significant difference leaves that hypothesis unsettled. The midazolam dosing used in each arm was based on the reported bioavailability of both routes for the drug and not confirmed by measuring drug level in study patients; we could have missed higher or lower drug absorption in some patients. It is possible that a higher dose than we gave may have provided benefit without further adverse effects; however, we elected to use the midrange of drug recommended dose for the buccal route (0.3 mg/kg)[23] and based the intramuscular dose on the bioavailability of both routes. Interpretation of our secondary outcomes should be cautious because in those patients requiring additional anti-seizure treatment if investigational treatments failed at five minutes, time to establishment of intravenous access and subsequent lorazepam infusion could vary. Moreover, five intramuscular and 10 buccal group patients received medication to try to terminate the seizure either at home or during transport, and although these efforts failed, they may have affected time to seizure cessation in the two treatment groups. Finally, a possibly extended seizure duration before emergency department presentation in some patients means that our study is not strictly comparable with other published reports limited to patients (e.g., inpatients) with shorter seizure durations before treatment. Finally, we prospectively chose to exclude from analysis enrolled subjects who later proved to have encephalitis, meningitis, inborn metabolic errors, etc., because even a small imbalance between treatment groups could have provided a misleading result. However, this limits the generalizability of our findings to conditions excluding those that we excluded.

Conclusion

We conclude that the efficacy and safety of intramuscular midazolam as first-line treatment for pediatric seizures compares favorably to buccal midazolam.

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Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.pediatrneurol.2020.03.011.

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