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Original Article

Efficacy and safety of levetiracetam intravenous infusion combined with midazolam continuous pump infusion for stepwise emergency treatment of convulsive status epilepticus in children: a retrospective cohort study

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Abstract: Objectives: To evaluate the efficacy and safety of intravenous levetiracetam (LEV) combined with continuous midazolam (MDZ) infusion versus MDZ monotherapy as second-line treatment for pediatric convulsive status epilepticus (CSE). Methods: This retrospective cohort study included 159 pediatric patients with generalized convulsive status epilepticus (GCSE) treated between June 2017 and December 2025. Patients received either LEV+MDZ (n=86) or MDZ alone (n=73). Outcomes included seizure cessation at 20 and 40 minutes, 24-hour seizure control, requirement for third-line antiseizure medication, adverse events, change in Status Epilepticus Severity Score (STESS), lengths of pediatric intensive care unit (PICU), and Pediatric Cerebral Performance Category (PCPC) score at discharge. Results: Compared to MDZ monotherapy, the combination group showed significantly greater reduction in STESS at 24 hours (1.94 ± 0.46 vs. 2.67 ± 0.53, P < 0.001) and a lower requirement for third-line medication (11.63% vs. 24.66%, P=0.032). Midazolam cumulative dose at 1 hour was lower with combination therapy (0.28 ± 0.10 vs. 0.32 ± 0.11 mg/kg, P=0.013). Incidence of adverse events was similar between groups (16.28% vs. 21.92%, P=0.365). Furthermore, the combination group had shorter PICU stay (2.73 ± 1.28 vs. 3.42 ± 1.56 days, P=0.003), shorter total hospitalization (6.52 ± 2.01 vs. 7.85 ± 2.27 days, P < 0.001), and better PCPC scores at discharge (1.89 ± 0.71 vs. 2.32 ± 0.82, P < 0.001). Conclusions: Early administration of LEV combined with MDZ was associated with reduced seizure severity, decreased need for rescue therapy, lower benzodiazepine exposure, shorter hospitalization, and improved short-term neurological outcome without increasing adverse events in pediatric patients with CSE.

Keywords: Pediatric convulsive status epilepticus, levetiracetam, midazolam, combination therapy, retrospective cohort study, efficacy, safety

Introduction

Convulsive status epilepticus (CSE) represents one of the most critical neurological emergencies in the pediatric population, characterized by prolonged, continuous seizure activity or recurrent seizures without full recovery of consciousness [1, 2]. It is associated with significant risks of neuronal injury, systemic complications, and long-term neurodevelopmental impairment. Management of CSE follows a time-sensitive, stepwise protocol aimed at rapid seizure termination to prevent irreversible cerebral damage and reduce mortality [3, 4]. First-line therapy universally involves the administration of benzodiazepines; However, a substantial proportion of children exhibit benzodiazepine resistance, necessitating prompt escalation to second-line anticonvulsants [5, 6].

The optimal choice of second-line therapy remains a subject of ongoing clinical debate and research [7]. Traditional options include continuous infusion of midazolam, a potent GABA-A receptor agonist with rapid onset and titratable sedative-anticonvulsant effects [8-10]. While

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effective, midazolam monotherapy is often limited by dose-related adverse effects, particularly respiratory depression and hypotension, and may fail to control seizures in refractory cases [5]. This has driven the exploration of combination strategies targeting different seizure pathways simultaneously, potentially enhancing efficacy while allowing for lower doses of individual agents and mitigating toxicity.

Levetiracetam has emerged as a promising adjunct in this context due to its unique mechanism of action, which involves synaptic vesicle protein 2A (SV2A) modulation, contributing to stabilization of neuronal excitability [11, 12]. Its favorable pharmacokinetic profile, including rapid attainment of therapeutic levels via intravenous loading and minimal drug-drug interactions or cardiorespiratory depression, makes it theoretically suitable for combination with midazolam in the acute setting [11, 12]. The concurrent use of these two agents - leveraging complementary mechanisms may offer synergistic seizure control, reduce the cumulative midazolam dose and infusion duration, and improve overall safety.

Despite this compelling rationale, robust clinical evidence evaluating the efficacy and safety of early co-administration of levetiracetam and midazolam, specifically within the structured framework of pediatric CSE stepwise emergency protocols, remains limited. Previous studies have typically examined monotherapies or sequential drug administration rather than early concurrent dual-drug strategies [2, 13]. Therefore, there is a clear need to investigate whether this combined offers tangible advantages over midazolam monotherapy in clinical practice. This study compares outcomes between these two treatment strategies in a cohort of pediatric patients with generalized convulsive status epilepticus (GCSE).

Materials and methods

Participants

This retrospective cohort study included 159 pediatric patients diagnosed with GCSE and treated emergently at The Second People's Hospital of Liaocheng between June 2017 and December 2025, aged 1 month to 16 years. Patients were divided into two groups based on second-line anticonvulsant therapy they received as part of the stepwise emergency protocol: the combination therapy group (n=86; continuous midazolam (MDZ) infusion concurrently or immediately followed by intravenous levetiracetam (LEV)) and the monotherapy group (n=73; MDZ monotherapy). Demographic and clinical data were retrieved from the hospital case system.

Inclusion criteria: (1) Age between 1 month and 16 years; (2) Clinical diagnosis of GCSE according to established criteria [14]; (3) Receipt of either combined therapy or MDZ monotherapy as part of first- or second-line treatment within the CSE protocol; (4) Availability of complete medical records documenting seizure events, treatment details (drugs, doses, timing), vital signs, laboratory results, and follow-up data for at least 24 hours post-treatment initiation; (5) No prior administration of other second-line antiseizure medications before the initiation of the study regimens; (6) For the combination group, intravenous LEV was administered concomitantly with or immediately following MDZ loading, as per protocol.

Exclusion criteria: (1) Non-convulsive status epilepticus or subtle motor SE without clear generalized tonic-clonic manifestations; (2) Known severe traumatic brain injury, hypoxic-ischemic encephalopathy, or major intracranial hemorrhage as the immediate cause of seizures; (3) Presence of end-stage renal disease, severe hepatic dysfunction, or significant cardiac disease; (4) Critical metabolic disturbances including severe hypoglycemia (< 40 mg/dL) or hyperglycemia requiring immediate correction, or known inborn errors of metabolism; (5) Known allergy or contraindication to levetiracetam, midazolam, or other benzodiazepines; (6) Patients receiving pre-hospital treatment with intravenous or intramuscular benzodiazepines whose seizures ceased spontaneously before hospital arrival and before the initiation of study protocols; (7) Patients with a history of behavioral disorders or psychiatric conditions.

Treatment methods

Initial stabilization and first-line therapy: All enrolled patients were managed according to a standardized, institutional stepwise emergency protocol for pediatric CSE, prioritizing immediate stabilization of airway, breathing, and circulation. Initial management included supplemental oxygen, establishment of secure intravenous access, bedside glucose assessment, and collection of blood samples for baseline laboratory studies. In alignment with international guidelines, the first-line pharmacological intervention for all cases was benzodiazepine. At our institution, this consisted of either intravenous lorazepam at a dose of 0.1 mg/kg (maximum 4 mg; Huazhong Pharmaceutical Co., Ltd.; Approval No. H20052310) or intravenous/intramuscular midazolam at a dose of 0.2 mg/kg (maximum 10 mg; Yichang Renfu Pharmaceutical Co., Ltd.; Approval No. H2006-7041). Patients whose convulsive activity persisted for more than 5 to 10 minutes following the initial benzodiazepine dose were escalated to second-line therapy, forming the basis for group assignment in this study.

Combined therapy: For patients assigned to the Combined Therapy Group, second-line intervention consisted of a dual-drug strategy. An intravenous loading dose of LEV (60 mg/kg, with a maximum dose of 4500 mg; Beijing Sihuan Pharmaceutical Co., Ltd.; Approval No. H20203692) was administered over 5 to 10 minutes. This infusion was administered concurrently with or immediately following the initiation of the MDZ continuous infusion. The MDZ regimen began with an intravenous loading dose of 0.15 to 0.2 mg/kg. Immediately thereafter, a continuous intravenous infusion was started at an initial rate of 1 μg/kg/min (equivalent to 0.06 mg/kg/h). The infusion rate was then titrated upwards in increments of 1 μg/kg/min every 5 to 10 minutes, guided by the clinical response (seizure cessation) and the patient's level of sedation. The titration continued until either seizure control was achieved or a maximum infusion rate of 10-12 μg/kg/min (0.6-0.72 mg/kg/h) was reached. The LEV solution for infusion was prepared by diluting the commercial preparation (100 mg/mL) in normal saline to a standard concentration of 50 mg/mL.

Monotherapy: In contrast, patients in the Monotherapy group received MDZ alone as the second-line agent. The MDZ dosing and titration protocol for this group was identical to that used in the combined group: an intravenous loading dose of 0.15-0.2 mg/kg, followed by a continuous infusion starting at 1 μg/kg/min. The rate was similarly titrated upwards every 5-10 minutes to a maximum of 10-12 μg/kg/min until clinical seizure cessation.

Rescue therapy and supportive care: For patients in either group whose seizures persisted despite receiving the maximum designated midazolam infusion rate for 20-30 minutes, third-line therapy was promptly initiated. This typically involved intravenous administration of phenytoin/fosphenytoin (20 mg phenytoin equivalents/kg) or valproic acid (20-40 mg/kg). Decisions regarding endotracheal intubation and mechanical ventilation were made by the treating intensivist based on standard clinical criteria, including loss of protective airway reflexes, significant respiratory depression, or persistent obtundation. Throughout the management course, all patients received comprehensive supportive care, encompassing fever management, hemodynamic support as needed, correction of electrolyte imbalances, and targeted treatment of the underlying etiology of the status epilepticus when it was identified.

Data collection

Data for this retrospective analysis were systematically extracted from the hospital's electronic medical record system using a standardized case report form. Collected variables encompassed patient demographics, clinical characteristics, treatment details, efficacy outcomes, safety events, and hospital course. Primary outcome was the proportion of patients achieving clinical seizure cessation within 20 minutes after initiation of second-line therapy. Secondary outcomes included seizure cessation at 40 minutes, maintenance of seizure control at 24 hours, seizure recurrence within 72 hours, and the requirement for third-line antiseizure medication. Safety outcomes comprised the incidence of treatment-related adverse events, including respiratory depression, hypotension, bradycardia, excessive sedation, and hyponatremia. Additional secondary outcomes were the Status Epilepticus Severity Score (STESS) at presentation and at 24 hours, length of Pediatric Intensive Care Unit (PICU), total hospital stay, and Pediatric Cerebral Performance Category (PCPC) score at discharge.

Evaluation methods

Efficacy was assessed based on documented seizure cessation, defined as the absence of clinically observable convulsive activity, as recorded by bedside nursing and physician notes. Requirement for rescue therapy with phenytoin/fosphenytoin or valproic acid was considered indicative of treatment failure [15]. Status

Epilepticus Severity Score (STESS) was calculated at presentation and 24 hours after treatment initiation to evaluate severity dynamics. STESS incorporates consciousness level, seizure type, age, and prior seizure history, with higher scores reflecting greater severity [16].

Safety and tolerability were evaluated by reviewing nursing flow sheets, physician progress notes, and laboratory reports for adverse events. Respiratory depression was defined as a need for increased oxygen supplementation or mechanical ventilation due to hypoventilation. Hypotension was defined as systolic blood pressure below the 5th percentile for age, bradycardia as heart rate below the age-adjusted normal range, excessive sedation as a Richmond Agitation-Sedation Scale score of -4 or -5 not explained by ongoing seizure activity, and hyponatremia as serum sodium < 135 mmol/L [15].

Hospital course and neurological outcome were assessed using the PCPC score at discharge, which categorizes overall functional status from 1 (normal) to 6 (brain death) [17]. Length of stay in the PICU and total hospital stay were recorded in days.

Ethical statement

This study used anonymized, existing clinical data from medical records without any prospective patient interventions. The research posed minimal risk to participants and had no direct effect on patients care. Accordingly, the Ethics Committee of the Second People's Hospital of Liaocheng approved the study to proceed without obtaining individual informed consent. All procedures were performed in accordance with the ethical standards of the Second People's Hospital of Liaocheng and the 1964 Helsinki Declaration.

Statistical analysis

All statistical analyses were performed using SPSS (version 22.0) and R (version 4.3.1). Continuous variables with normal distribution were expressed as mean ± standard deviation (SD) and compared using independent or paired samples t-tests, as appropriate. Continuous variables with non-normal distributed were presented as median (interquartile range) and analyzed using the Mann-Whitney U test. Categorical variables were presented as frequencies (%) and compared using Pearson's χ^2 test or Fisher's exact test. Predictors for seizure cessation were identified using univariate and multivariate logistic regression, with results expressed as odds ratios (OR) and 95% confidence intervals (CI). A two-sided *p*-value < 0.05 was called significant.

Results

Baseline demographic and clinical characteristics

Baseline demographic, clinical, and laboratory characteristics of the two treatment groups were well-balanced, with no significant differences observed in age, BMI, sex, developmental delay, prior antiseizure medication use, seizure duration before admission, etiology of GCSE, or any of the measured physiological or laboratory values (all $P > 0.05$) (**Tables 1**, **2**), indicating baseline comparability between the two groups.

Treatment response and seizure control outcomes

Both groups demonstrated significant reductions in the STESS after treatment (both $P < 0.001$). However, the combination group demonstrated a greater reduction in STESS at 24 hours post-treatment compared to the monotherapy group (1.94 ± 0.46 vs. 2.67 ± 0.53, $P < 0.001$) (**Table 3**), suggesting that combined therapy was associated with a more pronounced improvement in seizure severity.

While rates of seizure cessation at 20 minutes, 40 minutes, as well as maintenance of seizure control at 24 hours, were numerically higher in the combination group, these differences did not reach significance (all $P > 0.05$). However, significantly fewer patients in the combination group required third-line antiseizure medication (11.63% vs. 24.66%, $P=0.032$). Rates of seizure recurrence within 72 hours and need for intubation were lower in the combination group but did not achieve statistical significance (**Table 4**). These results indicate that the combination regimen may reduce the need for escalation to rescue therapy.

Treatment details and medication dosing

The initial midazolam loading dose was similar between groups ($P=0.190$). However, the total midazolam dose administered within the first hour was significantly lower in the combination

Table 1. Comparison of baseline demographic and clinical characteristics between the two treatment groups

Data	Monotherapy Group (n=73)	Combined Therapy Group (n=86)	t/χ^2	*P* value
Age (years)	6.42 ± 2.87	6.25 ± 2.92	0.361	0.718
BMI (kg/m^2)	16.32 ± 2.84	16.18 ± 2.67	0.326	0.745
Sex, n (%)			0.048	0.827
Male	42 (57.53%)	48 (55.81%)		
Female	31 (42.47%)	38 (44.19%)		
Developmental delay, n (%)	9 (12.33%)	11 (12.79%)	0.008	0.930
Prior ASM therapy, n (%)	21 (28.77%)	26 (30.23%)	0.041	0.840
Seizure duration before admission (min)	28.64 ± 12.27	27.85 ± 11.84	0.411	0.682
Etiology of GCSE, n (%)			0.097	0.953
Febrile seizure	38 (52.05%)	46 (53.49%)		
CNS infection	22 (30.14%)	24 (27.91%)		
Known epilepsy	13 (17.81%)	16 (18.60%)		

Notes: BMI, body mass index; ASM, antiepileptic drug; GCSE, generalized convulsive status epilepticus.

Table 2. Comparison of baseline laboratory and physiological parameters between the two treatment groups

Data	Monotherapy Group (n=73)	Combined therapy Group (n=86)	t/χ^2	*P* value
Body temperature (°C)	38.42 ± 0.76	38.51 ± 0.81	0.748	0.456
Systolic BP (mmHg)	104.63 ± 11.28	103.97 ± 10.84	0.371	0.711
Hemoglobin (g/dL)	11.72 ± 1.33	11.86 ± 1.28	0.671	0.503
Leukocyte count (×10^9/L)	12.83 ± 3.76	13.14 ± 3.92	0.497	0.620
Platelets count (×10^9/L)	279.34 ± 68.20	284.56 ± 71.33	0.469	0.640
Serum creatinine (mg/dL)	0.38 ± 0.12	0.40 ± 0.11	1.423	0.157
Sodium (mmol/L)	138.92 ± 5.63	139.24 ± 5.17	0.376	0.708
Blood pH	7.36 ± 0.05	7.35 ± 0.06	1.361	0.175

Notes: BP, Blood Pressure.

Table 3. Comparison of changes in status epilepticus severity score (STESS) between the two groups before and after treatment

STESS Score	Monotherapy Group (n=73)	Combined therapy Group (n=86)	t	*P* value
Pre-treatment	4.31 ± 0.82	4.28 ± 0.79	0.242	0.809
Post-treatment	2.67 ± 0.53	1.94 ± 0.46	9.151	< 0.001
t	14.351	23.738		
P value	< 0.001	< 0.001		

Notes: STESS, Status epilepticus severity score.

group (0.28 ± 0.10 mg/kg vs. 0.32 ± 0.11 mg/kg, *P*=0.013). Furthermore, fewer patients in the combination group required a second midazolam dose (27.91% vs. 43.84%, *P*=0.036) (**Table 5**).

Treatment-related adverse events

The overall incidence of treatment-related adverse events was comparable between the two groups (21.92% vs. 16.28%, χ^2=0.820, *P*=0.365). Specific adverse events, including respiratory depression (9.59% vs. 6.98%), hypotension (5.48% vs. 3.49%), bradycardia (0.0% vs. 1.16%), excessive sedation (4.11% vs. 3.49%), and hyponatremia (2.74% vs. 1.16%), occurred at similar frequencies in both groups (**Figure 1**). These findings suggest that the addition of intravenous levetiracetam did not signifi-

Table 4. Comparison of seizure control outcomes between the two groups [n (%)]

Data	Monotherapy Group (n=73)	Combined therapy Group (n=86)	χ^2	*P* value
Seizure cessation at 20 min	48 (65.75%)	68 (79.07%)	3.549	0.060
Seizure cessation at 40 min	65 (89.04%)	82 (95.35%)	2.251	0.133
Seizure control maintained at 24 h	56 (76.71%)	75 (87.21%)	2.999	0.083
Requirement for 3rd-line ASM	18 (24.66%)	10 (11.63%)	4.620	0.032
Seizure recurrence within 72 h	14 (19.18%)	8 (9.30%)	3.230	0.072
Intubation required	9 (12.33%)	5 (5.81%)	2.087	0.149

Notes: ASMs, antiepileptic drugs.

Table 5. Comparison of midazolam and levetiracetam dosing between the two groups

Data	Monotherapy Group (n=73)	Combined Therapy Group (n=86)	t/χ^2	*P* value
Midazolam loading dose (mg/kg)	0.18 ± 0.05	0.17 ± 0.05	1.315	0.190
Midazolam total dose at 1 h (mg/kg)	0.32 ± 0.11	0.28 ± 0.10	2.511	0.013
Patients requiring 2nd midazolam dose, n (%)	32 (43.84%)	24 (27.91%)	4.391	0.036

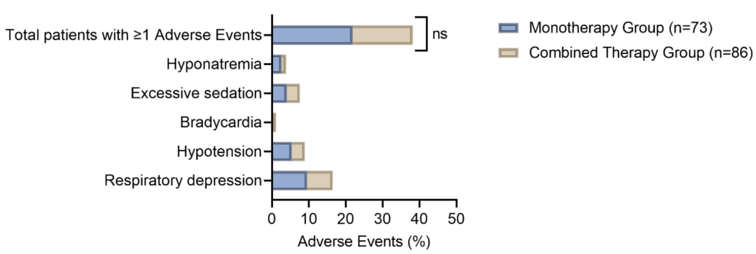

Figure 1. Treatment-related adverse events during hospitalization.

cantly increase the short-term adverse event burden.

Clinical outcome and hospitalization parameters

Patients in the combination group had a significantly shorter PICU stay (2.73 ± 1.28 days vs. 3.42 ± 1.56 days, *P*=0.003) (**Figure 2A**) and a shorter total hospital stay (6.52 ± 2.01 days vs. 7.85 ± 2.27 days, *P* < 0.001) (**Figure 2B**). Additionally, combined therapy was associated with better neurologic outcomes at discharge, as reflected by a lower PCPC score (1.89 ± 0.71 vs. 2.32 ± 0.82, *P* < 0.001) (**Figure 2C**).

Univariate and multivariate analysis for predictors of seizure control at 20 minutes

Multivariate logistic regression identified the combined therapy regimen as an independent predictor of achieving seizure cessation within 20 minutes (OR 2.267, 95% CI 1.384-3.715, *P*=0.001). Other significant predictors included shorter seizure duration before admission (OR 0.975, 95% CI 0.956-0.995, *P*=0.013) and a lower baseline STESS score (OR 0.698, 95% CI 0.571-0.853, *P* < 0.001), whereas age, prior ASM therapy, developmental delay, and etiology were not significant predictors (**Table 6**).

Discussion

This retrospective cohort study evaluated the efficacy and safety of a combined regimen of intravenous levetiracetam and continuous midazolam infusion compared to midazolam monotherapy as second-line treatment within a stepwise emergency protocol for pediatric CSE. Although previous studies [18, 19] had explored combinations of levetiracetam and benzodiazepines, most had focused on sequential administration or monotherapy comparisons, with limited data on early concurrent dual-drug therapy initiated within a structured stepwise protocol. Our study provides real-world verification of this strategy using a pragmatic dosing regimen and demonstrates associated benefits including reduced need for treatment escalation and lower midazolam exposure. The findings suggest potential advantages of the early dual-mechanism approach without increasing short-term adverse events, although further dose-optimization studies are still needed.

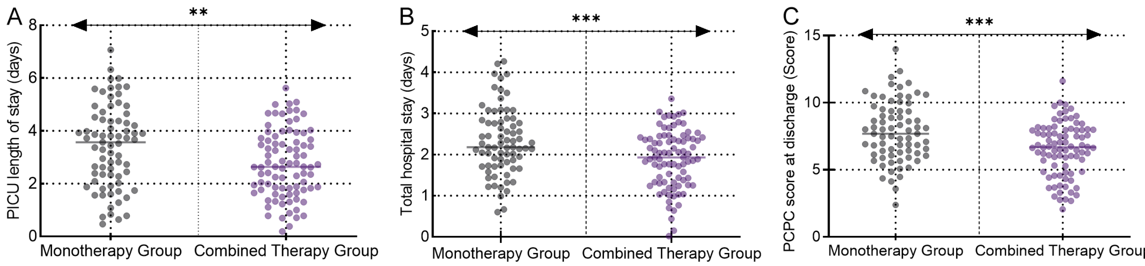

Figure 2. Comparison of clinical outcome, and neurological function at discharge between the two groups. A. PICU length of stay (days); B. Total hospital stay (days); C. PCPC score at discharge (Score). Note: PICU, pediatric intensive care unit; PCPC, Pediatric Cerebral Performance Category. ***P* < 0.01; ****P* < 0.001.

Table 6. Univariate and multivariate logistic regression analysis of factors associated with seizure cessation within 20 minutes

Variable	Univariate logistic analysis			Multivariate logistic analysis		
	OR	95% CI	P	OR	95% CI	P
Treatment group (Combined vs. Monotherapy)	2.114	1.312-3.403	0.002	2.267	1.384-3.715	0.001
Age (years)	0.957	0.892-1.026	0.214	0.961	0.894-1.033	0.278
Seizure duration before admission (min)	0.972	0.953-0.991	0.004	0.975	0.956-0.995	0.013
Prior ASM therapy (Yes vs. No)	0.743	0.482-1.145	0.178	0.762	0.491-1.182	0.226
Developmental delay (Yes vs. No)	0.681	0.432-1.074	0.099	0.694	0.437-1.103	0.121
Etiology: Febrile seizure (Ref: Known epilepsy)	1.423	0.912-2.221	0.119	1.401	0.893-2.198	0.142
STESS score at presentation	0.712	0.588-0.862	< 0.001	0.698	0.571-0.853	< 0.001

Notes: OR, odds ratio; CI, Confidence Interval; ASM, Antiepileptic drugs; STESS, status epilepticus severity score.

Regarding treatment response, the addition of levetiracetam was associated with a more pronounced reduction in seizure severity, as assessed by the STESS at 24 hours. While early seizure cessation rates were numerically higher in the combination group, the difference did not reach statistical significance in the primary comparison. However, multivariate analysis identified combined therapy as an independent predictor of achieving seizure cessation within the first 20 minutes, after adjusting for other clinical factors. More notably, fewer patients in the combination group required escalation to third-line antiseizure medications. This aligns with the rationale that targeting multiple seizure pathways simultaneously may enhance overall seizure control and prevent progression to refractory status [20-22]. Rosati et al. [5] emphasized the importance of early effective intervention in pediatric status epilepticus to avoid treatment escalation, and our findings suggest the combined strategy may contribute to this goal.

The observed reduction in the requirement for rescue therapy may be mechanistically explained. Midazolam primarily exerts its effect by potentiating GABAergic inhibition [23], while levetiracetam modulates synaptic vesicle protein SV2A, which stabilizes neuronal excitability and regulates neurotransmitter release [24, 25]. These complementary mechanisms may produce synergistic or additive anticonvulsant effects, possibly allowing for more effective seizure termination before extreme pharmacologic measures are needed [26, 27]. This concept of leveraging different mechanisms is supported by preclinical models of refractory status epilepticus [27, 28].

Consistent with the potential for synergistic efficacy, dosing analysis revealed that patients receiving combination therapy had lower overall midazolam exposure within the first hour and were less frequently administered a second dose. This finding is clinically meaningful, as a primary concern with midazolam infusion is the dose-dependent risk of respiratory depression and hypotension [29]. By achieving comparable or improved seizure control with a lower benzodiazepine load, the combined regimen may offer a favorable safety profile [30].

This observation resonates with the pharmacokinetic advantages of levetiracetam, notably its minimal cardiorespiratory depression, making it a suitable adjunct to sedative anticonvulsants [31].

In terms of safety, the overall incidence of treatment-related adverse events, including respiratory depression, hypotension, and excessive sedation, was similar between the two groups. This indicates that the addition of intravenous levetiracetam did not introduce new or excessive short-term toxicity in the acute setting. The safety profile of levetiracetam has been noted in other comparative studies, such as the meta-analysis by Jin et al. [11], which reported a favorable side effect profile compared to traditional agents like phenytoin.

The potential benefits of the combination strategy extended beyond immediate seizure control to several clinically relevant outcomes. Patients in the combination group experienced a shorter duration of stay in the PICU and a reduced total hospital length of stay. Furthermore, neurological outcome at discharge, assessed by the PCPC score, was more favorable in the combination group. These findings suggest that more effective early seizure management, potentially leading to less cumulative neuronal injury and reduced exposure to high-dose sedatives, may facilitate faster clinical recovery and improved functional outcomes [32, 33]. While few studies have directly evaluated these downstream outcomes for specific drug combinations in pediatric status epilepticus, efficient seizure termination is consistently linked to improved long-term prognosis [34, 35].

The results of this study hold several practical implications for managing pediatric convulsive status epilepticus. Early administration of levetiracetam combined with midazolam presents a viable second-line strategy that may increase the likelihood of seizure control without the need for escalation to rescue therapy. This approach aligns with the principle of timely, aggressive management to prevent progression to refractory status. The associated reduction in midazolam exposure could translate into a lower risk of iatrogenic complications, particularly in a vulnerable pediatric population. Moreover, the potential for shorter PICU and hospital stays carries significant benefits for healthcare resource utilization and patient recovery. This strategy may be particularly valuable in settings with limited access to advanced rescue therapies or continuous neuromonitoring.

This study had several limitations inherent to its retrospective design. The non-randomized allocation of treatments introduced the potential for selection bias and unmeasured confounding factors, despite balanced baseline characteristics. The sample size, while adequate for detecting several differences, may have been underpowered for some secondary outcomes, such as seizure recurrence rates, and precluded meaningful subgroup analyses by specific age categories (e.g., infants vs. school-age children). The single-center setting limits the generalizability of the findings to other institutions with different treatment protocols or patient populations. Data on long-term neurodevelopmental outcomes beyond hospital discharge were not available, which represents a critical endpoint in pediatric status epilepticus research. Furthermore, heterogeneity in the timing and sequencing of drug administration within the combination group may have influenced outcomes, and the optimal administration time window or dose ratio of levetiracetam to midazolam was not explored. Additionally, the study period spanned 8.5 years (June 2017 to December 2025). Although the institutional stepwise emergency protocol for pediatric CSE, including the specific dosing regimens for midazolam and levetiracetam, remained unchanged throughout this period, and all laboratory assessments were performed using consistent methods in the same central laboratory, the potential for time-related bias due to subtle changes in clinical practice, drug production batches, or supportive care cannot be completely excluded. This temporal bias represented an additional limitation of the retrospective design.

Future research should aim to validate these findings in larger, prospective, and preferably multicenter randomized controlled trials. Such studies would allow for standardized protocols, clearer delineation of the optimal timing and dosing of the combination, and rigorous assessment of long-term outcomes, including neurocognitive function, post-discharge seizure recurrence, and long-term antiseizure medication requirements. These long-term endpoints are essential to confirm whether early combination therapy improves the overall prognosis of pediatric convulsive status epilepticus beyond the acute hospitalization period. Age-stratified analyses (e.g., infants, school-age children, adolescents) and dose-optimization studies to determine the ideal administration time window and dose ratio of levetiracetam to midazolam are also needed. Investigations into biomarkers predictive of response to either monotherapy or combination therapy could further personalize treatment approaches. Finally, cost-effectiveness analyses would provide valuable guidance for clinical decision-making and healthcare resource allocation.

Conclusion

This retrospective cohort study demonstrated that, in pediatric convulsive status epilepticus, the early combination of intravenous levetiracetam with continuous midazolam infusion, as part of a stepwise emergency protocol, is associated with reduced need for rescue therapy, lower midazolam exposure, shorter hospital stays, and better short-term neurological outcome, without increasing adverse events. However, because this study did not evaluate long-term outcomes such as neurocognitive function, seizure recurrence, or chronic medication use after discharge, the impact of combination therapy on long-term prognosis remains uncertain. These findings support consideration of this dual-mechanism strategy as a safe and effective second-line option for acute clinical management. Further prospective trials with extended follow-up are warranted to confirm long-term benefits.

Disclosure of conflict of interest

None.

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