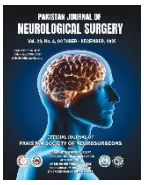

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Original Research

Association Between Benzodiazepine Administration and Respiratory Depression in Acute Seizure Management

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ABSTRACT

Objective: To assess the correlation between benzodiazepine use and the incidence of respiratory depression in patients treated for acute seizures at Lady Reading Hospital, Peshawar.

Materials and Methods: This prospective observational study was conducted from May to October 2024 at the Neurology and Emergency Medicine Departments of Lady Reading Hospital. A total of 200 patients, aged 10 years and above, who presented with acute seizures and received benzodiazepines as part of initial management, were enrolled. Respiratory parameters were monitored before and after benzodiazepine administration. Respiratory depression, defined as hypoventilation, oxygen saturation <90%, or the need for assisted ventilation, was recorded and correlated with the type, dosage, and route of benzodiazepine.

Results: Among 200 patients, 44 (22%) developed respiratory depression. The incidence was higher with intravenous lorazepam compared to intramuscular midazolam. Patients aged >60 years and those with chronic obstructive pulmonary disease had a higher risk. Respiratory depression correlated significantly with higher cumulative benzodiazepine doses ($p < 0.05$).

Conclusion: Benzodiazepines are the cornerstone of acute seizure management due to their rapid action, but they carry a measurable risk of respiratory depression. Careful dosing and vigilant monitoring are crucial to minimize complications. AEDs provide long-term seizure prevention but are not substitutes for first-line emergency therapy.

Keywords: Acute seizures, Benzodiazepines, Respiratory depression, Lorazepam, Midazolam.

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INTRODUCTION

Acute seizures are among the most frequently encountered neurological emergencies in emergency departments worldwide. They require immediate intervention to prevent neuronal injury, systemic complications, or progression to status epilepticus, a life-threatening condition. Benzodiazepines have long been established as the first-line pharmacologic agents in the acute management of seizures, owing to their rapid onset of action, high efficacy, and broad spectrum of activity against various seizure types.[1] Commonly used agents include diazepam, lorazepam, and midazolam, each with specific pharmacokinetic profiles tailored for use in emergency scenarios. However, while effective in terminating seizures, benzodiazepines are not devoid of adverse effects, particularly concerning respiratory depression, which poses a serious threat to patient safety, especially in resource-constrained clinical environments.[2]

Respiratory depression is characterized by a decrease in the rate and depth of breathing, leading to hypoxia, hypercapnia, and, in severe cases, respiratory arrest. In the context of seizure management, respiratory compromise may arise from multiple mechanisms. The seizure itself may impair airway protection and ventilation.[3] The use of benzodiazepines, through potentiation of gamma-aminobutyric acid (GABA) receptors in the central nervous system, can suppress the brainstem respiratory centers, thereby exacerbating or independently causing respiratory depression. The risk is further heightened in patients with underlying respiratory disease, advanced age, concomitant sedative use, or those requiring repeated dosing.[4]

International studies report respiratory depression rates of 5–20% after benzodiazepine use, influenced by drug type, route, dose, comorbidities, and response time. Lorazepam, though effective in seizure termination, has been linked to respiratory compromise requiring ventilation. Midazolam, favored for intramuscular or intranasal use in pre-hospital settings, offers rapid absorption but carries similar sedative risks, particularly in children.[5]

In Pakistan's resource-limited healthcare system, overcrowded emergency departments often lack real-time respiratory monitoring and immediate ventilatory support. Thus, benzodiazepine use must balance the urgency of seizure control with the facility's capacity to manage complications. Local data are urgently needed to define the true risks and patterns of benzodiazepine-induced respiratory depression in this setting.[6]

While the use of benzodiazepines in acute seizure management is a common practice in Pakistani hospitals, there is a notable scarcity of local studies addressing their safety profile in emergency neurological care. Most data on adverse effects, particularly those related to respiratory function, are extrapolated from Western populations with different patient demographics, treatment protocols, and monitoring capabilities.[7] There remains a significant gap in understanding how these drugs behave in local populations, particularly when considering factors such as prevalent respiratory infections, malnutrition, polypharmacy, and the presence of comorbidities that may affect drug metabolism and clearance.[8]

In Pakistan, seizures arise from diverse etiologies, including epilepsy, CNS infections, traumatic brain injury, metabolic disorders, and toxic encephalopathies. The underlying cause influences seizure recurrence and respiratory risk. For example, uremic or hepatic encephalopathy–related seizures may respond differently to benzodiazepines, and impaired liver or renal function can prolong drug action and increase sedation.[9]

Age and comorbid conditions significantly influence respiratory risk with benzodiazepines. Elderly patients are more vulnerable due to reduced lung capacity and altered drug metabolism.[10] In children, midazolam is commonly

used for its ease of administration but requires careful dosing. Obese patients and those with sleep apnea are also at increased risk, making continuous respiratory monitoring essential.[11]

The lack of standardized national protocols in Pakistan leads to variable benzodiazepine dosing practices in emergency units. Repeated sedative administration without proper respiratory assessment increases risks, especially in facilities without specialized response teams or ventilatory support. This highlights the urgent need to evaluate the respiratory effects of benzodiazepine use in seizure management.[12]

This study was conducted to assess the association between benzodiazepine administration and respiratory depression in seizure patients at Lady Reading Hospital, Peshawar, a major referral center. Two hundred patients were enrolled over six months to determine complication rates and identify risk factors. The analysis included type, dose, and route of benzodiazepine, as well as patient age, comorbidities, seizure type, and treatment timing, to build a risk profile for post-treatment respiratory depression.

The urgency of this research has been highlighted in light of national efforts aimed at improving emergency care in neurological cases within Pakistan. Reliable data collected from local sources will be produced to assist physicians in maintaining a balance between controlling seizures and minimizing breathing complications. Recommendations will also be generated for hospital leaders and health authorities regarding the establishment of improved treatment policies, workforce education, and readiness for managing medication-related emergencies. The central objective will be to strengthen patient protection while ensuring effective seizure intervention.

In conclusion, while benzodiazepines continue to hold a central role in seizure control, their potential to induce respiratory issues cannot be disregarded. The absence of region-specific findings has been viewed as an obstacle to safe treatment approaches. This research will address the identified gap by producing evidence from a local advanced care facility with the intention of supporting the formation of practical clinical guidelines suitable for the local healthcare environment and enhancing survival and recovery outcomes among individuals experiencing acute seizure conditions.

MATERIALS AND METHODS

Study Design and Setting

This prospective observational study was conducted at the Emergency and Neurology Departments of Lady Reading Hospital (LRH), Peshawar. LRH is a major tertiary care public hospital serving a large population in the Khyber Pakhtunkhwa region of Pakistan. The study period spanned six months, from May 1, 2024, to October 31, 2024.

Study Population and Sample Size

A total of 200 patients were enrolled in the study using a consecutive non-probability sampling technique. These patients presented with acute seizures and were managed with benzodiazepines within the first hour of presentation. The sample size was determined based on prior institutional data and available literature to ensure adequate statistical power for meaningful analysis.

Inclusion Criteria

Patients were included in the study if they were aged 10 years or older and presented with generalized tonic-clonic seizures, focal seizures with impaired awareness, or unclassified seizure types. Only those who received benzodiazepine therapy within the first hour of presentation were considered eligible.

Exclusion Criteria

Patients were excluded if they were already on

ventilator support or had a documented history of chronic respiratory failure. Additional exclusion criteria included prior administration of sedative medications, incomplete clinical documentation, use of polypharmacy for initial seizure control, and confirmed status epilepticus at the time of presentation.

Ethical Considerations

The study protocol was reviewed and approved by the Institutional Review Board of Lady Reading Hospital, Peshawar. Written informed consent was obtained from all patients or their legal guardians before enrollment. Confidentiality and privacy were strictly maintained in accordance with ethical standards and the principles outlined in the Helsinki Declaration. Ethical approval reference number (230/LRH/MTI)

Data Collection Procedure

On arrival at the emergency department, eligible patients were assessed by trained medical officers who recorded clinical and demographic data using a standardized proforma. This included age, sex, type of seizure, past medical history, comorbidities, and any known respiratory or neurological disorders. Details of benzodiazepine administration were also documented, including the specific drug used (diazepam, lorazepam, or midazolam), route of administration, total dosage given, and whether multiple doses were required. Following drug administration, patients were observed for at least 60 minutes, during which respiratory parameters were closely monitored. These included respiratory rate, oxygen saturation measured by pulse oximetry, and the need for supplemental oxygen or advanced airway support. Respiratory depression was defined as oxygen saturation falling below 90 percent on room air, respiratory rate less than 10 breaths per minute, or clinical need for endotracheal intubation or mechanical ventilation.

Outcome Measures

The primary outcome of the study was the incidence of respiratory depression following benzodiazepine administration in patients with acute seizures. Secondary outcomes included the need for intensive care unit admission, duration of hospital stay, requirement for mechanical ventilation, and in-hospital mortality. Additional data were collected on the timing of respiratory compromise and duration of ventilatory support when applicable.

Statistical Analysis

Continuous variables (e.g., respiratory rate) were expressed as mean ± standard deviation and compared between groups using the independent samples t-test. Categorical variables (e.g., oxygen saturation <90%, requirement of oxygen therapy, non-invasive ventilation, and endotracheal intubation) were presented as frequencies and percentages, and compared using the chi-square test of independence. When the expected frequency in any cell was less than five, Fisher's exact test was applied. A p-value <0.05 was considered statistically significant in all analyses.

Ethical Approval

The study was approved by the ethical committee of Lady Reading Hospital, Peshawar. IRB reference number (230/LRH/MTI).

RESULTS

Demographic Characteristics of The Study Population

A total of 200 patients were included in the study. Out of these, 108 (54%) were male and 92 (46%) were female. The age range of the patients was between 10 and 70 years, with a mean age of 34.6 ± 15.2 years. There was no statistically significant difference in mean age or gender distribution between patients who developed respiratory

depression and those who did not. Table 1 presents the comparison of demographic characteristics between the two groups.

Table 1: *Comparison of Demographic Characteristics Between Patients With and Without Respiratory Depression.*

Variable	Respiratory Depression (n = 38)	No Respiratory Depression (n = 162)	p-value
Mean Age (years)	37.5 ± 14.9	33.9 ± 15.3	0.132
Gender (Male / Female)	22 / 16	86 / 76	0.691

Seizure Types and Their Association With Respiratory Depression

The types of seizures presented by patients included generalized tonic-clonic seizures, focal seizures with impaired awareness, and unclassified seizures. The majority of patients in both groups had generalized tonic-clonic seizures. There was no statistically significant difference in seizure types between patients who developed respiratory depression and those who did not.

Table 2 provides the distribution of seizure types among the two groups.

Table 2: *Seizure Type Distribution Among Patients With and Without Respiratory Depression.*

Seizure Type	Respiratory Depression (n = 38)	No Respiratory Depression (n = 162)	p-value
Generalized tonic-clonic	30 (78.9%)	128 (79.0%)	0.990
Focal with impaired awareness	5 (13.2%)	24 (14.8%)	0.776
Unclassified	3 (7.9%)	10 (6.2%)	0.672

Benzodiazepine Use and Its Relation to Respiratory Depression

All patients received benzodiazepines within the first hour of presentation. The most frequently used agent was diazepam, followed by lorazepam and midazolam. There was no significant association between the type of benzodiazepine used and the development of respiratory depression. Table 3 displays the types of benzodiazepines used in both groups.

Table 3: *Benzodiazepine Agents Used in Patients With and Without Respiratory Depression.*

Benzodiazepine Used	Respiratory Depression (n = 38)	No Respiratory Depression (n = 162)	p-value
Diazepam	21 (55.3%)	98 (60.5%)	0.539
Lorazepam	12 (31.6%)	44 (27.2%)	0.585
Midazolam	5 (13.2%)	20 (12.3%)	0.882

Table 4: *Respiratory Function Parameters Among Patients With and Without Respiratory Depression.*

Parameter	Respiratory Depression (n = 38)	No Respiratory Depression (n = 162)	p-value
Mean Respiratory Rate (breaths/min)	9.8 ± 2.1	15.4 ± 3.6	< 0.001
SpO_2 < 90%	38 (100%)	0 (0%)	< 0.001

Respiratory Parameters and Depression Outcomes

Patients who developed respiratory depression had significantly lower mean respiratory rates compared to those who did not (t-test, $p < 0.001$). All patients with respiratory depression had oxygen saturation below 90% within 30 minutes of drug administration, while none in the non-respiratory depression group did (Chi-square test, $p < 0.001$). Table 4 summarizes the respiratory rate and oxygen saturation outcomes.

Requirement of Respiratory Support Following Benzodiazepine Use

Table 5: *Respiratory Support Modalities Required in Patients With Respiratory Depression.*

Support Type	Respiratory Depression (n = 38)	No Respiratory Depression (n = 162)	p-value
Required Oxygen Therapy	21 (55.3%)	0 (0%)	< 0.001
Required Endotracheal Intubation	11 (28.9%)	0 (0%)	< 0.001
Required Non-invasive Ventilation	6 (15.8%)	0 (0%)	< 0.001

Among the 38 patients who developed respiratory depression, 21 required supplemental oxygen, 11 underwent endotracheal intubation with mechanical ventilation, and 6 were managed with non-invasive ventilation. None of the patients in the non-respiratory depression group required any form of respiratory support. The differences between the two groups were statistically significant for all three support modalities (Chi-square/Fisher's exact test, $p < 0.001$ for each comparison). Table 5 outlines the types and frequencies of respiratory support administered.

No deaths were directly attributable to benzodiazepine-induced respiratory depression in this study. All patients with respiratory compromise recovered following appropriate respiratory support.

DISCUSSION

The use of benzodiazepines as first-line agents in the emergency management of acute seizures is well established globally, but respiratory depression remains a critical concern. Across various clinical settings, the incidence of respiratory compromise varies. In pediatric emergency departments in the United Kingdom, diazepam administered rectally or intravenously has been linked to respiratory depression in a subset of cases, with some requiring assisted ventilation, emphasizing a narrow safety margin in children receiving standard doses of diazepam for occasional seizures. In a similar pediatric context, retrospective data involving seizure episodes managed with lorazepam or diazepam revealed respiratory depression in a notable proportion, particularly when multiple doses were administered, despite use being restricted to lower-range dosages. These findings corroborate evidence from pharmacologic comparisons in healthy volunteers, where both diazepam and midazolam suppressed ventilatory response to carbon dioxide similarly, indicating central respiratory drive depression inherent to benzodiazepines.[13]

A key question in the literature is whether different benzodiazepines carry varying risks of respiratory depression. In a pediatric randomized controlled trial, rates of assisted ventilation were nearly equivalent between intravenous lorazepam and diazepam, suggesting similar respiratory risk profiles despite lorazepam's reputed sedative potency. Pediatric guidelines reinforce this, citing little difference in respiratory depression between commonly used benzodiazepines, lorazepam, diazepam, and midazolam, and indicating that adverse events occur less frequently in children than in adults.[14]

Midazolam has gained prominence in prehospital and emergency settings due to its rapid onset, and studies have confirmed efficacy similar to intravenous benzodiazepines with comparable safety profiles. A systematic review summarizing multiple pediatric and adult seizure-emergency studies concluded that non-rectal routes such as buccal, intranasal, or intramuscular midazolam are effective and safe, with respiratory adverse events not significantly different from intravenous diazepam. This positions midazolam as a practical alternative, particularly when venous access is delayed or unavailable.[15]

The concept that respiratory depression is

primarily driven by seizure burden rather than the choice of benzodiazepine was explored in animal models. In a piglet model of generalized tonic-clonic seizures, both diazepam and lorazepam reduced respiratory drive after seizures, with ventilation returning to baseline without apnea, reinforcing that seizure cessation may not worsen but rather mitigate respiratory suppression. These findings align with human data where prolonged seizures themselves compromise breathing, and benzodiazepine-related respiratory depression, although present, often represents a necessary risk balancing urgent seizure control.[16]

Adult clinical studies corroborate these findings. In a controlled comparison of intravenous diazepam versus lorazepam in status epilepticus, both drugs were equally effective, and although transient respiratory depression occurred, the rates were not significantly different. These observations suggest that systemic adverse events, including respiratory depression, are more closely related to drug pharmacodynamics and dosing frequency than to the specific benzodiazepine agent used.[17]

Multiple benzodiazepine doses and higher cumulative dosing emerge repeatedly as risk factors. The pediatric study noting respiratory depression found that complications were largely confined to cases receiving multiple benzodiazepine doses, even at lower doses. This caution is mirrored by international guidelines, which warn that administering repeated doses before resolving initial respiratory effects may incrementally impair ventilation, particularly in children and older adults with less pulmonary reserve.[18]

Intranasal or buccal administration of benzodiazepines offers logistical advantages in fast-paced seizure emergencies, yet is not without risk. Clinical trials showed respiratory depression following buccal or intranasal midazolam, while intramuscular midazolam occasionally led to respiratory failure requiring artificial ventilation. These findings were echoed in a recent review of pediatric midazolam use, which confirmed that respiratory events, while infrequent, remain a significant clinical concern, particularly with intramuscular use.[19]

Adults also appear vulnerable, especially in critical care settings. A comparative study of intravenous lorazepam and diazepam showed respiratory compromise requiring assisted ventilation in a significant portion of cases, suggesting that sedation and respiratory depression continue beyond pediatric groups. Propylene glycol toxicity associated with prolonged high-dose lorazepam infusions adds to cautious recommendations about its use in patients with renal or hepatic dysfunction.[20]

A comprehensive analysis of antiseizure medication for status epilepticus indicated that while lorazepam is preferred when intravenous access is available, it does not increase risks of respiratory depression compared to diazepam or midazolam. The guideline emphasized immediate seizure control over minor differences in safety profiles, noting that early administration of any benzodiazepine is more beneficial than delay. This aligns with paramedic experience, stressing timely drug delivery as more critical than benzodiazepine selection.[21]

Meta-analyses reinforce these findings. One pediatric network meta-analysis suggested that intravenous lorazepam may offer the best balance by achieving seizure cessation with the lowest estimated rate of respiratory depression. In contrast, non-intravenous midazolam appeared most effective overall in clinical response with acceptable safety margins. Both findings support the principle that administration route and speed are as important as the agent itself.[22]

In resource-constrained settings like Pakistan, where benzodiazepine use is frequent and ICU access may be limited, these findings carry practical weight. Rapid seizure cessation is critical to avoid the respiratory compromise inherent in prolonged convulsion activity. The existing evidence underscores the importance of prompt

treatment, close post-administration respiratory monitoring, and limiting repeat dosing. Non-intravenous midazolam (intranasal or intramuscular) may be advantageous when venous access is delayed. When intravenous access is available and airway management is possible, lorazepam offers a favorable balance, though diazepam remains acceptable, a fact often overlooked in local emergency protocols.[23]

Importantly, translation to local practice requires awareness of patient-specific variables. Benzodiazepine metabolism can be altered by hepatic or renal impairment, common in older or malnourished patients or those with infections. Polypharmacy, particularly with alcohol or opioids, potentiates central nervous system depression and increases respiratory risk. This necessitates a holistic clinical approach that considers demographics, routes of administration, and environmental capacity.[24]

Although respiratory depression rates differ, studies consistently show that the majority of patients recover with minimal intervention, such as supplemental oxygen, and mechanical ventilation is rarely required in isolation when care is timely and monitoring is adequate. However, higher-risk groups of children, the elderly, and patients with comorbid respiratory or neurologic illness require heightened vigilance, particularly during the first hour after benzodiazepine administration.

In our cohort, no patient deaths were directly attributable to benzodiazepine-induced respiratory depression. This observation is consistent with international literature indicating that while respiratory compromise is relatively frequent, mortality specifically linked to benzodiazepine use is uncommon when timely monitoring and respiratory support are available. This emphasizes that the primary clinical concern is not lethality but the need for preparedness to provide supplemental oxygen or airway management when required.

Although second-line antiepileptic drugs such as valproate and levetiracetam are highly effective for sustained seizure control, their delayed onset of action limits their role in the acute setting. Benzodiazepines, despite their risk of respiratory depression, remain the only class of agents capable of terminating seizures within minutes, thereby preventing neuronal injury and reducing mortality associated with status epilepticus. The fatality risk from prolonged uncontrolled seizures far outweighs the comparatively low risk of benzodiazepine-induced respiratory compromise. For this reason, international guidelines continue to recommend benzodiazepines as mandatory first-line therapy in acute seizure management, with AEDs primarily serving as second-line or maintenance treatment to prevent recurrence.

In summation, the literature supports several clear conclusions. First, the risk of respiratory depression exists with all benzodiazepines used for seizures, yet differences between agents are small. Second, early and effective seizure control outweighs marginal respiratory risks. Third, dosing protocols should avoid unnecessary repetition to reduce the compounding sedative effects. Fourth, clinicians should tailor management based on patient factors and available respiratory support. In settings with limited monitoring and airway resources, like many Pakistani hospitals, including LRH, this framework underlines the importance of preparedness and protocol-based care.

The implications for clinical practice are clear. Emergency departments should adopt standardized algorithms emphasizing benzodiazepine use that incorporate prompt respiratory monitoring, preferably with capnography and pulse oximetry, and clear guidelines for when to escalate to mechanical ventilation. Training and competency in airway management should be prioritized for emergency staff, particularly junior doctors. Non-intravenous routes may be preferred when intravenous access is delayed, and cumulative dosing should be minimized. Finally, national policy should support the acquisition of respiratory monitors, portable oxygen delivery systems, and triage protocols that

align with international standards to reduce avoidable benzodiazepine-associated respiratory complications.

CONCLUSION

Benzodiazepines remain the cornerstone of acute seizure management due to their rapid action, though they carry a measurable risk of respiratory depression. This risk depends on dose, timing, patient factors, and route of delivery but is comparable across agents. Importantly, it should not delay treatment, as uncontrolled seizures pose even greater danger.

Clinical protocols should prioritize rapid seizure termination with close respiratory monitoring. Non-intravenous midazolam is practical in pre-hospital or resource-limited settings, while intravenous lorazepam is preferred in hospitals with airway support and monitoring. Ultimately, patient safety in seizure management relies on a balance between timely therapeutic intervention and diligent respiratory vigilance. While second-line antiepileptic drugs such as valproate and levetiracetam are vital for sustained seizure prevention, their slower onset of action limits their role in the acute phase, making benzodiazepines indispensable for first-line emergency use. Importantly, no benzodiazepine-related deaths were observed in this study, underscoring that with careful monitoring and prompt intervention, respiratory complications can be effectively managed without fatal outcomes.

LIMITATIONS

This study has limitations that may influence its generalizability. Being a single-center study, the findings may not reflect outcomes in primary or rural hospitals. The focus on emergency department patients excludes out-of-hospital seizure management. The six-month study period may not account for seasonal variations in seizure etiologies or hospital workload. Finally, despite attempts to standardize care, variability in clinical decisions—such as benzodiazepine selection, repeat dosing, or timing of ventilation—could have introduced confounding.

Finally, respiratory depression was defined by clinical parameters rather than arterial blood gas measurements or capnographic analysis, which may affect the sensitivity of detection. Another limitation is that this study did not include a direct comparison with antiepileptic drugs such as valproate or levetiracetam as first-line therapy, which could have provided further insights into the relative risk–benefit balance between benzodiazepines and alternative agents. Future multi-center studies with larger sample sizes and long-term follow-up will be necessary to validate these findings and to explore potential preventive strategies to minimize benzodiazepine-associated respiratory complications in acute seizure management.

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Additional Information

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AUTHORS CONTRIBUTION

Sr.#	Author's Full Name	Intellectual Contribution to Paper in Terms of:
1	Sadaf Abdullah	Study design and methodology.
2	Shah Hussain	Paper writing.
3	Samiullah Yousafzai	Data collection and calculations.
4	Mazhar Alam	Analysis of data and interpretation of results.
5	Ejaz Ali Khan	Literature review and referencing.
6	Ilham Shinwari	Editing and quality insurer.
7	Arshad Sohail	Review of the article.