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Research Paper

Combined Ketamine and Midazolam Versus Midazolam Alone for Initial Treatment of Pediatric Generalized Convulsive Status Epilepticus (Ket-Mid Study): A Randomized Controlled Trial

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ABSTRACT

Background: Approximately one third of children with generalized convulsive status epilepticus (GCSE) are not controlled by initial benzodiazepine therapy. We investigated the efficacy of adding ketamine to midazolam for first-line treatment of pediatric GCSE.

Methods: This randomized controlled trial included 144 children with GCSE aged between six months and 16 years, who were equally randomized to receive ketamine plus midazolam (Ket-Mid group) or placebo plus midazolam (Pla-Mid group). Primary outcome was cessation of clinical seizures at five-minute study timepoint. Secondary outcomes were the need for a second midazolam bolus; cessation of clinical seizures at 15-, 35-, and 55-minute timepoints; 24-hour seizure control; and adverse effects.

Results: Cessation of clinical seizures at five-minute occurred in 76% of children in the Ket-Mid group compared with 21% in the Pla-Mid group (risk ratio [RR] 3.7; 95% confidence interval [CI] 2.3-5.9; $P < 0.001$). Compared with the Pla-Mid group, the Ket-Mid group had higher percentages of seizure cessation at 15-minute (76.4% vs 23.6%; RR, 3.2; 95% CI, 2.1-5.0), 35-minute (83.3% vs 45.8%; RR, 1.8; 95% CI, 1.4-2.4), and 55-minute (88.9% vs 72.2%; RR, 1.2; 95% CI, 1.04-1.45) study timepoints as well as lower percentages of repeating midazolam (23.6% vs 79.2%; RR, 0.3; 95% CI, 0.19-0.46) and endotracheal intubation (4.2% vs 20.8%; RR, 0.2; 95% CI, 0.06-0.66). Both groups showed no significant differences in other outcome measures.

Conclusions: Ketamine-midazolam combination may be more effective than midazolam alone for the initial treatment of pediatric GCSE, but this should be confirmed in future research.

Introduction

Generalized convulsive status epilepticus (SE) (GCSE) is the most prevailing neurological emergency in children.[1-3] Current guidelines recommend benzodiazepines (BDZs) as the initial antiseizure medication (ASM) for GCSE, but up to 40% of patients are resistant to first-line BDZ therapy.[4-7] Additionally, about half of BDZ-refractory GCSE are not aborted by second-line ASMs, such as levetiracetam, valproate, and phenytoin.[5,8,9] As GCSE continues for a longer duration, it becomes more resistant to control and is associated with progressive brain damage and increased risk of death, chronic epilepsy, and long-lasting neurocognitive deficits.[6,10-12] Accordingly, early termination of GCSE is crucial for improving clinical outcomes as "time is brain."[4,6,13,14]

Ethics approval and consent to participate: The study was approved by the Medical Research Ethics Committee, Faculty of Medicine, Sohag University (Approval no Soh-Med-23-03-12MS; dated March 08, 2023). Informed consent was obtained from the parents or authorized legal representatives of participating children. All study procedures were conducted in accordance with the 1954 Declaration of Helsinki and its 2013 revision.

Clinical trial registration: Prospectively registered on ClinicalTrials.gov (Identifier: NCT05779657; dated March 09, 2023).

Availability of data and material: The datasets used and analyzed during the current study are available from the corresponding author upon a reasonable request.

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Conflicts of interests: The authors have no competing interests to declare.

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Rapid control of GCSE may be better achieved by combining BDZs with another ASM that works via a different mechanism as a first-line treatment.[14-16] Ketamine seems a promising option for such combination due to its anticonvulsive and neuroprotective effects as well as availability, affordability, and high safety profile.[15,17-21] Unlike BDZs that work as allosteric agonist for γ-aminobutyric acid $(GABA)_A$ receptors, ketamine is a noncompetitive glutamate antagonist acting on *N*-methyl-d-aspartate (NMDA) receptors.[15,22] Ongoing seizure activity is associated with rapidly progressive downregulation of inhibitory $GABA_A$ receptors and upregulation of excitatory NMDA receptors, rendering prolonged seizures more resistant to GABAergic agents but remaining responsive to NMDA antagonists.[12,16,22] Therefore, using ketamine in conjunction with BDZs represents a rational combination to target both enhanced NMDA-mediated neuroexcitation and remaining functionally active $GABA_A$ receptors.[15,19,22,23] Data from animal models of SE indicate that ketamine works synergistically with BDZs in not only terminating seizures but also mitigating neuronal damage.[24-29] Furthermore, an increasing number of observational studies on adults and children with refractory SE (RSE) and super-refractory SE (SRSE) have demonstrated cessation or reduction in seizures after ketamine administration, commonly in conjunction with midazolam infusion.[13,19,30,31] Additionally, combined ketamine and BDZs have been safely used for a long time in pediatric procedural analgosedation.[18,32] However, no randomized controlled trials (RCTs) have explored the utility of ketamine-BDZ combination in the management of children with GCSE.

Given the current knowledge on rapidly progressive pathophysiologic changes in synaptic receptors during SE[12,16,23] coupled with data on the significantly delayed time to administration of first-line BDZs[11] and the consequent suboptimal efficacy of BDZs in the initial treatment of GCSE,[5,6,11,14,33] the authors thought that ketamine could be more useful when combined with BDZs as first-line ASMs for GCSE to avoid the severe consequences of prolonged seizures rather than utilizing it as a late subsequent option for RSE and SRSE when significant brain damage has already occurred. In this RCT, we investigated the short-term efficacy of adding ketamine to midazolam as first-line ASMs for pediatric GCSE. The study hypothesis is that in children with GCSE ketamine plus midazolam, compared with midazolam alone, as first-line ASMs would be more successful in terminating clinical seizures at five minutes following drug administration.

Methods

Design and setting

This randomized, two-group, parallel, 1:1, superiority, double-blind, placebo-controlled trial was performed between March 2023 and August 2024 at the pediatric emergency room of Sohag University Hospital (southern Egypt).

Participants

Eligibility criteria were children aged between six months and 16 years who presented with GCSE. GCSE was operationally defined as clinically detectable generalized tonic-clonic convulsions that persist or recur without complete regaining of consciousness in between for longer than five minutes.[7] Seizure duration before hospital arrival was parent reported. Exclusion criteria were previous treatment with any ASMs for the presenting seizure episode, traumatic brain injury (TBI), conditions associated with increased intracranial pressure (e.g., hydrocephalus, central nervous system [CNS] mass lesions), hypertension, glaucoma, hyperthyroidism, pheochromocytoma, end-stage kidney or liver diseases, cardiac disease (arrhythmia, severe heart disease, or pulmonary hypertension), history of alcohol intake, hypoglycemia or hyperglycemia, inborn errors of metabolism, known allergy or contraindication to any of the study drugs, known or suspected psychiatric disorder, failure to secure intravenous access in the first five minutes of stabilization phase, cessation of seizures during the stabilization phase (0-5 minutes), and failure to obtain informed consent.

Randomization and masking

Participants were randomized in a 1:1 ratio to receive ketamine and midazolam (Ket-Mid group) or placebo and midazolam (Pla-Mid group) using random numbers in permuted blocks of four generated by Research Randomizer software.[34] An individual outside the research team secured these random numbers into serially ordered opaque envelopes. For every participant, the envelope in turn was opened and the allocated medications were given. Pharmacy diluted ketamine 50 mg/mL intravenous form (KETAMAX-50; Troikaa Pharmaceuticals Ltd, Uttarakhand, India) to a 1:10 concentration using normal saline (Intra Pharm, Alexandria, Egypt). A pharmacist filled the ketamine 5 mg/mL solution (active drug) and normal saline (placebo) into identical 12-mL containers with sealed verification codes. The study participants and their parents, treating physicians and paramedical staff, investigators, and outcome assessors were unaware of the ketamine/placebo assignment.

Intervention

All participants received the standard emergency measures for GCSE following the institutional protocol. These measures included first-aid measures, airway management, overseeing vital signs, assessment of oxygenation, provision of oxygen by nasal cannula or mask, endotracheal intubation if necessary, evaluation of blood glucose and treatment of any hypoglycemia, placing intravenous line, and blood sampling for laboratory tests.

Participants with seizures lasting beyond the five-minute stabilization phase received 0.4 mL/kg (maximum 12 mL) over two minutes of the randomly assigned study drug (equivalent to ketamine 2 mg/kg [maximum 60 mg] in case of active drug) simultaneously with midazolam (Midathetic; Amoun Pharmaceuticals Co., Al Qalyubia, Egypt) 0.2 mg/kg over 2 minutes via two separate peripheral intravenous lines. Study timepoint 0 was the moment at administration of the randomly allocated study drug. Another midazolam dose was given to participants with seizures persisting longer than five minutes following the first dose. Afterward, patients with continuous seizures at 15- and 35-minute study timepoints received intravenous levetiracetam (Tiratam; Al Andalous for Pharmaceuticals Ind., Cairo, Egypt) 60 mg/kg over 5 minutes and intravenous phenytoin (Phenytin; Nile Co. for Pharmaceutical and Chemical Industries, Cairo, Egypt) 20 mg/kg over 20 minutes, respectively. For incessant convulsions at 55-minute study timepoint, patients were shifted to the pediatric intensive care unit, where they received a loading dose of intravenous midazolam 0.2 mg/kg (2 mg/min) and then 0.05-2 mg/kg/h continuous infusion. All participants underwent comprehensive medical care, including provision of proper fluids and electrolytes, control of fever, maintaining adequate oxygenation and ventilation through oxygen and noninvasive or invasive ventilation, hemodynamic support by fluids and vasopressors, and specific treatment of any identifiable cause.

Study time frame and outcome measures

The trial time frame was confined to 24 hours starting from the time of intake of the randomly assigned study drug. The primary

outcome measure was the participants' proportion who attained cessation of clinical seizures at the five-minute study timepoint. The secondary outcomes were the need for repeating midazolam during the first 15 minutes of study time frame; cessation of clinical seizures at 15-, 35-, and 55-minute timepoints; seizure control (no recurrence of clinical seizures after initial cessation); hypotension; hypertension; arrhythmia; emergence phenomenon (one or more of hallucination, delirium, vivid dreams, blurred/double vision, nausea/vomiting, and hypersalivation); skin rash; need for endotracheal intubation; and mortality.

Sample size calculation

The sample size of this superiority trial was calculated using Stata/BE 17 (StataCorp, College Station, TX, USA) assuming 50% efficacy of midazolam in stopping clinically observed seizures at the five-minute study timepoint (primary outcome) and an additional 25% efficacy for add-on ketamine over placebo, keeping two-sided type I error (α) = 0.05 and type II error (β) = 0.2. This calculation resulted in 58 individuals per group, which was raised to 72 subjects per group to account for possible 20% dropouts.

Statistical analysis

We analyzed data on an intention-to-treat basis using Stata/BE 17. Data were displayed as frequency (%) for categorical data, mean (S.D.) for normally distributed quantitative data, and median (IQR) for non-normally distributed quantitative data. Binary outcome measures were compared between the study and comparison groups using chi-square or Fisher exact test as appropriate. We performed a subgroup analysis to compare the intervention (ketamine) effect on the primary outcome measure among different age categories (6-12, >12-60, and >60 months), seizure etiologies (febrile, known epilepsy, CNS infection, unknown/others), and seizure durations at hospital arrival ($\leq$ or >30 min) using the Mantel-Haenszel method. We further examined the homogeneity of the intervention effect on the primary outcome measure across age, seizure etiology, and seizure duration at hospital arrival through logistic regression models that contained terms for intervention, age/etiology/duration, and intervention-age/etiology/duration interaction. Finally, we investigated the possible factors affecting primary outcome measure through univariate logistic regression analysis, followed by multivariate model that included variables demonstrating statistically significant associations in univariate analysis. Statistical significance was specified at a two-tailed P value <0.05. No multiple comparison adjustment was planned *ex ante* or performed posthoc.

Ethical considerations

This study was reviewed and approved by the Research Ethics Committee of Sohag Faculty of Medicine (Approval no. Soh-Med-23-03-12MS; dated March 8, 2023). Emergency oral informed consent was obtained from the parents or legally authorized representatives of participating children followed by written informed consent. All study procedures were conducted in accordance with the 1954 Declaration of Helsinki and its 2013 revision. The study protocol was prospectively registered on ClinicalTrials.gov (Identifier: NCT05779657; dated March 9, 2023).

Results

The study participation flow chart is depicted in Figure. Among the 144 participants, 32% were in the first year of life, 37% were aged between one and five years, and 31% were aged greater than five years. The most frequent causes of GCSE were febrile seizure (43%) and known epilepsy (42%) followed by CNS infection (11%), whereas 4% had other or unknown etiologies. The median duration from GCSE onset to hospital arrival was 34 minutes, and more than half (58%) of the participants experienced seizures lasting >30 minutes upon hospital presentation. None of the study participants received ASMs for their acute seizure episodes before hospital arrival. Standard management protocols were followed in the clinical care of all enrolled children. The baseline clinical and laboratory features of participants in both groups are provided in Table 1.

The outcomes between the study and comparison groups are demonstrated in Table 2. Cessation of clinical seizures at five-minute study timepoint occurred in 76.4% of children in the Ket-Mid group and 20.8% of children in the Pla-Mid group (risk ratio [RR], 3.7; 95% confidence interval [CI], 2.3-5.9; $P < 0.001$). Compared with the Pla-Mid group, the Ket-Mid group had statistically significant higher percentages of clinical seizure cessation at 15-minute (76.4% vs 23.6%; RR, 3.2, 95% CI, 2.1-5.0), 35-minute (83.3% vs 45.8%; RR, 1.8; 95% CI, 1.4-2.4), and 55-minute (88.9% vs 72.2%; RR, 1.2; 95% CI 1.04-1.45) study timepoints as well as lower percentages of repeating midazolam (23.6% vs 79.2%; RR, 0.3; 95% CI, 0.19-0.46) and endotracheal intubation (4.2% vs 20.8%; RR, 0.2; 95% CI, 0.06-0.66). Both groups showed no significant differences in other outcome measures.

Subgroup analysis revealed that adjunct ketamine exerts significantly higher efficacy in stopping clinical seizures at 5-minute study timepoint (primary outcome) among children with GCSE >30 minutes at hospital presentation compared with those with shorter seizures (RR [95%CI], 28.3 [4.0-198] vs 1.9 [1.3-2.9], $P < 0.001$) (Table 3). In contrast, the Mantel-Haenszel test revealed no significant difference in the add-on ketamine effect on primary outcome among different age categories ($P = 0.495$) and seizure etiologies ($P = 0.777$) (Tables 4 and 5). These results were also confirmed by logistic regression analyses, which showed a significant interaction of ketamine effect on primary outcome with seizure duration at hospital entrance (interaction term $P = 0.001$) but not with age or seizure etiology (interaction terms $P > 0.05$).

In univariate logistic regression, factors significantly associated with primary outcome were add-on ketamine, shorter duration from GCSE onset to hospital arrival, known epilepsy etiology, prior ASM therapy, nonfebrile seizure etiology, and lower body temperature. (Supplemental Table S1). A multivariate model showed that add-on ketamine therapy (adjusted odds ratio [aOR], 27.7; 95% CI, 9.3-82.8, $P < 0.001$), shorter seizure duration at hospital presentation (aOR, 0.94; 95% CI, 0.91-0.97, $P < 0.001$), and epileptic seizure etiology (aOR, 8.9; 95% CI, 2.1-39.4; $P = 0.004$) are independent predictors for primary outcome (Supplemental Table S2).

Discussion

This is the first RCT to investigate the efficacy of adjunct ketamine to midazolam as a first-line ASM combination for pediatric GCSE. We found that ketamine plus midazolam is more effective than midazolam alone in terminating clinical seizures at 5, 15, 35, and 55 minutes following drug administration, particularly for GCSE >30 minutes, and significantly reduced the need for endotracheal intubation. These findings indicate that ketamine plus midazolam is a potentially promising first-line ASM combination for children with prolonged GCSE, but future studies are highly warranted to confirm our results and further evaluate the clinical utility of the ketamine-midazolam dual therapy for the initial and subsequent treatment of pediatric GCSE.

Consistent with our findings, experimental research has demonstrated that adjuvant NMDA receptor antagonists (e.g.,

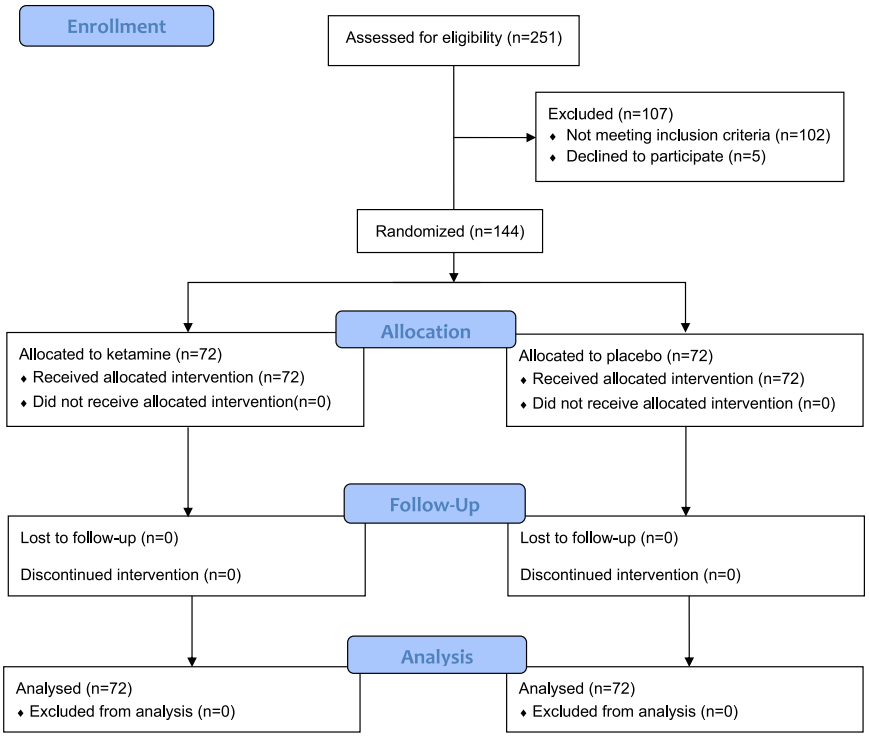

FIGURE. Study participants flow chart. The color version of this figure is available in the online edition.

ketamine, dizocilpine) work synergistically with BDZs (e.g., midazolam, diazepam) to terminate or attenuate seizures in different animal models of SE.[24-29] For instance, in a lithium/pilocarpine induced-SE rat model, ketamine-midazolam combination was more effective in reducing seizure severity than double dose midazolam or ketamine monotherapies as well as midazolam-valproate or ketamine-valproate combinations.[27] Importantly, the synergy between ketamine and BDZs may extend to neuroprotective effects against epileptogenesis, neuronal injury, and functional impairment.[24,25,27,28] Our findings are also supported by numerous cohorts and case series on adults and children with RSE and SRSE, describing cessation or reduction of seizures after ketamine infusion in 40%-90% of cases.[19,30,31] In most of these studies, ketamine was coadministered with midazolam, which aligns with their synergistic effects noted in animal experiments.[30,31,35,36] Rare reports have also described the earlier use of ketamine as a second-line ASM in children with SE.[18,37] However, strong evidence for ketamine efficacy requires RCTs because observational studies are subject to bias and confounding.[19,31]

The remarkable efficacy of combined midazolam and ketamine as first-line ASMs for GCSE may be explained by rapidly targeting both diminished inhibitory and enhanced excitatory mechanisms of seizure self-perpetuation. Continuous seizure activity is associated with endocytosis and trafficking of BDZ-sensitive γ2 subunit-containing $GABA_A$ receptors away from synapse, which is associated with a time-dependent reduction in synaptic inhibition and responsiveness to BDZs.[12,38,39] At the same time, there is a progressive increase in the surface expression of glutamate-sensitive N2B subunit-containing NMDA receptors at synaptic and extrasynaptic sites, resulting in glutamatergic overexcitation.[12,16] These changes in synaptic receptors create a vicious cycle in which the inhibitory/excitatory imbalance induces circuit overactivity and neuronal injury with further neuroplastic changes that consequently enhance self-sustained seizures.[12,16,23] Accordingly, the midazolam-ketamine combination is highly advantageous since it allows midazolam to target the remaining functionally active $GABA_A$ receptors and ketamine to antagonize the enhanced NMDA receptor-mediated neuroexcitation and its consequent epileptiform burst discharge, thereby interrupting mechanisms underlying self-perpetuating SE and brain damage.[15,18,20,22,23,39]

Furthermore, there is a reciprocal interaction between progressive loss of $GABA_A$ receptor-mediated synaptic inhibition and enhancement of NMDA receptor-mediated excitation during SE.[12] Reduced GABAergic inhibition enhances circuit hyperactivity, membrane depolarization, and removal of magnesium block leading to NMDA receptor-mediated glutamatergic overexcitation.[29,40] In turn, enhanced NMDA receptor-mediated Ca^{++} influx during SE triggers several enzymes, including calcineurin and protein phosphatase 2A, which induce dephosphorylation of $GABA_A$ receptors, facilitating their desensitization, internalization, and trafficking away from synapses with consequent progressive loss of GABAergic inhibition and diminished responsiveness to BDZs.[12,23,41-44] This interplay may further explain the synergistic effects of the ketamine-midazolam combination in SE where BDZs may potentiate ketamine effect and ketamine could maintain or restore responsiveness to BDZs even in prolonged SE.[29,41,42,45] Additionally, ketamine confers immunomodulatory effects by reducing inflammatory mediators, which could attenuate neuroinflammation, seizure severity, and neuronal injury.[18,20,46] These anti-inflammatory effects of ketamine may also mitigate resistance to other ASMs.[14,18] Finally, BDZs could inhibit hepatic cytochrome P450 enzyme-mediated *N*-demethylation of ketamine, which may increase its biological half-life and therapeutic effects.[22,47]

Regarding short-term safety outcomes, the current study showed that add-on ketamine therapy significantly reduced the need for endotracheal intubation and tended to decrease the likelihood of hypotension. Similarly, prior studies showed that ketamine is advantageous to avoid endotracheal intubation and improve hemodynamic stability in patients with RSE and SRSE.[19,48,49] This advantage could be attributed to the favorable

TABLE 1.
Baseline Characteristics of Study Participants

Characteristics	Total ($n = 144$)	Ket-Mid Group ($n = 72$)	Pla-Mid Group ($n = 72$)	*P* Value
Age (months)*	31 (10.5-74.5)	30 (9.5-74.5)	31 (11-78)	0.677
Male sex†	82 (56.9%)	43 (59.7%)	39 (54.2%)	0.501
Body mass index (kg/m^2)‡	15.7 (2.38)	15.5 (2.23)	15.9 (2.52)	0.424
Head circumference (cm)‡	45.5 (3.06)	45.1 (3.35)	45.9 (2.71)	0.111
Developmental delay†	40 (27.8%)	19 (26.4%)	21 (29.2%)	0.710
Prior ASM treatment†	60 (41.7%)	29 (40.3%)	31 (43.1%)	0.735
Seizure duration before presentation (minutes)*	34 (30-40)	34 (27.5-40)	33.5 (30-45)	0.708
Etiology of GCSE†				
Febrile	62 (43.1%)	30 (41.7%)	32 (44.4%)	0.736
Known epilepsy	60 (41.7%)	29 (48.3%)	31 (51.7%)	0.735
CNS infection	16 (11.1%)	9 (12.5%)	7 (9.7%)	0.596
Unknown/others	6 (4.2%)	4 (5.6%)	2 (2.8%)	0.681
Body temperature (°C)‡	38.0 (0.82)	37.9 (0.90)	38.0 (0.73)	0.536
Systolic BP (mmHg)‡	99.2 (9.40)	99.1 (9.32)	99.4 (9.55)	0.846
STEPSS*	3 (2-4)	3 (2-4)	3 (2-4)	0.684
Hemoglobin (g/dL)‡	10.9 (1.66)	10.9 (1.58)	11.0 (1.76)	0.795
Leukocyte count ($\times 10^9$/L)*	11.6 (8.16-16.22)	11.6 (7.65-17.0)	11.3 (8.29-15.5)	0.783
Platelet count ($\times 10^9$/L)*	265 (210-352)	263 (207-354)	270 (213-350)	0.895
Blood sugar (mg/dL)*	114 (96-137)	116 (95-134)	110 (97-138)	0.878
Serum creatinine (mg/dL)*	0.38 (0.30-0.49)	0.38 (0.30-0.48)	0.37 (0.30-0.49)	0.459
Serum ALT (U/L)*	37 (33-40)	37 (34-41)	36 (32-40)	0.242
Serum bilirubin (mg/dL)*	0.3 (0.25-0.37)	0.3 (0.25-0.36)	0.3 (0.24-0.38)	0.784
Ionized calcium (mmol/L)‡	1.10 (0.15)	1.11 (0.15)	1.10 (0.14)	0.619
Serum sodium (mmol/L)†	137.1 (6.58)	137.2 (6.00)	137.1 (7.17)	0.957
Serum potassium (mmol/L)‡	3.92 (0.61)	3.93 (0.64)	3.91 (0.58)	0.809
Blood pH‡	7.36 (0.09)	7.37 (0.07)	7.35 (0.10)	0.109
pCO_2, mm Hg*	32 (28.0-35.8)	31 (26.3-35)	32 (28.6-37.0)	0.196
HCO_3^-, mmol/L‡	18.4 (4.42)	18.7 (4.56)	18.0 (4.28)	0.336

Abbreviations:
ALT = Alanine aminotransferase
ASMs = Antiseizure medications
BP = Blood pressure
CNS = Central nervous system
GCSE = Generalized convulsive status epilepticus
IQR = Interquartile range
Ket-Mid = Ketamine and midazolam
Pla-Mid = Placebo and midazolam
STEPSS = Status epilepticus in pediatric patients severity score
* Median (IQR).
† Number (%).
‡ Mean (S.D.).

ketamine properties in maintaining protective airway reflexes and spontaneous respiratory drive as well as inhibiting catecholamine reuptake, which may counteract the hypotensive effects of BDZs.[15,18,21] The potential efficacy of the ketamine-midazolam dual therapy in preventing endotracheal intubation is highly important for improving clinical outcomes since intubation by itself is a poor prognostic factor among critically ill children due to its association with increased risk of severe hypoxemia, hemodynamic collapse,

TABLE 2.
Outcomes Among Study Participants

Outcomes	Ket-Mid Group ($n = 72$)	Pla-Mid Group ($n = 72$)	Risk Ratio (95% CI)	*P* Value
Seizure cessation at 5 min	55 (76.4%)	15 (20.8%)	3.7 (2.3-5.9)	<0.001
Second midazolam dose	17 (23.6%)	57 (79.2%)	0.3 (0.19-0.46)	<0.001
Seizure cessation at 15 min	55 (76.4%)	17 (23.6%)	3.2 (2.1-5.0)	<0.001
Seizure cessation at 35 min	60 (83.3%)	33 (45.8%))	1.8 (1.4-2.4)	<0.001
Seizure cessation at 55 min	64 (88.9%)	52 (72.2%)	1.2 (1.04-1.45)	0.012
Seizure control at 24 hr	57 (79.2%)	48 (66.8%)	1.2 (0.97-1.45)	0.091
Hypotension	2 (2.8%)	7 (9.7%)	0.29 (0.06-1.33)	0.166
Intubation	3 (4.2%)	15 (20.8%)	0.2 (0.06-0.66)	0.002
Arrhythmia	1 (1.4%)	3 (4.2%)	0.3 (0.04-3.13)	0.620
Emergence phenomenon	2 (2.8%)	0	NA	0.497
Death	1 (1.4%)	3 (4.2%)	0.3 (0.04-3.13)	0.620

Abbreviations:
CI = Confidence interval
Ket-Mid = Ketamine and midazolam
NA = Not applicable
Pla-Mid = Placebo and midazolam
Data are presented as number (%).

TABLE 3.
Seizure Cessation at 5 Minutes After Study Medication by Duration of Seizure Before Presentation

Seizure Duration Before Presentation	Ket-Mid Group ($n = 72$)	Pla-Mid Group ($n = 72$)	Risk Ratio (95% CI)
≤30 min ($n = 61$)	26/30 (86.7%)	14/31 (45.2%)	1.9 (1.3-2.9)
>30 min ($n = 83$)	29/42 (69.1%)	1/41 (2.4%)	28.3 (4.0-198)

Abbreviations:
CI = Confidence interval
Ket-Mid = Ketamine and midazolam
Pla-Mid = Placebo and midazolam
Data are presented as number (%).
Mantel-Haenszel risk ratio (95% CI): crude = 3.7 (2.3, 5.9); combined = 3.7 (2.4, 5.9); $P < 0.001$.

TABLE 5.
Seizure Cessation at 5 Minutes After Study Medication in Different Seizure Etiologies

Etiology	Ket-Mid Group ($n = 72$)	Pla-Mid Group ($n = 72$)	Risk Ratio (95% CI)
Febrile seizure ($n = 62$)	18/30 (60.0%)	4/32 (12.5%)	4.8 (1.8-12.6)
Known epilepsy ($n = 60$)	29/29 (100%)	9/31 (29.0%)	3.4 (2.0-6.0)
CNS infection ($n = 16$)	4/9 (44.4%)	1/7 (14.3%)	3.1 (0.44-22)
Unknown/others ($n = 6$)	4/4 (100%)	1/2 (50.0%)	2 (0.50-8.0)

Abbreviations:
CI = Confidence interval
CNS = Central nervous system
Ket-Mid = Ketamine and midazolam
Pla-Mid = Placebo and midazolam
Data are presented as number (%).
Mantel-Haenszel risk ratio (95% CI): crude = 3.7 (2.3, 5.9); combined = 3.6 (2.3, 5.7); $P = 0.777$.

hospital-acquired infections, longer length of hospital stay, worse functional outcomes, and mortality.[18,48,50] Other adverse events, including arrhythmia and emergence reaction, were rarely observed and comparable between both study groups. This finding is consistent with previous studies on pediatric RSE and SRSE, which reported no or a few adverse effects attributed to ketamine.[19,36,48] Of note, BDZ coadministration has been described to mitigate several ketamine-related side effects, such as hypertension, psychomimetic effects, and intracranial hypertension, which provide another advantage of such combination.[22,32,36,51] Our study did not measure intracranial pressure, but prior studies on ketamine use for RSE and SRSE showed no clinically relevant effects on cerebral hemodynamics and intracranial pressure.[35,52]

In the present study, midazolam monotherapy could terminate seizures in only 23.6% of children in the comparison group. This outcome likely originates from the latency to midazolam administration due to the delayed hospital arrival by a median of 34 minutes following the onset of GCSE. Pharmacoresistance to BDZs builds up rapidly during SE secondary to multiple mechanisms, including synaptic receptors trafficking with downregulated $GABA_A$ receptors and upregulated NMDA receptors coupled with reduced inhibitory effects of $GABA_A$ receptor activation as well as associated neuroinflammation and neuronal damage.[14,18,38,39] Indeed, the potency of BDZs to halt seizures drastically drops within 10-15 minutes of SE onset[29,41,53,54] and longer time from SE onset to first BDZ administration is associated with higher risk of BDZ resistance, longer SE duration, and worse clinical outcomes.[6,10-12,33] The pronounced time-dependent increase in resistance to BDZs may also explain, at least in part, the higher effect size of ketamine-midazolam combination relative to midazolam alone in terminating seizures longer than 30 minutes in our study, which is likely due to reduced responsiveness to midazolam to a greater extent than to midazolam-ketamine combination. Accordingly, the anticonvulsive efficacy of add-on ketamine therapy may be quite low during very early seizures (e.g., first five to 10 minutes), when BDZs' responsiveness is high, but likely becomes more pronounced in prolonged seizures in parallel with progressive increase in BDZs' resistance and upregulation of NMDA receptors. However, animal data indicate that NMDA receptor antagonists could enhance BDZs' responsiveness to a greater extent when administered during the early than the late phase of SE.[29,45,54] Taken together, it is tempting to speculate that ketamine-midazolam as a first-line ASM combination has a specific time window of maximum anticonvulsive efficacy outside the very early and late seizure phases, but this hypothesis requires validation in future research.

Our finding of a marked delay to first-line BDZ administration has also been reported in several studies, showing median times from SE to first-line ASM administration and hospital arrival of 42 and 56 minutes, respectively.[11] This finding is highly concerning since this time exceeds the 30-minute timepoint for GCSE, which is associated with a higher risk for irreversible neuronal damage, and correlates with pronounced pharmacoresistance to BDZs.[6,7,14,38] In this critical situation of prolonged naive GCSE, several commentators underscore that current stepwise protocols with first-line BDZ monotherapy are suboptimal and argue for starting with synergistic ASM polytherapy for prolonged GCSE (stage 1 plus; longer than 10 minutes) that targets multiple rapidly evolving pathophysiologic mechanisms responsible for self-sustained SE, pharmacoresistance, and neuronal damage.[14,15,18,19] Therefore, using ketamine in conjunction with BDZs as first-line ASMs could be more useful in rapidly terminating seizures through early correction of excitatory/inhibitory imbalance and restoration of BDZs' responsiveness rather than its late use for RSE and SRSE when extensive neuronal damage has already occurred.[15,16,20]

The present study found no significant interaction of SE etiology and participant's age with add-on ketamine effect on primary outcome. However, our study may be subpowered for definitive subgroup analysis. Prior studies indicate that acute primary CNS etiology (e.g., cerebrovascular diseases, CNS infection, TBI) is associated with worse clinical outcome and poor response to BZDs.[55,56] The late presentation of participants with GCSE (stage 1 plus; probably BDZ resistant) and the exclusion of those with TBI and CNS mass lesions may also contribute to the lack of statistically significant difference among different SE etiologies in the current study. Observational studies indicate higher ketamine effectiveness in RSE and SRSE secondary to epilepsy than other causes.[36,52,57-59] The potential for higher add-on ketamine efficacy in epileptic patients may stem from molecular changes during epilepsy development with reduced expression of BDZ-sensitive $\alpha1\gamma2$ subunits-containing GABA receptors coupled with upregulated NMDA receptor-mediated neurotransmission.[12,60,61] On the other side, our study did not include newborns whose seizures may be more

TABLE 4.
Seizure Cessation at 5 Minutes After Study Drug Administration in Different Age Categories

Age Categories	Ket-Mid Group ($n = 72$)	Pla-Mid Group ($n = 72$)	Risk Ratio (95% CI)
6-12 mo ($n = 46$)	15/24 (62.5%)	3/22 (13.6%)	4.6 (1.5-13.7)
>12-60 mo ($n = 53$)	18/24 (75.0%)	8/29 (27.6%)	2.7 (1.4-5.1)
>60 mo ($n = 45$)	22/24 (91.7%)	4/21 (19.1%)	4.8 (2.0-11.7)

Abbreviations:
CI = Confidence interval
Ket-Mid = Ketamine and midazolam
Pla-Mid = Placebo and midazolam
Data are presented as number (%).
Mantel-Haenszel risk ratio (95% CI): crude = 3.7 (2.3, 5.9); combined = 3.7 (2.3, 6.0); $P = 0.495$.

responsive to ketamine due to higher expression of N2B subunit-containing NMDA receptors.[62,63] Indeed, some studies showed seizure cessation after ketamine imitation in neonatal refractory SE, but concerns remain regarding possible ketamine-related neurotoxicity in this age group.[62,63] Taken together, adequately powered and more inclusive studies are recommended to better elucidate the efficacy of add-on ketamine across different SE etiologies and age groups.

We chose cessation of seizures at 5 minutes following drug administration as the primary outcome due to its pragmatic clinical importance since guidelines recommend provision of a second BDZ dose for seizures lasting longer than 5 minutes after the first dose.[2,4,6] Furthermore, ketamine is a fast-acting drug owing to its high lipid solubility and low plasma protein binding capacity; following its intravenous bolus, it rapidly crosses the blood-brain barrier with an onset of action in less than one minute and typical duration of 5 to 10 minutes.[18,19,22,47] Therefore, the five-minute duration seems suitable to evaluate its anticonvulsant efficacy following a single intravenous bolus. On the other hand, the short duration of action may explain the reduced extra-efficacy of ketamine when evaluated at later timepoints, up to having no statistically significant add-on value for 24-hour seizure control. It is possible that higher or repeated ketamine doses may be more beneficial, but this postulation requires further studies. The intravenous ketamine dose in our study (2 mg/kg) is derived from the dose range typically used in pediatric procedural sedation (1- 4 mg/kg),[21,32,64] prior observational studies on pediatric SRSE (bolus 1-3 mg/kg),[18,19,30,36] and animal-to-human dose conversions (1-3 mg/kg)[15]. Besides the intravenous route, intramuscular and intranasal routes are clinically important for use in prehospital settings.[37]

The major strengths of the current study are the randomized, double-blind, controlled design; strict eligibility criteria; and no dropouts. Nevertheless, some limitations must be acknowledged. First, we evaluated seizure cessation clinically without confirmatory electroencephalography (EEG), which raises the possibility that some participants clinically classified as responders might have electrographic-only seizures.[3] However, our management protocol mimics the medical practice in emergency settings where EEG is not commonly available.[65] Furthermore, cessation of convulsions was also assessed clinically in multiple famous pediatric studies on SE.[8,9,66] Importantly, possible electrographic-only seizures would likely be distributed nonpreferentially between the study and comparison group; such possible nondifferential misclassification of primary outcome will not affect the study conclusion as it would drive the effect size toward rather than away from the null value. Nevertheless, the use of EEG in future studies is recommended for investigating the electrographic response to ketamine and correlation between clinical and electrographic seizure cessation. This approach is particularly important since prior studies on SRSE described that ketamine response is associated with the appearance of a characteristic background of superimposed beta rhythm in EEG rather than the classic burst suppression pattern following traditional anesthetic ASMs.[31,35,36,67]

Other limitations are related to the lack of advanced investigations and the restricted 24-hour study time frame, which did not allow for the investigation of possible neuroprotective or neurotoxic effects of ketamine. In particular, data from animal studies support that ketamine administered post-SE could confer short- and long-term neuroprotective effects regardless of its ability to abort seizures.[20,24,27-29] Therefore, future studies should include serial assessment of neuroinjury biomarkers in CSF and plasma, neuroimaging scans, electrophysiological studies, and neuropsychologic tests to evaluate ketamine's role in mitigating SE-induced neuronal injury, future epilepsy, and long-lasting neurocognitive deficits.[20] On the other hand, ketamine-related neurotoxic effects have been reported in young rats but never in humans.[18,19] This neurotoxicity was described in animals that are neurodevelopmentally equivalent to human second-trimester fetus or extremely preterm newborn after ketamine use of human equivalent doses of 20- 40 mg/kg; such high doses and very young age fall outside the typical use of ketamine.[19,46] Accordingly, these adverse effects seem a remote possibility with the use of one or two small ketamine doses beyond the neonatal periods.[18,19]

Moreover, the present study was conducted in Egypt, a low-middle-income country, and included children with GCSE who presented late without prior ASM treatment. Therefore, the findings may not be generalizable to high-resource settings like the United States and Europe, where emergency medical services routinely provide BDZs to patients with seizures during transport to the hospital. However, this study provides equipoise for similar studies to be replicated in similar resource-limited areas. Furthermore, an emergency medical service study in the United States reported that ketamine could terminate seizures in all 47 adults and 13 of 16 children with BDZ-refractory SE during the prehospital and emergency ward phases.[37] Therefore, future RCTs may also investigate the efficacy of ketamine-midazolam combination for prehospital management of patients with SE.

Finally, it was not feasible to include children with TBI and other surgical causes, such as CNS mass lesions, since these patients are usually referred to the surgical emergency room in our hospital, which is separate from the pediatric emergency room where this study was performed, and potential emergency neurosurgical interventions for these cases could interfere with the study treatment protocol and outcome assessment. Further replication studies are warranted among this specific category of children with SE secondary to surgical causes.

Conclusion

Add-on ketamine may present extra-efficacy over midazolam alone as first-line ASMs for children with GCSE, particularly for GCSE longer than 30 minutes. Future research is warranted to confirm our findings and to investigate different ketamine doses, formulations, and routes of administration as well as electrographic validation of seizure control, long-term efficacy and safety outcomes, larger sample size, and more inclusive study population.

Declaration of generative AI and AI-assisted technologies in the writing process

The authors declare that they have not used any generative AI or AI-assisted technologies in the writing of this manuscript.

CRediT authorship contribution statement

Amr A. Othman: Writing – review & editing, Resources, Investigation, Data curation. **Abdelrahim A. Sadek:** Writing – review & editing, Supervision, Resources, Methodology, Conceptualization. **Esraa A. Ahmed:** Writing – review & editing, Validation, Methodology, Investigation. **Elsayed Abdelkreem:** Writing – original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary data

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