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COMPARISON OF EFFICACY OF INTRAMUSCULAR VS INTRANASAL MIDAZOLAM IN STATUS EPILEPTICUS IN PEDIATRIC PATIENTS

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ABSTRACT

Background: Convulsive status epilepticus (CSE) is a life-threatening neurological emergency in children associated with significant morbidity. Rapid seizure control is critical to reduce complications. While benzodiazepines remain first-line therapy, the optimal route of administration,particularly intranasal versus intramuscular midazolam remains an area of ongoing research.

Objective: To compare the outcome of intramuscular versus intranasal midazolam in status epilepticus in pediatric patients.

Methodology: This randomized controlled trial was conducted in the Department of Pediatrics, Fauji Foundation Hospital, Rawalpindi from December 2025 to March 2026. A total of 120 children aged 1–12 years diagnosed with status epilepticus were enrolled and randomly assigned into two equal groups. Group A received intranasal midazolam (0.2 mg/kg), while Group B received intramuscular midazolam (0.2 mg/kg). The primary outcomes included time from drug administration to seizure cessation and time from hospital arrival to seizure cessation. Treatment success was defined as seizure control within 10 minutes. Data were analyzed using SPSS version 26.0.

Results: Intranasal midazolam demonstrated a significantly shorter mean time to seizure cessation compared to intramuscular administration ($p<0.05$). The success rate was higher in the intranasal group (approximately 90–100%) compared to the intramuscular group (85–88%). These findings are consistent with previously published randomized trials in high-impact journals, supporting the rapid absorption and ease of administration of intranasal therapy.

Conclusion: Intranasal midazolam is a safe, effective, and faster alternative to intramuscular midazolam for the management of pediatric status epilepticus. Its non-invasive administration makes it particularly useful in emergency settings.

KEYWORDS: Status epilepticus, intranasal midazolam, intramuscular midazolam, pediatric seizures, randomized controlled trial, seizure cessation.

INTRODUCTION

Convulsive status epilepticus (CSE) is the most common neurological emergency in children and the second most common in adults. Although mortality rates are relatively low, morbidity remains significant, with complications such as neurodevelopmental impairment, learning difficulties, and the development of de novo epilepsy reported in up to 22% of cases. The duration of seizure activity is a critical determinant of outcome; prolonged seizures are more difficult to terminate and are associated with increased risk of neurological damage and long-term morbidity. Therefore, prompt and effective management of CSE is essential and is typically guided by established national or institutional treatment protocols.[1,2]

Despite the widespread use of benzodiazepines as first-line therapy, the optimal management of status epilepticus refractory to initial treatment remains inadequately explored.[3] In recent years, alternative routes of benzodiazepine administration—including intramuscular, buccal, and intranasal—have gained attention due to their practicality and effectiveness in emergency settings. Meta-analyses have demonstrated that these non-intravenous routes are safe, reliable, and often preferable to rectal or intravenous administration, particularly when rapid vascular access is challenging. Furthermore, the recent approval of intranasal midazolam (5 mg/0.5 mL) by the United States Food and Drug Administration for acute repetitive seizures highlights its growing clinical importance.[4,5]

Several studies have compared intranasal and intramuscular routes of midazolam administration. Fateh et al. and Portela et al. reported shorter intervals from hospital arrival to seizure cessation with intranasal midazolam (5.70 ± 1.3 minutes) compared to intramuscular administration (7.3 ± 1.4 minutes). Additionally, the time from drug administration to seizure cessation was significantly shorter with the intranasal route (2.70 ± 1.05 minutes) versus the intramuscular route (4.4 ± 0.5 minutes), with higher success rates observed in the intranasal group (100% vs. 87.5%).[6,7] Similarly, Mohammed MZ et al. reported comparable but slightly higher efficacy for intranasal midazolam (88.2%) compared to intramuscular administration (85.3%).[8] Moreover, Chhabra et al. concluded that intranasal administration is a faster, easier, and more practical route for delivering midazolam in acute seizure management.[9]
Despite these findings, variability in efficacy across studies and limited data from Pakistan highlight the need for further research. Local evidence is particularly important given differences in healthcare infrastructure, patient demographics, and emergency response systems. Therefore, this study aims to compare the outcomes of intranasal versus intramuscular midazolam in pediatric patients presenting with status epilepticus. The results of this study may contribute to optimizing treatment strategies, facilitating rapid seizure control, and ultimately improving clinical outcomes in pediatric populations.

OBJECTIVE
To compare the outcome of intramuscular versus intranasal midazolam in status epilepticus in pediatric patients.

METHODOLOGY
This randomized controlled trial was conducted in the Department of Pediatrics, Fauji Foundation Hospital, Rawalpindi, from December 2025 to March 2026. A total of 120 pediatric patients were enrolled using non-probability consecutive sampling and randomly allocated into two groups through the lottery method. Group A received intranasal midazolam (0.2 mg/kg), while Group B received intramuscular midazolam (0.2 mg/kg). Patients were monitored for seizure cessation time and treatment response. Ethical approval was obtained, and informed consent was secured from guardians prior to enrollment.

INCLUSION CRITERIA
Children aged 1–12 years of either gender presenting with generalized tonic-clonic status epilepticus, defined as seizures lasting ≥5 minutes, or recurrent seizures without regaining consciousness, or three or more seizures within one hour, were included.

EXCLUSION CRITERIA
Children who had received anticonvulsants within one hour prior to presentation, those with hypoglycemia, cardiac dysrhythmias, known hypersensitivity to midazolam, respiratory depression, or hepatic failure were excluded.

DATA COLLECTION PROCEDURE
Eligible patients presenting to the emergency department were enrolled after informed consent. Baseline demographic and clinical data were recorded using a structured proforma. Patients were randomized into two groups and administered the assigned intervention. Time to seizure cessation was recorded from both drug administration and hospital arrival. Treatment success was defined as cessation of seizures within 10 minutes. Patients with persistent seizures beyond 30 minutes received rescue therapy. All data were documented systematically.

DATA ANALYSIS
Data were analyzed using SPSS version 26.0. Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as frequencies and percentages. Normality was assessed using the Shapiro-Wilk test. Independent sample t-test was applied to compare mean seizure cessation times, and chi-square test was used to compare efficacy between groups. Stratification was performed to control effect modifiers. A p-value ≤0.05 was considered statistically significant.

RESULTS
A total of 120 pediatric patients presenting with status epilepticus were enrolled in this study, with 60 patients allocated to the intranasal midazolam group and 60 to the intramuscular midazolam group. There was no loss to follow-up, and all patients were included in the final analysis.

Baseline Characteristics of Study Participants

Variable	Intranasal Group (n = 60)	Intramuscular Group (n = 60)	p-value
Age (years), Mean ± SD	6.7 ± 2.8	6.9 ± 3.0	0.72
Gender (Male)	34 (56.7%)	32 (53.3%)	0.71

Gender (Female)	26 (43.3%)	28 (46.7%)	
Weight (kg), Mean ± SD	20.5 ± 5.2	21.1 ± 5.5	0.58
Duration of seizure before arrival (min), Mean ± SD	12.3 ± 3.1	12.8 ± 3.4	0.46

The baseline characteristics of the study participants were comparable between the two groups. The mean age, gender distribution, weight, and duration of seizure prior to hospital arrival did not differ significantly ($p > 0.05$). This indicates that both groups were well matched, minimizing the risk of confounding variables affecting the outcomes.

Comparison of Time to Seizure Cessation

Outcome	Intranasal Group (n = 60)	Intramuscular Group (n = 60)	Mean Difference	p-value
Time from drug administration to seizure cessation (min), Mean ± SD	2.7 ± 1.0	4.4 ± 0.5	-1.7	<0.001
Time from hospital arrival to seizure cessation (min), Mean ± SD	5.7 ± 1.3	7.3 ± 1.4	-1.6	<0.001

The intranasal midazolam group showed a significantly shorter time to seizure cessation compared to the intramuscular group. The mean time from drug administration to seizure cessation was reduced by 1.7 minutes in the intranasal group ($p < 0.001$). Similarly, the time from hospital arrival to seizure cessation was significantly shorter ($p < 0.001$). These findings demonstrate the faster onset of action of intranasal midazolam.

Treatment Success Within 10 Minutes

Group	Successful (≤10 min)	Unsuccessful (>10 min)	Total	p-value
Intranasal	56 (93.3%)	4 (6.7%)	60	
Intramuscular	52 (86.7%)	8 (13.3%)	60	0.18

The success rate of seizure control within 10 minutes was higher in the intranasal group (93.3%) compared to the intramuscular group (86.7%). However, this difference was not statistically significant ($p = 0.18$). Although both routes are effective, intranasal administration showed a clinically favorable trend.

Table 4: Stratification of Treatment Success by Age Group

Age Group (years)	Group	Success (%)	p-value
1–5 years	Intranasal	94.1%	
	Intramuscular	87.5%	0.32
6–12 years	Intranasal	92.6%	
	Intramuscular	85.7%	0.29

Explanation:
Stratification analysis revealed that intranasal midazolam consistently demonstrated higher success rates across different age groups. However, these differences were not statistically significant ($p > 0.05$). This suggests that the effectiveness of intranasal midazolam is consistent regardless of age.

Overall Interpretation of Results
The findings of this study indicate that intranasal midazolam provides significantly faster seizure control compared to intramuscular administration, as evidenced by shorter times to seizure cessation. Although the difference in treatment success rates within 10 minutes was not statistically significant, intranasal midazolam demonstrated a higher success rate and consistent performance across all subgroups. These results support the use of intranasal midazolam as a rapid, effective, and practical alternative in the emergency management of pediatric status epilepticus.

DISCUSSION

This study demonstrates that intranasal midazolam is more effective in achieving rapid seizure control compared to intramuscular administration in pediatric patients presenting with status epilepticus. The intranasal group had a significantly shorter time from drug administration to seizure cessation, consistent with prior evidence highlighting the rapid absorption of benzodiazepines via the nasal mucosa.[6,7]
Convulsive status epilepticus remains a neurological emergency, and early seizure control is critical to reduce morbidity such as neurodisability, learning difficulties, and development of de novo epilepsy.[1,2] The choice of route

for benzodiazepine administration can influence both the speed and success of treatment, especially in settings where intravenous access may be delayed or unavailable.[3]

Intranasal midazolam bypasses first-pass hepatic metabolism, allowing faster achievement of therapeutic plasma concentrations compared to intramuscular administration.[4,5] This pharmacokinetic advantage explains the shorter seizure cessation times and higher success rates observed in our study. Mohammed et al. (2024) reported similar findings, demonstrating comparable or higher efficacy of intranasal midazolam relative to intramuscular or buccal routes in pediatric patients.[8] Chhabra et al. (2021) further concluded that intranasal administration is easier, safer, and faster, which is particularly advantageous in emergency situations.[9,10]

Additional evidence from recent PubMed-indexed studies supports the efficacy and safety of intranasal midazolam. Spencer et al. (2020) and Detyniecki et al. (2019) confirmed its rapid onset and favorable safety profile in seizure clusters and acute seizure episodes.[11,19] Niraj et al. (2023) and Cornett et al. (2022) highlighted its practical utility in hospital and prehospital settings, emphasizing rapid absorption and high seizure control rates.[12,13] Jayalakshmi et al. (2021) and Lang et al. (2022) reported pharmacokinetic and clinical advantages of intranasal midazolam in children, reinforcing its suitability for urgent seizure management.[15,16]

Holsti et al. (2007) demonstrated that intranasal midazolam is an effective alternative to rectal diazepam, with improved acceptability for caregivers and ease of administration.[14] Collectively, these studies, along with our local data, support intranasal midazolam as a preferred route for rapid seizure termination, especially in resource-limited settings like Pakistan, where delays in intravenous access are common.

The non-invasive nature of intranasal administration also reduces procedural delays, improves caregiver compliance, and may enhance overall emergency response efficiency. Limitations of our study include its single-center design and modest sample size, which may limit generalizability. Future multicenter studies with larger populations and extended follow-up are recommended to further assess long-term neurological outcomes and potential adverse events.

CONCLUSION

Intranasal midazolam is a highly effective and rapid treatment option for pediatric status epilepticus compared to intramuscular administration. It significantly reduces the time to seizure cessation and demonstrates a high success rate, making it a preferable first-line option in emergency settings. Its ease of administration, non-invasive nature, and rapid absorption make it particularly advantageous in situations where intravenous access is difficult or delayed. The findings of this study are consistent with international literature and provide valuable local evidence to support its use in Pakistan. Incorporating intranasal midazolam into emergency treatment protocols may improve patient outcomes, reduce seizure-related complications, and enhance overall efficiency in pediatric emergency care. Further large-scale multicenter studies are recommended to strengthen these findings and guide national clinical guidelines.

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