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Ketamine plus midazolam compared to midazolam infusion for the management of refractory status epilepticus

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ABSTRACT

Background: Data for the use of ketamine (Ket) in treatment of refractory and super-refractory status epilepticus (RSE, SRSE) is lacking despite its widespread growing use. We examined the efficacy of ketamine plus midazolam (MDZ) infusions for treating RSE versus midazolam alone. We hypothesized that ketamine initiation would result in earlier seizure termination.

Methods: Data was obtained from electronic health records (EHR) of adult patients who received intravenous anesthetic agents for RSE in our neurointensive care unit. Two cohorts were identified. The MDZ cohort received midazolam as the only intravenous anesthetic agent for RSE. The Ket+MDZ cohort received midazolam infusion followed by ketamine infusion. The primary outcomes were time from midazolam infusion start to SE end in both cohorts, and time from ketamine infusion start (Ket Start) to SE end in the Ket+MDZ cohort versus midazolam infusion start (MDZ start) to SE end in the MDZ cohort.

Results: 73 patients were included (MDZ cohort n=17, Ket + MDZ cohort n=56). Cohorts did not differ significantly in age, sex, race, RSE etiology, or GCS on admission. Mean APACHE II score was higher in the Ket +MDZ cohort (26 ± 7.32 SD) versus the MDZ cohort (22 ± 5.89 SD)(P=.015). In survival analyses, cohorts did not differ significantly in time from midazolam start to SE end (HR=0.965, 95 % CI=0.556–1.673, P=.899; median [IQR]: MDZ: 25 h [4.5–58]; Ket+MDZ: 21.5 h [IQR 13.5–49]). Time from Ket start (Ket+MDZ group) versus time from MDZ start (MDZ group) to SE end was significantly shorter in the Ket+MDZ cohort (HR=1.895, 95 % CI=1.083–3.314, P=.025). The pattern of results was similar when including APACHE II and MDZ maximum dosage as covariates.

Conclusion: Time to SE end was significantly shorter after addition of ketamine infusion to midazolam infusion, versus after initiation of midazolam infusion monotherapy. Patients with higher disease severity favored Ket+MDZ. Randomized controlled trials are warranted in determining optimal anesthetics in RSE and SRSE.

1. Introduction

Status epilepticus (SE) is a neurological emergency defined by the International League Against Epilepsy (ILAE) as a prolonged seizure that exceeds the intrinsic termination mechanisms at a certain point in time from the onset of the seizure (t_1) and persists beyond a second point in time at which cortical damage occurs (t_2). Refractory status epilepticus (RSE) is defined as SE that persists beyond t_2 time point despite treatment with first and second line antiseizure medications (ASM). It defines super refractory status epilepticus (SRSE) as an SE that persists for greater than 24 h after the addition of a third-line drug, typically an intravenous anesthetic [1]. The incidence of RSE and SRSE is estimated to be approximately 40 % among patients presenting with SE, with mortality rates approaching 50 % [2].

The molecular pathophysiology of SE is complex, and seizures are perpetuated by an imbalance between excitatory and inhibitory mechanisms in neuronal tissue [3]. Glutamate is the main excitatory neurotransmitter which stimulates the N-methyl-D-aspartate (NMDA)

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receptor; γ-Aminobutyric acid (GABA) is the primary inhibitory neurotransmitter [4]. After several minutes of constant seizure activity, GABA surface receptors decrease through "internalization" resulting in a reduction in GABAergic activity. Clinically, internalization results in rapidly progressive resistance to the GABA agonist class of medication [4]. Concomitantly, "externalization" of glutamate receptors from the cytosol to the cell membrane occurs, resulting in increased neural excitatory activity, this phenomenon is referred to as "receptor trafficking." Clinically, receptor trafficking results in glutamate blockade becoming more effective than GABA agonism in later stages of SE [4,5]. NMDA antagonism may be neuroprotective as excitatory amino acid mediated toxicity is thought to underlie neuronal injury in SE [5]. Impaired GABAergic activity becomes clinically relevant as resistance to benzodiazepines necessitates the use of medications with alternate mechanisms, such as ketamine, a noncompetitive NMDA receptor antagonist.

Retrospective case series support the use of ketamine for the treatment of RSE and SRSE, however there are no prospective randomized control trials to support the use of ketamine in treatment of RSE or SRSE [6,7]. In this study, we examine the efficacy of ketamine plus midazolam infusions for treating RSE and SRSE compared to midazolam infusion. We hypothesized that initiation of ketamine infusion would result in earlier seizure termination.

2. Methods

2.1. Study design

This study was performed at Thomas Jefferson University Hospital, an academic teaching institution with a forty-bed neurointensivist-managed neurological intensive care unit. The protocol of this retrospective study, which involved review of electronic health records (EHR), was approved by the Institutional Review Board (IRB) of Thomas Jefferson University Hospital and was conducted in accordance with ethical standards. The IRB waived the requirement for patient consent given the retrospective nature of the study.

2.2. Data collection

Data was obtained from EHR of patients ages 18 years or older who received intravenous anesthetic agents for treatment of RSE in the neurointensive care unit. Data was entered into Research Electronic Data Capture Database (REDCap) [8]. At our institution, ketamine infusion for RSE was introduced in 2015. Thus, two cohorts of participants were identified; the first cohort was treated before the introduction of ketamine infusion at our institution and received midazolam infusion as the only intravenous anesthetic agent for the treatment of RSE (MDZ cohort). The second cohort was treated under our institution's current protocols and received midazolam plus ketamine infusions (Ket + MDZ cohort). At our institution, under the current protocols, ketamine infusion is often considered for the treatment of RSE if seizures persist despite midazolam infusion rate of 0.8 mg/kg/hr. Therefore, to ensure that the cohorts were comparable in RSE course and treatment up to the typical point of ketamine initiation, participants were excluded from the MDZ cohort if they received midazolam maximum dose <0.8 mg/kg/hr and from the Ket + MDZ cohort if midazolam infusion was < 0.8 mg/kg/hr at the time of ketamine initiation. This criterion ensured that patients were only included in the study if they failed treatment with MDZ only at 0.8 mg/kg/hr. Participants were excluded from the MDZ cohort and Ket + MDZ cohort if they received medications in atypical chronology. Typical chronology was defined as the following sequence: SE start, initial ASM, midazolam infusion, and (for the Ket+MDZ cohort) ketamine infusion. Atypical chronology was defined as any deviation from this sequence. Participants were excluded from both cohorts if SE end date or time were missing. Basic demographic and clinical characteristics were collected including age, gender, race, GCS on admission (≤ 8 versus > 8), APACHE II score, etiology of RSE, midazolam maximum dose (Table 1).

2.3. Definitions of SE and its start and endpoints

SE was defined as 5 minutes or more of continuous clinical and/or electrographic seizure activity or recurrent seizure activity without return to baseline between seizures [9]. RSE was defined as SE that fails to respond to first-line medications, specifically a benzodiazepine, and at least one appropriately dosed second-line medication, specifically an ASM such as levetiracetam, valproic acid, phenytoin, or lacosamide [9]. SRSE was defined as SE that persists for more than 24 h after the addition of a third-line drug, specifically an intravenous anesthetic agent [1]. Table 2

The start time of SE was defined as the first mention of seizure or SE in the EHR progress notes or EEG read; if this information was not available, time of first ASM administration was used. The time of initial ASM was defined as initial administration of a benzodiazepine or first administration of a loading dose of an ASM in the medication administration record (MAR). All continuous electroencephalography (cEEG) reports were interpreted and generated by the Thomas Jefferson University Hospital Longterm cEEG service which is composed of board-certified epileptologists. SE end time was defined as the time of last electrographic seizure on cEEG. Time from midazolam infusion start to SE end time was calculated for both cohorts. Time from ketamine infusion start to SE end was calculated for the Ket + MDZ cohort (Table 3). The primary outcomes were 1) time from midazolam infusion start to SE end in both cohorts, and 2) time from ketamine infusion start to SE end in the Ket+MDZ cohort versus time from midazolam infusion start to SE end in the MDZ cohort.

2.4. Dosing and timing

MDZ Monotherapy (previous institutional protocol): Participants were started on midazolam infusion for seizure suppression at the discretion of the treating physician if seizures persisted despite adequate trial of an initial benzodiazepine dose followed by a second acceptable ASM. Our institutional pathway for midazolam infusion for SE included a bolus dosage of 0.1 mg/kg with infusion initiation at 0.1 mg/kg/hr followed by re-bolus dosage of 0.1 mg/kg and doubling the rate of the infusion every 15 minutes for persistent RSE with a maximum infusion rate of 2.9 mg/kg/hr.

Ketamine + MDZ (current institutional protocol): Participants were started on ketamine infusion for seizure suppression at the discretion of the treating physician if seizures persisted despite midazolam infusion. As noted above, at our institution, ketamine infusion is often considered for the treatment of RSE if seizures persist despite midazolam infusion rate of 0.8 mg/kg/hr. The institutional pathway for ketamine for RSE included a bolus dosage of 1.5 mg/kg IV push every 3–5 minutes until seizure cessation up to a maximum of 4.5 mg/kg with infusion initiation at 1.2 mg/kg/hr followed by re-bolus and rate increase by 0.6–1.2 mg/kg/hr until seizure control is achieved with a maximum infusion rate of 10 mg/kg/hr.

2.5. Statistical analysis

Statistical analyses were performed using SPSS Version 28. Differences between the MDZ and Ket + MDZ cohorts were examined using chi-squared tests, Fisher's exact tests, analysis of variance (ANOVA), and Mann-Whitney U tests, as appropriate. Cox proportional hazards survival analysis was used to test differences between the MDZ and Ket + MDZ cohorts in 1) the time from midazolam infusion start to SE end and 2) the time from ketamine start to SE end (Ket+MDZ cohort) versus time from MDZ start to SE end (MDZ cohort). A second set of survival analyses was then conducted with any pretreatment demographic or clinical covariates that differed between groups, namely, APACHE II score. A

Table 1
Basic demographic and clinical characteristics.

	MDZ (n=17)				Ket+ MDZ (n=56)				*P*
Sex [n (%)]									
Male	10 (58.8 %)				29 (51.8 %)				.782
Female	7 (41.2 %)				27 (48.2 %)				
Race									
White	10 (58.8 %)				22 (39.3 %)				.324
Black	5 (29.9 %)				28 (50.0 %)				
Other	2 (11.8 %)				6 (10.7 %)				
Etiology of SE									
Anoxia	5 (29.4 %)				25 (44.6 %)				.399
Non-anoxia	12 (70.6 %)				31 (55.4 %)				
Epilepsy	0 (0 %)				8 (14.3 %)				
Tumor	0 (0 %)				2 (3.6 %)				
TBI	3 (17.3 %)				0 (0 %)				
Stroke	2 (11.8 %)				1 (1.8 %)				
Toxic/metabolic	1 (5.9 %)				4 (7.1 %)				
Other/unknown	3 (17.6 %)				10 (17.9 %)				
Multiple	3 (17.6 %)				6 (10.7 %)				
GCS									
≤ 8	14 (82.4 %)				49 (87.5 %)				.689
> 8	3 (17.6 %)				7 (12.5 %)				
	MDZ (n=17)				Ket+ MDZ (n=56)				*P*
	Mean	SD	Min	Max	Mean	SD	Min	Max	
Age at admission (y)	60	22	23	90	54	18	22	85	.230
APACHE II Score	21.4	5.9	12	33	26.3	7.3	13	46	.015
	Mdn	IQR	Min	Max	Mdn	IQR	Min	Max	
MDZ max dose (mg/kg/hr)	2.1	1.6–2.9	1.1	2.9	1.6	1.2–2.1	0.8	2.9	.022
MDZ dose at Ket initiation (mg/kg/hr)	—	—	—	—	1.6	1.0–1.6	0.8	3.3	—
Ket max dose (mg/kg/hr)	—	—	—	—	1.8	1.2–3.6	1.2	8.4	—

Abbreviations: Acute Physiology and Chronic Health Evaluation (APACHE), Glasgow Coma Scale (GCS), ketamine (Ket), median (Mdn), midazolam (MDZ), status epilepticus (SE), traumatic brain injury (TBI).

Table 2
Descriptive statistics of status epilepticus (SE) resolution.

	MDZ (n=17)				Ket + MDZ (n=56)			
Resolution of SE [N(%)]	17 (100 %)				55 (98.2 %)			
Time to SE end (hours) starting at	Median	IQR	Min	Max	Median	IQR	Min	Max
SE start	51	36–97	11	261	49	22–83.5	7	629
Initial ASM	51	36–96	11	189	46	22–78.5	7	629
Midazolam start	25	6–48	0	168	21.5	13.5–49	1	492
Ketamine start	—	—	—	—	4.5	1–14.5	0	476
MDZ start (MDZ cohort) or Ket start (Ket+MDZ cohort)	25	6–48	0	168	4.5	1–14.5	0	476

Abbreviations: Anti-seizure medication (ASM), ketamine (Ket), midazolam (MDZ), status epilepticus (SE)

third set was then conducted with the addition of any treatment-related clinical covariates that differed between groups, namely, MDZ maximum dose. APACHE score was dichotomized for inclusion as a covariate with a cutoff of 1–20 versus ≥ 21, as this cutoff is predictive of mortality in ICU patients [10]. All models met the assumptions of proportional hazards and of no influential outliers. Logistic regression was used to evaluate the differences between the cohorts in the odds of SE duration lasting ≥ 24 h 1) after midazolam infusion start (both cohorts) and 2) after ketamine start (Ket+MDZ cohort) versus after MDZ start (MDZ cohort), both without covariates and with APACHE II then MDZ maximum dose as covariates.

Within each cohort, anoxia was examined as a secondary predictor of SE duration using survival analyses and Fisher's exact tests. Only time from midazolam start to SE end was compared to enable fairer comparisons between cohorts. Fisher's exact tests were used in lieu of logistic regression due to cells with zero counts that prohibited estimation of odds ratios.

Secondary outcomes included tracheostomy and percutaneous endoscopic gastrostomy (PEG), disposition and death, and length of stay (LOS). Tracheostomy and PEG were combined into a single variable of tracheostomy and/or PEG versus neither. Disposition and death were originally categorized into discharge home, discharge to facility, withdrawal of care but did not expire in the hospital, expired after withdrawal of care, or expired not after withdrawal of care (Table 4). Due to the sample size, the final variable for inferential analyses was death or withdrawal of care during hospitalization versus neither. LOS was dichotomized as >14 days versus ≤ 14 days. Logistic regression examined secondary outcome by treatment cohort with and without adjustment for APACHE II scores and MDZ maximum dose. A chi-squared test was used when empty cells prohibited estimation of logistic regression results.

3. Results

3.1. Basic demographic and clinical characteristics

We identified 147 patients who received anesthetic infusion for RSE, 80 who received midazolam infusion and 67 who received ketamine plus midazolam infusion. Participants were excluded from the MDZ cohort (n=54) or the Ket + MDZ cohort (n=9) if the maximum midazolam dose or dose at ketamine start, respectively, was <0.8 mg/kg/hr. An additional 9 patients were excluded from the MDZ cohort due to missing SE end date/time, and another 2 patients were excluded from the Ket + MDZ cohort for atypical chronology. A total of 73 patients were included in the final analysis, 17 patients in the MDZ cohort and 56 patients in the Ket + MDZ cohort.

Table 3
Logistic regression results for status epilepticus (SE) resolution.

Outcome	Predictor (s)	Wald Test Z	df	Odds Ratio	95 % CI		P
					Lower	Upper	
MDZ start to SE end	Ket + MDZ vs. MDZ	0.58	1	0.65	0.22	1.96	.445
MDZ start to SE end	Ket + MDZ vs. MDZ	0.50	1	0.67	0.22	2.03	.479
	APACHE II score > 20	0.14	1	0.81	0.27	2.40	.706
MDZ start to SE end	Ket + MDZ vs. MDZ	0.78	1	0.59	0.18	1.90	.378
	APACHE II score > 20	0.10	1	0.84	0.28	2.49	.751
	MDZ maximum dose	0.50	1	0.80	0.42	1.49	.478
MDZ start (MDZ cohort) or Ket start (Ket+MDZ cohort) to SE end	Ket + MDZ vs. MDZ	11.00	1	0.13	0.04	0.44	.001
MDZ start (MDZ cohort) or Ket start (Ket+MDZ cohort) to SE end	Ket + MDZ vs. MDZ	9.97	1	0.14	0.04	0.47	.002
	APACHE II score > 20	1.06	1	0.52	0.15	1.82	.304
MDZ start (MDZ cohort) or Ket start (Ket+MDZ cohort) to SE end	Ket + MDZ vs. MDZ	8.45	1	0.15	0.04	0.54	.004
	APACHE II score > 20	1.15	1	0.50	0.14	1.77	.283
	MDZ maximum dose	0.18	1	1.18	0.56	2.49	.671

Abbreviations: confidence interval (CI), ketamine (Ket), midazolam (MDZ), status epilepticus (SE)

There was no significant difference between MDZ and Ket + MDZ cohorts in terms of sex, race, RSE etiology, GCS on admission (≤ 8 versus > 8), or age (Table 1). Of the 17 participants in the MDZ cohort and the 56 participants in the Ket + MDZ cohort, 41.2 % (n=7) and 48.2 % (n=27) were female, respectively (*P* =.782). Although there was no significant difference in race between groups, descriptively more patients in the MDZ group were White 58.8 % (n=10) compared to 39.3 % (n=22) in the Ket + MDZ group (*P*=.324). Anoxia was the most common etiology of RSE within both cohorts (29.4 % of the MDZ group, 44.6 % of the Ket+MDZ group, *P*=.399); other etiologies were combined into a single non-anoxia group for analyses due to small sample sizes. There were differences between the MDZ and the Ket + MDZ cohorts in APACHE II score and midazolam maximum dose. The mean APACHE II score was higher in the Ket + MDZ cohort (26 ± 7.32 SD) compared to the MDZ cohort (22 ± 5.89 SD) (*P*=.015). 79 % of patients in the Ket + MDZ cohort and 65 % of patients in the MDZ cohort had APACHE II score ≥ 21 on admission. The median midazolam maximum dose was greater in the MDZ cohort [2.10 mg/kg/hr, IQR 1.53–2.90] than the Ket + MDZ cohort [1.6 mg/kg/hr, IQR 1.20–2.0] (*P*=.022).

3.2. Duration of SE after anesthetic infusion

Survival analysis was used to analyze the relationship between treatment group and SE duration. SE resolved in 100 % of the MDZ group (n=17) and 98 % of the Ket + MDZ group (n=55) (Fisher's exact *P*=1.00). There was no significant difference between cohorts in time from midazolam start to SE end, either in the univariate analysis (HR=0.965, 95 % CI=0.556–1.673, *P*=.899) (Fig. 1) or when including APACHE II (HR=0.861, 95 % CI=0.480–1.542, *P*=.614) or APACHE II and MDZ maximum dose as covariates (HR=0.873, 95 % CI=0.478–1.593, *P*=.658). The median time from midazolam start to SE end was 25 h [IQR 4.5–58] in the MDZ cohort and 21.5 h [IQR 13.5–49] in the Ket + MDZ cohort. Fig. 2

Median time from initiation of midazolam infusion to SE end for the MDZ cohort was 25 h [IQR 4.5–58] compared to 4.5 h [IQR 1.0–14.5] from ketamine infusion to SE end in the Ket + MDZ cohort (HR=1.895, 95 % CI=1.083–3.314, p=.025) (Fig. 1). When including APACHE II score (p=.114) or both APACHE II (p=.147) and MDZ maximum dose (p=.234) as covariates, there was no statistically significant difference between groups; however, the same trend was observed (HR=1.724, 95 % CI=0.977–3.043, p=.060; HR=1.604, 95 % CI=0.892–2.885, p=.115).

3.3. SE duration ≥ 24 h after anesthetic infusion

Logistic regression was used to analyze the relationship between treatment group and SE duration lasting ≥ 24 h. When examining midazolam start to SE end, there was no difference between groups in the odds of SE lasting ≥ 24 h, both in univariate analyses (OR=0.652, 95 % CI=0.217–1.956, p=.445) and when including APACHE II score (OR=0.67, 95 % CI= 0.221–2.032, p=.479) or APACHE II score and MDZ maximum dose as covariates (OR=0.59, 95 % CI= 0.184–1.903, p=.378). The percentage of patients with SE duration ≥ 24 h after midazolam start was 59 % in the MDZ cohort compared to the 48 % in the Ket + MDZ cohort. When examining ketamine start to SE end (Ket+MDZ cohort) versus MDZ start to SE end (MDZ cohort), there was a significant difference between groups in the odds of SE lasting ≥ 24 h, both in univariate analyses (OR=0.134, 95 % CI= 0.04–0.445, p=.001) and when including APACHE II score (OR=0.142, 95 % CI= 0.042–0.477, p=.002) or APACHE II score and MDZ maximum dose as covariates (OR=0.154, 95 % CI= 0.044–0.543, p=.004) (Table 3). In the MDZ cohort, SE lasted ≥ 24 h after initiation of MDZ in 10/17 patients (59 %); by comparison, in the Ket+MDZ cohort, SE lasted ≥ 24 h after

Table 4
Secondary Outcomes.

	MDZ (n=17)	Ket+ MDZ (n=56)	*P*, unadjusted	*P*, adjusted for APACHE II	*P*, adjusted for APACHE II and MDZ dose
Tracheostomy or PEG	7 (41.2 %)	16 (28.6 %)	.33	.38	.25
Disposition			.32	.44	.30
Home	1 (5.9 %)	3 (5.4 %)			
Facility	8 (47.1 %)	19 (33.9 %)			
Withdrawal of care but did not expire in hospital	0 (0 %)	3 (5.4 %)			
Died after withdrawal of care	7 (41.2 %)	19 (33.9 %)			
Died not after withdrawal of care	1 (5.9 %)	12 (21.4 %)			
Length of stay > 14 days (non-deceased patients only)*	9/9 (100 %)	17/22 (77.3 %)	.12	—	—

Abbreviations: Ketamine (Ket), midazolam (MDZ), percutaneous endoscopic gastrostomy (PEG), status epilepticus (SE)

* Chi-square test. All others are logistic regression, with treatment group as the independent variable. In logistic regression for disposition, the outcome is death or withdrawal of care vs neither.

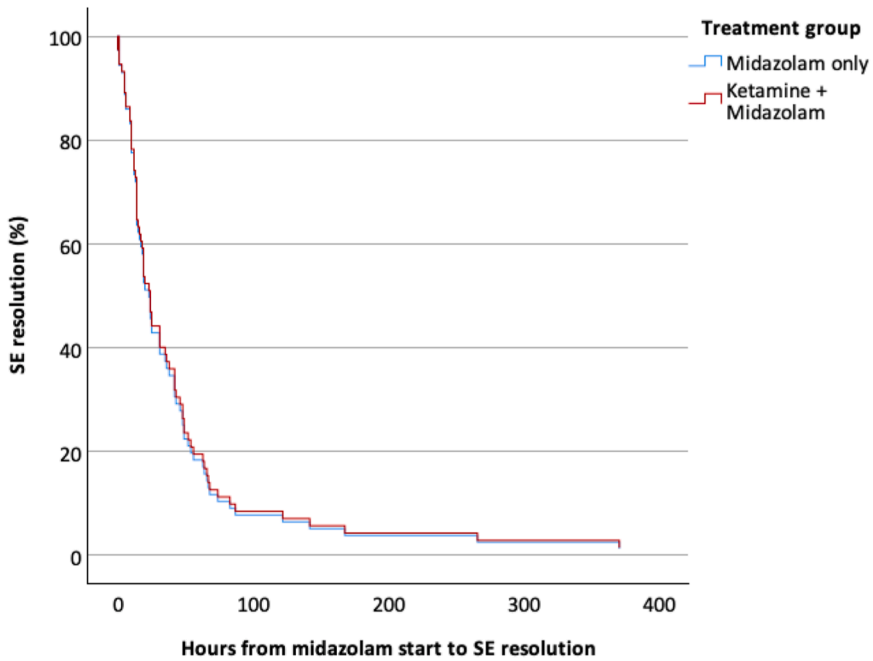

Fig. 1. Survival curve of time from midazolam start to SE end in Ket+MDZ group versus MDZ-only group (HR=0.965, 95 % CI=0.556–1.673, *P*=.899).

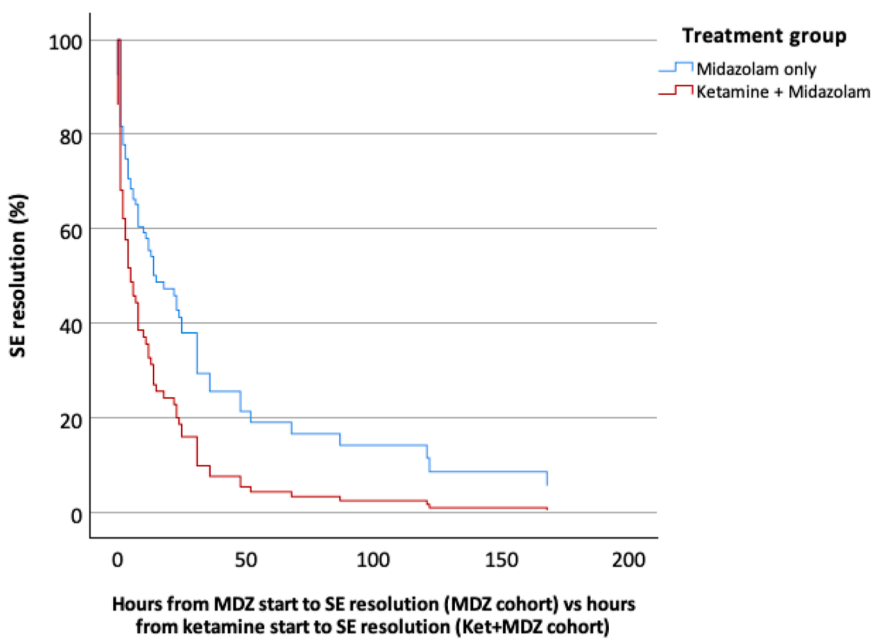

Fig. 2. Survival curve of time from ketamine start to SE end in the Ket + MDZ group versus midazolam start to SE end in the MDZ group (HR=1.895, 95 % CI=1.083–3.314, p=.025).

initiation of ketamine in only 9/56 patients (16 %).

3.4. Anoxia and SE duration

Secondary analysis included SE etiology, defined as anoxia versus other, as a predictor of outcome (Fig. 3). In the MDZ cohort, median time from midazolam initiation to SE end was significantly longer in patients with anoxia (n=5), at 87 h [IQR 31–122], compared to 13 h [IQR 2–31] in patients with other etiology of SE (n=12) (HR=0.19, 95 % CI=0.04–0.85, p=.030). In the Ket + MDZ cohort, SE duration was not related to etiology (HR 1.09, 95 % CI=0.63–1.89, p=.752). Median time to SE end was 36 h [IQR 12–48] in patients with anoxia (n=26) and 19 h [IQR 14–49] in patients with other etiology of SE (n=31).

Results were comparable when examining the likelihood of SRSE. In the MDZ group, 100 % of patients with anoxia had SE last ≥ 24 h, significantly higher than the 42 % of patients with other etiology of SE (p=.044). In the Ket + MDZ cohort, SRSE was not related to etiology. 56 % of patients with anoxia and 42 % of patients with other etiology of SE had SE last ≥ 24 h (p=.420).

3.5. Secondary outcomes

Secondary outcomes of tracheostomy/PEG, death, and LOS did not differ significantly between treatment groups (Table 4). The percentage

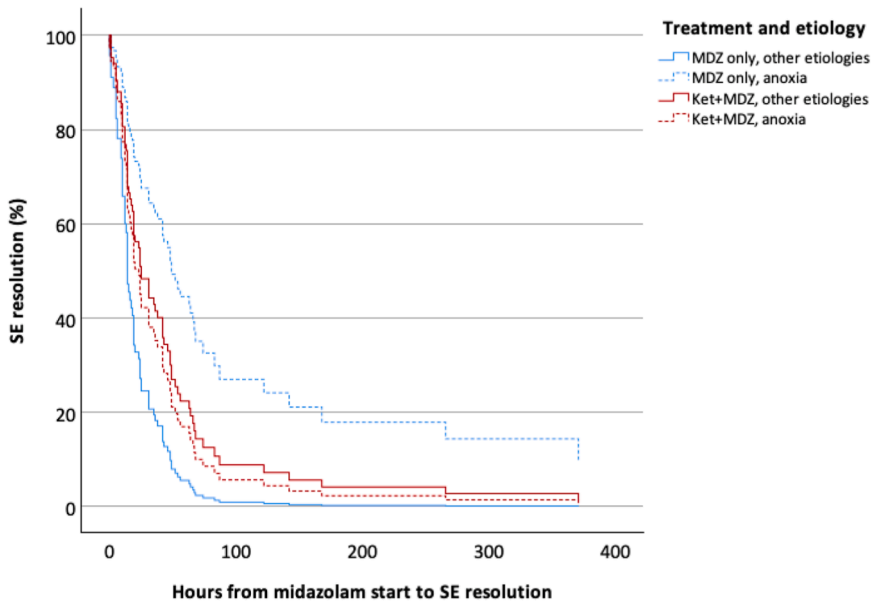

Fig. 3. Survival curve of time from midazolam start to SE end within the Ket+MDZ and MDZ-only groups, split by etiology (anoxia versus other). *Abbreviations: Ketamine (Ket), midazolam (MDZ), status epilepticus (SE).

of patients who underwent tracheostomy and/or PEG placement was 41.2 % in the MDZ cohort and 28.6 % in the Ket + MDZ cohort. The percentage of patients who expired or had withdrawal of care during hospitalization was 47.1 % in the MDZ cohort and 60.7 % in the Ket + MDZ cohort. High APACHE II score had a trend towards being associated with higher odds of death or withdrawal of care during hospitalization (OR= 2.62, 95 % CI= 0.87–7.90, p=.088). LOS was confounded with death, as patients who expired had shorter LOS (p<.001). Therefore, the analysis of the association between treatment group and LOS was limited to non-deceased patients only. The percentage of non-deceased patients with LOS > 14 days was 100 % in the MDZ cohort and 77.3 % in the Ket + MDZ cohort. Although death was related to shorter length of stay, it was not related to SE duration or the likelihood of SE lasting >24 h, whether using MDZ start as the start point (p=.349, p=.201) or using ketamine start (if applicable) as the start point (p=.789, p=.565).

4. Discussion

We identified 73 patients who received either midazolam infusion or ketamine plus midazolam infusions for RSE and grouped them into two cohorts referred to as MDZ cohort (n=17) and Ket + MDZ (n=56) respectively. The primary outcomes were time from midazolam infusion start to SE end, and time from start of midazolam infusion to SE end for the MDZ cohort and start of the ketamine infusion to SE end for the Ket + MDZ cohort. There was no significant difference in midazolam start to SE end between groups both in the univariate analysis and when including APACHE II score and maximum midazolam dosage as a covariate. Time from Ket start to SE end (Ket+MDZ cohort) versus MDZ start to SE end (MDZ cohort) was significantly shorter in the Ket + MDZ cohort as compared to the MDZ cohort in the univariate analysis. When APACHE II score and maximum midazolam dosage were examined as covariates, this effect weakened to a trend. However, the odds of RSE lasting ≥ 24 h, and therefore becoming SRSE, were significantly lower in the Ket + MDZ group in both univariate and multivariate analyses.

There were some significant clinical differences between cohorts. The mean APACHE II score was higher in the Ket + MDZ cohort than the MDZ cohort despite restricting the MDZ cohort to midazolam infusion ≥ 0.8 mg/kg/hr, suggesting that the participants in the Ket + MDZ cohort had increased illness severity. The median maximum midazolam infusion rate was higher in the MDZ cohort compared to the Ket + MDZ cohort. In the absence of ketamine infusion, midazolam infusion rate was increased to achieve seizure suppression. To account for these differences, APACHE II score and midazolam maximum dose were included as covariates in primary analyses and were not significantly associated with RSE duration. There was no significant difference between groups in sex, race, anoxic versus other RSE etiology, GCS on admission, or age. The small number of differences between groups, despite the non-randomized, retrospective design of this study is a notable strength.

APACHE II score was dichotomized for inclusion as a covariate of interest with cutoff score of ≥ 21 which has previously been correlated with increased mortality [10]. 79 % of patients in the Ket + MDZ cohort had an APACHE II score of ≥ 21 as compared to 65 % of the MDZ cohort. The group difference between APACHE II scores would bias results in favor of the MDZ cohort because these patients would be expected to have lower mortality risk. Therefore, it is notable that time from midazolam start to SE end was comparable in both cohorts, despite the higher median APACHE II score.

Secondary analysis included etiology as a predictor of SE duration. Interestingly, in the MDZ cohort, anoxia patients were significantly more likely to have SE duration ≥ 24 h, therefore classifying them as SRSE, as compared to other etiologies. However, in the Ket + MDZ cohort, there was no significant difference in the likelihood the SE duration ≥ 24 h between groups. These results may suggest that ketamine infusion appears to bring the outcomes of anoxia patients with SE in line with patients of other etiologies. These results must be interpreted with caution however due to the very small sample size in the MDZ cohort (N=17). However, these results raise an interesting question as to whether ketamine has neuroprotective effects in anoxia.

Secondary outcomes included tracheostomy and/or PEG, death, and length of stay > 14 days. No significant difference was observed between groups, regardless of whether APACHE II was included as a covariate. High APACHE II had a trend towards being associated with high odds of death and/or withdrawal of care in hospital. Thus, as with the RSE duration findings, it is notable that these secondary outcomes were comparable between treatment groups despite greater severity (i.e., higher APACHE II scores) in the Ket + MDZ group. Although the primary endpoints of this study suggest that the addition of ketamine infusion might result in earlier seizure termination, the secondary outcomes suggest that early termination of RSE with ketamine did not improve the

overall clinical outcomes (Table 4). Secondary outcome analysis suggests that the addition of ketamine for patients with higher APACHE II score, and therefore greater disease severity, results in comparable outcomes to patients with lower disease severity.

There is limited literature available to aid clinicians choosing between intravenous anesthetic agents for the treatment of RSE. Commonly used agents include propofol, midazolam, and pentobarbital. The Neurocritical Care Society Guideline for Evaluation and Management of SE indicates that there is insufficient evidence to determine which continuous infusion medication is the preferred agent for the treatment of RSE, and comments that ketamine is an alternative therapy for RSE due to limited data on safety and efficacy [9]. Several retrospective case series and systematic reviews have been published studying the role of ketamine for the treatment of RSE and SRSE and reported response to ketamine ranges from 27 % to 100 % [6,11–14]. Additionally, animal studies have demonstrated that ketamine has neuroprotective effect [15]. A retrospective case series of 68 patients with SRSE treated with midazolam plus ketamine demonstrated that 81 % of patients had at least 50 % seizure burden decreased within 24 h of starting ketamine and 63 % of patients had complete cessation of seizures within 24 h. The average dose of midazolam was 1.0 ± 0.8 mg/kg/hr at the time of ketamine initiation. Ketamine was associated with decreased vasopressor requirements [6]. A retrospective study of 58 adult patients treated with ketamine for RSE and SRSE demonstrated a good response to ketamine in 56.9 % of patients. Rates of good response to ketamine were similar in anoxia-related and non-anoxia related SE (anoxic 50 % versus non-anoxic 61.8 %) [13].

Several retrospective studies have been published evaluating the efficacy and safety of ketamine, however, to our knowledge, no study has been published in the adult literature directly comparing midazolam versus ketamine plus midazolam for the treatment of RSE and SRSE. A recent retrospective cohort study examining the efficacy and adverse effects of midazolam and ketamine infusion for RSE in the neonatal and pediatric population demonstrated that seizures terminated in 61 % of patients who received ketamine infusion as compared to 28 % of patients that received midazolam infusion [7]. Regarding the adverse effects of ketamine infusion, the nature of these effects appears to vary; review studies have reported cardiac arrythmias, transient arterial hypertension, sialorrhea, hepatotoxicity, and metabolic acidosis [4,14]. Recent studies suggest that ketamine has no effect on intracranial pressure at prolonged high anesthetic dosages [6].

4.1. Limitations and future directions

This study is a retrospective, single-center study which limits generalizability. The small size of the MDZ group, and its imbalance relative to the Ket + MDZ group, further limits generalizability and reliability of findings. This imbalance reduced our power to detect difference between the cohorts and within-group effects in the MDZ group. Thus, it is notable that despite these limitations we found some between-group differences in RSE duration, and a significant effect of etiology within the MDZ group but not within the Ket + MDZ group.

Another limitation is that ketamine infusion was started at the discretion of the treating physician. We also excluded participants who received midazolam infusion <0.8 mg/kg/hr in attempts to exclude patients with less severe RSE from the MDZ group and promote comparability between groups in RSE course and severity. This prohibited us from analyzing data from patients who received early initiation of ketamine. Our institution has recently adopted earlier initiation of ketamine for RSE when midazolam infusion is at ≥ 0.4 mg/kg/hr. Future prospective randomized control trials are required to evaluate the utility of early ketamine plus midazolam infusion compared to midazolam followed by ketamine infusion for the treatment of RSE and SRSE.

5. Conclusions

In this retrospective cohort study, we examined the efficacy of ketamine plus midazolam infusions for the treatment of RSE/SRSE compared to midazolam infusion and hypothesized that initiation of ketamine infusion would result in earlier seizure termination. The primary outcomes were time from midazolam infusion start to SE end (both cohorts), and time from ketamine infusion start (Ket Start) to SE end in the Ket+MDZ cohort versus midazolam infusion start (MDZ start) to SE end in the MDZ cohort. Despite higher disease burden in the Ket + MDZ cohort, time from midazolam start to SE end was comparable in both cohorts. Patients with anoxic etiology of SE appeared to respond better to Ket + MDZ. Time from Ket start to SE end (Ket+MDZ cohort) was significantly shorter than time from MDZ start to SE end (MDZ cohort). Our data suggests that the addition of ketamine might result in earlier seizure termination and reduce the duration of RSE. Randomized controlled trials are warranted in determining optimal agents in RSE and SRSE.

Statement of human and animal rights

This study was approved by the Institutional Review Board (IRB) of Thomas Jefferson University Hospital and was conducted in accordance with ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. For this type of study, formal consent is not required.

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CRediT authorship contribution statement

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Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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