High-dose midazolam infusion for refractory status epilepticus

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ABSTRACT

Objective: This study compares 2 treatment protocols allowing low vs high continuous IV midazolam (cIV-MDZ) doses.

Methods: We compared adults with refractory status epilepticus treated with a protocol allowing for high-dose cIV-MDZ (n = 100; 2002–2011) with those treated with the previous lower-dose cIV-MDZ (n = 29; 1996–2000). We collected data on baseline characteristics, cIV-MDZ doses, seizure control, hospital course, and outcome.

Results: Median maximum cIV-MDZ dose was 0.4 mg/kg/h (interquartile range [IQR] 0.2, 1.0) for the high-dose group and 0.2 mg/kg/h (IQR 0.1, 0.3) for the low-dose group ($p < 0.001$) with similar duration of infusion. Median time from status epilepticus onset to cIV-MDZ start was 1 day (IQR 1, 3) for the high-dose group and 2 days (IQR 1, 5) for the low-dose group ($p = 0.016$). "Withdrawal seizures" (occurring within 48 hours of discontinuation of cIV-MDZ) were less frequent in the high-dose group (15% vs 64%, odds ratio 0.10, 95% confidence interval 0.03–0.27). "Ultimate cIV-MDZ failure" (patients requiring change to a different cIV antiepileptic medication) and hospital complications were not different between groups. Hypotension was more frequent with higher cIV-MDZ doses but was not associated with worse outcome. Discharge mortality was lower in the high-dose group (40% vs 62%, odds ratio 0.34, 95% confidence interval 0.13–0.92 in multivariate analysis).

Conclusions: High-dose cIV-MDZ treatment of refractory status epilepticus can be performed safely, is associated with a lower seizure rate after cIV-MDZ discontinuation, and may be associated with lower mortality than traditional lower-dose protocols.

Classification of evidence: This study provides Class III evidence that midazolam at higher infusion rates is associated with a reduction in seizure recurrence within 48 hours after discontinuation and may be associated with lower mortality. *Neurology*® 2014;82:359–365

GLOSSARY

AED = antiepileptic drug; **cEEG** = continuous EEG; **CI** = confidence interval; **cIV** = continuous IV; **ICU** = intensive care unit; **IQR** = interquartile range; **MDZ** = midazolam; **OR** = odds ratio; **RSE** = refractory status epilepticus; **SE** = status epilepticus.

Status epilepticus (SE) is a neurologic emergency that requires prompt management.[1–3] SE that does not respond to standard treatment regimens is labeled as refractory SE (RSE).[2,4] Recent guidelines recommend anesthetic doses of midazolam for these patients,[2] but so far no adequately powered randomized controlled trial has compared different treatment strategies for RSE.[2,5,6] The difficulty of conducting such a study has been recently highlighted by the early termination of a prospective trial comparing propofol and barbiturates for patients with RSE.[7] Thus, the best currently available options for guiding therapy of these very sick patients are careful investigation of the underlying pathophysiology as well as comprehensive observational studies.

We previously reported our initial experience with the use of midazolam infusions for the treatment of RSE,[8] after which we changed our institutional protocol to allow for the use of much higher midazolam infusion doses when necessary (from a maximum of 0.4 to 2.9 mg/kg/h). In this study, we compare the 2 treatment cohorts based on an intention-to-treat analysis.

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METHODS

Study population. We compared 2 cohorts of patients with RSE treated with different maximum doses of continuous IV midazolam (cIV-MDZ) in the Neurologic Intensive Care Unit at Columbia University Medical Center. The first group has been previously described[8] and consists of patients with RSE who were treated between July 1996 and April 2000 with cIV-MDZ up to a suggested maximum dose of 0.4 mg/kg/h (low-dose cIV-MDZ group). The second group consists of patients with RSE who were treated between November 2002 and January 2011 with a higher suggested maximum cIV-MDZ dose up to 2.9 mg/kg/h (high-dose cIV-MDZ group). The intervening period between the 2 cohorts (May 2000 through October 2002) was not included to allow time for the protocol change to take effect.

We identified patients treated with the high-dose cIV-MDZ protocol by screening the continuous EEG (cEEG) monitoring reports of the Comprehensive Epilepsy Center, pharmacy records, and hospital medical records. Inclusion criteria were age 18 years or older, and having RSE treated with cIV-MDZ as the first cIV antiepileptic drug (AED). We excluded post–cardiac arrest RSE patients and patients with incomplete information regarding doses, timing of cIV-MDZ administration in relation to other cIV-AEDs, EEG data, or clinical response. Patients started on a cIV-MDZ drip for RSE before the start of cEEG required documented clinical seizures to be included. cEEG confirmation was required for diagnosing nonconvulsive SE.[9] If a patient had more than one RSE episode, only the first RSE episode was included for analysis.

Standard protocol approvals, registrations, and patient consents. Because of the retrospective and observational nature of this study, the need for written informed consent was waived by the hospital institutional review board.

Treatment protocol. Treatment of patients with SE at our institution follows a regimen starting with an IV benzodiazepine, followed by a standard IV antiepileptic medication. RSE was defined as lack of response to the initial standard treatment regimen for SE.[2,4] After the study describing our experience with the low-dose cIV-MDZ group,[8] and after discussions between the neurocritical care and epilepsy groups at our institution, the treatment protocol of patients with RSE was changed to allow for cIV-MDZ maintenance doses up to a suggested maximum of 2.9 mg/kg/h, because it was deemed to be a safe upper limit. The initial loading dose (0.1–0.2 mg/kg) and starting maintenance infusion (0.1 mg/kg/h) remained the same. After a 24-hour seizure-free period, cIV-MDZ was tapered off over 4 to 6 hours under cEEG monitoring to assess for seizure recurrence. Protocol details have been described previously.[8] Not all patients in the high-dose group received cIV-MDZ doses higher than that of patients in the low-dose group, as the treatment protocol does not mandate high doses, but allows for high-dose cIV-MDZ therapy if needed.

cEEG monitoring. EEG was recorded using a digital cEEG bedside monitoring system (Nicolet Bravo and XLTEK [Natus Medical Inc., San Carlos, CA]). Scalp electrodes were applied using the standard 10–20 system. cEEG recordings were analyzed and reported by board-certified clinical neurophysiologists at the Columbia University Comprehensive Epilepsy Center. Seizure control variables were based on these reports.

Seizure control variables. *Breakthrough seizures* were defined as any seizure occurring in between 6 hours after the start until the discontinuation of cIV-MDZ (MDZ infusions were only considered discontinued if stopped for at least 6 hours). *Withdrawal seizures* were defined as seizures occurring within 48 hours after discontinuation of cIV-MDZ infusion. *Ultimate cIV-MDZ failure* was defined as any patient requiring change from or transition to another cIV-AED due to failure of seizure control or intolerability of cIV-MDZ. The withdrawal seizure variable was not included if the change or transition to another cIV-AED occurred during the cIV-MDZ infusion or shortly after discontinuation of the cIV-MDZ because these patients did not have a withdrawal period from cIV-MDZ without the confounding presence of another cIV-AED.

Clinical and outcome variables. Variables were based on review of medical records. Demographic information, medical history, baseline functional status (Glasgow Outcome Scale),[10] the presumptive primary cause of RSE, and the Acute Physiology and Chronic Health Evaluation II scores[11] at the time that cIV-MDZ was started were recorded. Pharmacologic data included maximum cIV-MDZ doses (mg/kg/h), total duration of cIV-MDZ infusion, as well as the number of other AEDs used before, during, and after the cIV-MDZ infusion, and the time from SE onset to start of cIV-MDZ. Complications after the initiation of cIV-MDZ therapy were recorded including hypotension requiring pressors, troponin elevations with associated ECG changes, pulmonary edema (based on radiology reports), and new arrhythmias. Outcome measures included length of stay, ventilator days, need for tracheostomy, and need for percutaneous endoscopic gastrostomy placement. Clinical outcome variables were mortality at hospital discharge and withdrawal of care, and do-not-resuscitate status.

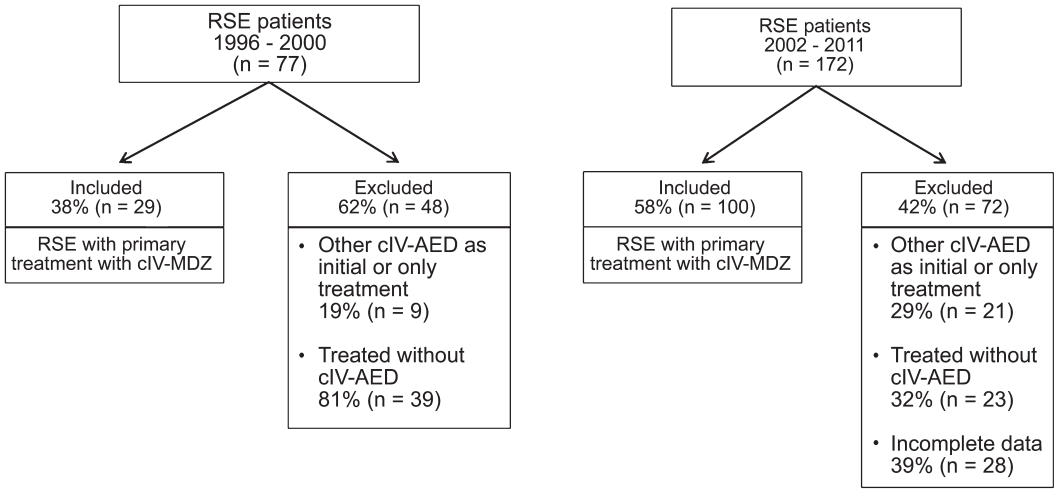
Statistical analysis. Data analyses were performed using commercially available statistical software (SPSS version 19; IBM Corp., Armonk, NY). We compared the low-dose cIV-MDZ group with the high-dose cIV-MDZ group on an intention-to-treat basis, because not all patients in the high-dose group received high cIV-MDZ doses. Continuous variables were analyzed using independent samples t test and Mann-Whitney tests. Categorical variables were analyzed using χ^2 tests and univariate logistic regression. A multivariable logistic regression model of discharge mortality was constructed using forward stepwise procedures. Candidate variables for multivariable analysis were identified from univariate analyses with $p < 0.25$. Significance level was set at $p < 0.05$.

RESULTS

Study population. Two hundred forty-nine patients with RSE were identified, of whom 29 were in the low-dose and 100 were in the high-dose cIV-MDZ group. We excluded 120 patients who were initially treated with a cIV-AED other than cIV-MDZ, did not receive any cIV-AED, or had incomplete data (figure). Excluded patients in the high-dose group were slightly younger than those who met inclusion criteria (53 ± 21 years vs 62 ± 17 years; $p = 0.002$), but there was no difference in sex or underlying etiology of RSE.

High- vs low-dose cIV-MDZ group. There were no differences in baseline characteristics between the groups (table 1). The high-dose group had higher median maximum cIV-MDZ doses than the low-dose group, but duration of cIV-MDZ infusions did not differ. Patients in the high-dose group had an earlier start of cIV-MDZ after SE onset compared with the low-dose group (table 2). There was a trend for receiving more non–cIV-AEDs during MDZ infusions in the high-dose

Figure Study population



AED = antiepileptic drug; cIV = continuous IV; MDZ = midazolam; RSE = refractory status epilepticus.

group, but the number of AEDs used after stopping cIV-MDZ was not different (table 2).

The suggested maximum cIV-MDZ dose in the low-dose group was 0.4 mg/kg/h, but 3 patients received higher doses (2 patients 0.5 mg/kg/h, and 1 patient 0.53 mg/kg/h). The suggested maximum cIV-MDZ dose in the high-dose group was 2.9 mg/kg/h, but 4 patients received higher doses (between 3.0 and 3.3 mg/kg/h). Half of the patients (n = 50) in the high-dose group received infusion doses above the 0.4 mg/kg/h suggested maximum dose for the low-dose group.

Seizure control. There was no difference in the rate of breakthrough seizures between the groups (table 3); moreover, there was no difference in the rate of breakthrough seizures that occurred after the first 24 hours of starting cIV-MDZ infusion (21% vs 31% for the high- and low-dose groups, respectively; odds ratio [OR] 0.59, 95% confidence interval [CI] 0.24–1.49). Patients with withdrawal seizures had greater odds of prior breakthrough seizures (OR 4.35, 95% CI 1.70–11.13).

Withdrawal seizures were less often seen in the high-dose group (table 3) and the association remained (OR 0.06, 95% CI 0.02–0.20) after controlling for the number of non–cIV-AEDs received during the MDZ infusion (OR 1.85, 95% CI 1.11–3.09) and for the time from SE onset to cIV-MDZ start (OR 1.01, 95% CI 0.89–1.14).

There was no difference in ultimate cIV-MDZ failure between the groups (table 3). Patients with cIV-MDZ failure from the high-dose group received median maximum cIV-MDZ doses 10 times higher than the ones with cIV-MDZ failure from the low-dose group (2.0 mg/kg/h [interquartile range, IQR, 1.0, 2.9] vs 0.2 mg/kg/h [IQR 0.1, 0.4], respectively; $p = 0.001$), with no difference in median duration of infusion (64 hours [IQR 41, 110] vs 48 hours [IQR 36, 120], respectively; $p = 0.76$). In patients with ultimate cIV-MDZ failure, a similar success rate for subsequent seizure control was observed between the groups after the switch to a different cIV-AED (67% [10 of 15] vs 60% [3 of 5] for the high- and low-dose groups, respectively; OR 1.33, 95% CI 0.17–10.74). There was a trend for later initiation of cIV-MDZ in patients with ultimate failure compared to those without (2 days [IQR 1, 6] vs 2 days [IQR 1, 3], respectively; $p = 0.07$).

Complications and hospital course. In-hospital complications were comparable between the groups (table 3). Higher median maximum cIV-MDZ doses increased the odds of hypotension requiring pressors (OR 1.89, 95% CI 1.15–3.11) and there was a trend for higher hypotension rates in the high-dose group (table 3), but there was no difference in mortality between those with or without hypotension requiring pressors (49% [30 of 61] vs 41% [26 of 64] discharge mortality, respectively; OR 1.41, 95% CI 0.70–2.87).

Intensive care unit (ICU) and hospital length of stay was not different between the groups: ICU length of stay was median 15 days for both groups (IQR 8, 27 vs 8, 26 days for the high- and low-dose groups, respectively; $p = 0.97$), and hospital length of stay was median 35 vs 36 days for the high- and low-dose groups, respectively (IQR 21, 53 vs 21, 69 days; $p = 0.42$). There was a trend for fewer ventilator days in the high-dose group (median 20 vs 26 days [IQR 10, 35 vs 16, 48] for the high- and low-dose groups, respectively; $p = 0.07$).

Outcome. Patients in the high-dose group had a lower discharge mortality compared with the low-dose group (table 3). This association was also present in

Table 1 Baseline characteristics

	Low-dose cIV-MDZ (n = 29)	High-dose cIV-MDZ (n = 100)
Demographics		
Age, y	55 ± 19	62 ± 17
Sex, female	20 (69)	64 (64)
Ethnicity, white	20 (69)	53 (53)
Medical history		
Epilepsy	10 (35)	30 (30)
Stroke (ischemic or hemorrhagic)	11 (38)	24 (24)
Baseline functional status		
GOS score[10,a]	4 (4, 5)	4 (3, 5)
Presumptive etiology of RSE		
Acute etiology of RSE[b]	22 (76)	67 (67)
Epilepsy	5 (17)	21 (21)
CNS infection	4 (14)	12 (12)
Hemorrhagic stroke	8 (28)	23 (23)
Ischemic stroke	2 (7)	3 (3)
Trauma	2 (7)	11 (11)
Tumor	2 (7)	6 (6)
Toxic-metabolic	5 (17)	6 (6)
Degenerative	0 (0)	6 (6)
Other	0 (0)	4 (4)
Unknown	1 (3)	8 (8)
Clinical status		
APACHE II score[11,c]	20 (16, 23)	19 (15, 24)

Abbreviations: APACHE II = Acute Physiology and Chronic Health Evaluation II; cIV-MDZ = continuous IV midazolam; GOS = Glasgow Outcome Scale; RSE = refractory status epilepticus.
Values are mean ± SD, median (interquartile range), and n (%). Independent samples t test used for age; Mann-Whitney test used for baseline GOS and APACHE II; and χ^2 tests used for categorical variables. All results were nonsignificant.
[a] GOS score: 1 = death; 2 = persistent vegetative state; 3 = severe disability; 4 = moderate disability; and 5 = good recovery.
[b] Chronic etiology: epilepsy, tumor, and degenerative categories. The remaining etiologies were acute.
[c] Three cases from the high-dose cIV-MDZ group had missing APACHE II scores.

multivariate analysis after controlling for Acute Physiology and Chronic Health Evaluation II scores and presumptive epilepsy etiology of RSE (table 4), and remained when calendar year of admission (OR 1.2, 95% CI 0.95–1.51) and time from SE to cIV-MDZ start (OR 0.99, 95% CI 0.89–1.1) were added to the model. The overall rates of withdrawal of care and do-not-resuscitate status were not different between the groups.

DISCUSSION This study compares 2 cohorts of patients with RSE treated with protocols allowing for low vs high cIV-MDZ doses. Patients in the high-dose cIV-MDZ group had lower rates of withdrawal seizures suggesting better efficacy for lasting seizure control. Hypotension increased with higher doses of cIV-MDZ, but because hypotension was not associated with worse outcome, high MDZ doses appear to be safe if used in a controlled setting such as the ICU. At the time of hospital discharge, the high-dose group had a lower mortality, including after controlling for other predictors of outcome.

Baseline characteristics were not different between the low- and high-dose cIV-MDZ groups. The overall frequency of prior epilepsy (31%) was less and acute etiologies causing RSE (69%) were more common than in prior studies (25%–52% and 50%–66%, respectively).[7,12–15]

The suggested maximum MDZ infusion rate of 0.4 mg/kg/h in the low-dose group compares well to the typically reported doses in contemporary reports from that time (0.39–0.8 mg/kg/h).[16–19] In subsequent reports, isolated cases received high cIV-MDZ doses in adult (1.26 and 4.0 mg/kg/h)[20,21] and pediatric (1.92 mg/kg/h) RSE,[22] but no large series has investigated this approach. Recent guidelines advocate for

Table 2 Pharmacologic data

	Low-dose cIV-MDZ (n = 29)	High-dose cIV-MDZ (n = 100)	p
MDZ infusion			
Time from SE onset to cIV-MDZ start, d	2 (1, 5)	1 (1, 3)	0.016[a]
Maximum cIV-MDZ dose, mg/kg/h	0.2 (0.1, 0.3)	0.4 (0.2, 1.0)	<0.001[a]
Duration of MDZ infusion, h	72 (48, 144)	72 (41, 116)	0.57
No. of antiepileptic drugs			
Before cIV-MDZ infusion	3 (3, 4)	3 (3, 4)	0.86
During cIV-MDZ infusion	2 (2, 3)	3 (2, 4)	0.06
After cIV-MDZ infusion	2 (2, 4)	3 (2, 4)	0.31

Abbreviations: cIV-MDZ = continuous IV midazolam; SE = status epilepticus.
Values are median (interquartile range).
[a] Significant differences; Mann-Whitney tests.

higher maximum cIV-MDZ doses[2,23] despite a lack of evidence showing the benefit and safety of this approach. We found higher median maximum cIV-MDZ infusion rates in the high-dose group even though not all patients in this group received higher maximum doses compared with the low-dose group. We also found earlier initiation of cIV-MDZ after SE onset in the high-dose group, which may suggest an increased aggressiveness in the treatment of RSE. However, the associations between the high-dose group and both lower withdrawal seizures and lower mortality remained after controlling for the earlier initiation of cIV-MDZ.

Withdrawal seizures (within 48 hours of stopping cIV-MDZ) were much less frequent in the high-dose group suggesting better efficacy for lasting seizure control. The 15% rate of withdrawal seizures seen in the high-dose group of our study compares favorably to the rate of 43% to 46% typically seen with pentobarbital and propofol, respectively.[6] Possible

Table 3 Seizure control, hospital course, and outcome

	Low-dose cIV-MDZ (n = 29)	High-dose cIV-MDZ (n = 100)	OR (95% CI)
Seizure control			
Breakthrough seizures	15 (52)	46 (46)	0.80 (0.35–1.82)
Withdrawal seizures[a]	16/25 (64)	11/75 (15)	0.10 (0.03–0.27)[b]
Ultimate cIV-MDZ failure	5 (17)	15 (15)	0.85 (0.28–2.57)
Complications and hospital course			
Hypotension requiring pressors	8/25 (32)	53 (53)	2.40 (0.95–6.06)
Troponin elevation and ECG changes	2 (7)	3 (3)	0.42 (0.07–2.63)
Pulmonary edema	4 (14)	15 (15)	1.10 (0.34–3.62)
Arrhythmia	1 (3)	6 (6)	1.79 (0.21–15.48)
Tracheostomy	16/27 (59)	46/95 (48)	0.65 (0.27–1.54)
PEG	14 (50)	48/95 (51)	1.02 (0.44–2.37)
Outcome			
DNR	12 (43)	40 (40)	0.89 (0.38–2.08)
Withdrawal of care	10 (36)	37 (37)	1.06 (0.44–2.53)
Mortality at discharge	18 (62)	40 (40)	0.41 (0.17–0.95)[b]

Abbreviations: CI = confidence interval; cIV-MDZ = continuous IV midazolam; DNR = do not resuscitate; OR = odds ratio; PEG = percutaneous endoscopic gastrostomy.
Values are n (%). Denominator reported in categories with missing data in more than one case.
[a] The withdrawal seizure variable was not included in 14 patients in the high-dose and 4 patients in the low-dose cIV-MDZ group because the change or transition to another cIV-antiepileptic drug occurred during the cIV-MDZ infusion or shortly after discontinuation of the cIV-MDZ. An additional 11 patients in the high-dose group had incomplete data for this variable. One patient in each group had both withdrawal seizures and ultimate cIV-MDZ failure.
[b] Significant differences; univariate logistic regression.

Table 4 Multivariate analysis of mortality at hospital discharge

Discharge mortality	Alive (n = 71)	Dead (n = 58)	OR (95% CI)
APACHE II score[a]	17 (12, 20)	21 (18, 26)	1.18 (1.09–1.27)
Epilepsy as presumptive cause of RSE	22 (31)	4 (7)	0.17 (0.05–0.61)
High-dose cIV-MDZ group	60 (85)	40 (69)	0.34 (0.13–0.92)

Abbreviations: APACHE II = Acute Physiology and Chronic Health Evaluation II; CI = confidence interval; cIV-MDZ = continuous IV midazolam; OR = odds ratio; RSE = refractory status epilepticus.
Values are median (interquartile range) and n (%).
[a] Three patients had missing APACHE II scores.

explanations for the lower rate of withdrawal seizures involve pharmacologic considerations. Withdrawal from higher median maximum doses may result in persistence of benzodiazepine serum levels after discontinuation of cIV-MDZ infusions. Furthermore, case reports suggest that prolonged half-lives[18,21] and increases in the volume of distribution and free MDZ fraction[21] may be seen with cIV-MDZ infusions for RSE.

There was no difference in the number of patients whose cIV-MDZ therapy failed and had to be switched to a different cIV-AED, despite failure in the high-dose group at much higher doses. Moreover, the rate of ultimate seizure control after the switch to a different cIV-AED did not differ between patients failing the low- vs high-dose cIV-MDZ protocol. These observations suggest that there may be a subgroup of patients with RSE who are highly refractory to therapy independent of the therapeutic approach. Interestingly, we found a trend for later start of cIV-MDZ in patients with ultimate cIV-MDZ failure.

There were no differences between the groups in hospital complications except for more hypotension with higher doses of cIV-MDZ. The 53% rate of hypotension requiring pressors in the high-dose group is between the 42% and 77% reported for propofol and pentobarbital, respectively, in a systematic RSE review,[6] and similar to the 50% and 55% for propofol and barbiturate, respectively, from a recent randomized trial of RSE.[7] Importantly, hypotension was not associated with increased mortality suggesting that this can be done safely as long as this therapy is administered in a controlled setting.

Mortality in the overall cohort was 45% at discharge, comparable to other RSE studies. In a systematic review of RSE studies, a mortality rate of 46% was reported for patients treated with midazolam and 52% and 48% for patients treated with propofol and pentobarbital, respectively.[6] Subsequent RSE series have reported discharge mortality ranging from 17% to 43%.[7,12–15,24] We found lower discharge mortality in the high-dose compared with the low-dose cIV-MDZ group (40% vs 62%, respectively), and the association remained after controlling for other predictors of outcome.

This study has several limitations. The 2 groups were treated in different time periods over several years and the lower number of patients in the low-dose group may have limited potential comparisons. Our cIV-MDZ data are limited to maximum cIV-MDZ doses and infusion duration between the groups and our seizure control data to the presence or absence of seizures during or after cIV-MDZ. Data such as hourly cIV-MDZ infusion rates and total number and duration of seizures would allow for the calculation of seizure and cIV-MDZ burden, as well as timing to termination of RSE after the start of infusion, measures that could provide a more detailed assessment of outcomes. We compared the number of noncontinuous AEDs and not AED levels, but the main difference between the groups is most likely in the availability of newer antiepileptic agents in recent years as suggested by the trend for more noncontinuous AEDs during the infusion in the new cohort. Changes in practice to a more aggressive approach toward RSE, advancements in critical care, and increased experience in treating patients with RSE over the years may potentially have an influence on outcomes. In the case of mortality, however, the association between the high-dose group and lower mortality remained after controlling for admission year. Our neurocritical care unit serves as a referral center, which may have introduced selection bias and may reflect a more highly refractory patient population limiting the generalizability of our findings. This is a retrospective single-center study; a prospective multicenter study would be able to address some of the above limitations, but the challenges in performing a large, multicenter, prospective RSE study are illustrated well by the early termination due to insufficient recruitment of the first randomized controlled trial for RSE.[7] Given the number of comparisons made, significant observations reported in this study should be interpreted with caution and at this time taken as trends.

These data comparing a cohort treated with a high-dose with those treated with a lower-dose cIV-MDZ protocol suggest that a high-dose protocol is safe and associated with fewer withdrawal seizures and lower mortality at discharge.

AUTHOR CONTRIBUTIONS

Dr. Fernandez, Dr. Lantigua, Dr. Lesch, and Ms. Shao: study design, data collection, data analysis, manuscript drafting. Dr. Foreman, Dr. Schmidt, Dr. Hirsch, and Dr. Mayer: data analysis, manuscript drafting. Dr. Claassen: study design, data collection, data analysis, manuscript drafting.

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DISCLOSURE

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