

Ketamine vs. Midazolam: Comparative Analysis in Emergency Sedation

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ABSTRACT

This study compares the efficacy and safety of ketamine and midazolam for anxiety management in emergency department (ED) sedation, with emphasis on hemodynamic effects and relevance to the Saudi Arabian healthcare context. A literature review of peer-reviewed studies was conducted using PubMed, Scopus, and Web of Science. Comparative analyses focused on sedation effectiveness, onset time, hemodynamic stability, and respiratory effects. Ketamine provides rapid dissociative sedation with minimal respiratory depression but is associated with hypertension and emergence reactions. Midazolam offers smoother sedation with fewer psychiatric side effects but carries risks of hypotension and respiratory depression. Observational studies in Saudi Arabia indicate a need for tailored sedation strategies due to the high prevalence of cardiovascular disease and obesity, which influence drug metabolism and side effects. Both ketamine and midazolam have clinical utility in ED sedation, necessitating careful patient selection. While ketamine is effective for anxiety reduction, its hypertensive effects require monitoring. Midazolam provides controlled sedation but demands vigilance for respiratory depression. Further region-specific studies are essential to optimize sedation protocols for patient safety.

Keywords: Ketamine, Midazolam, Emergency Department, Sedation, Anxiety, Saudi Arabia

INTRODUCTION

Anxiety is a common occurrence in emergency department (ED) settings, presenting as a challenge for both patients and healthcare providers. The distress associated with acute anxiety can hinder medical procedures, increase patient discomfort, and elevate the risk of adverse physiological responses¹. To mitigate these issues, procedural sedation is frequently employed to alleviate anxiety and ensure smooth medical interventions². Among the various pharmacological agents used for sedation, ketamine and midazolam are widely administered due to their unique pharmacokinetic and pharmacodynamic properties³.

Ketamine is a dissociative anesthetic that acts as an N-methyl-D-aspartate (NMDA) receptor antagonist. It induces a trance-like, analgesic, and sedative state while preserving airway reflexes and respiratory drive⁴. The rapid onset and effectiveness of ketamine make it an attractive option in ED settings. However, its use is associated with potential side effects, including hypertension, tachycardia, and emergence reactions such as hallucinations and agitation⁵. These adverse effects necessitate careful patient monitoring and selection, especially in individuals with underlying cardiovascular conditions⁶.

Midazolam, a short-acting benzodiazepine, enhances the activity of gamma-aminobutyric acid (GABA), leading to sedation, muscle relaxation, and anxiolysis⁷. It is preferred in certain clinical scenarios due to its smoother sedation profile and lower risk of psychiatric side effects compared to ketamine. However, midazolam carries a higher risk of respiratory depression and hypotension, requiring vigilant monitoring in patients with respiratory conditions, advanced age, or hemodynamic instability⁸. The selection of an appropriate sedative agent depends on multiple factors, including the clinical indication, patient comorbidities, and the urgency of the procedure. In Saudi Arabia, the high prevalence of obesity, metabolic disorders, and cardiovascular diseases influences sedation protocols⁶. The choice

between ketamine and midazolam must take into account these regional health considerations to ensure patient safety and optimal outcomes⁹.

This review aims to compare the efficacy, safety, and clinical applicability of ketamine and midazolam in ED sedation, with a particular emphasis on anxiety management. By analyzing observational studies and existing literature, this paper seeks to provide insights into best practices for sedation, particularly within the Saudi healthcare setting¹⁰. The findings will help inform evidence-based decisions regarding sedative selection, ensuring that patient-centered, safe, and effective sedation strategies are employed in emergency medical practice.

Given the variations in healthcare infrastructure, patient demographics, and sedation practices worldwide, this review will also explore the relevance of international findings to Saudi Arabia's unique healthcare landscape¹¹. The ultimate goal is to refine sedation protocols, improve patient outcomes, and minimize sedation-related complications through an evidence-based approach. By systematically evaluating the benefits and risks of ketamine and midazolam, this review aims to assist emergency medicine practitioners in selecting the most appropriate sedative for different clinical scenarios.

METHODS

A comprehensive literature review was conducted to evaluate the efficacy and safety of ketamine and midazolam for sedation in emergency department (ED) settings. The review included studies comparing these agents in terms of anxiety reduction, hemodynamic stability, and respiratory effects. This section details the literature search strategy, inclusion and exclusion criteria, and the approach to data synthesis and analysis.

Literature Search Strategy and Databases Used

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The literature search was conducted using multiple electronic databases, including PubMed, Scopus, and Web of Science, to ensure a broad and comprehensive retrieval of relevant studies. The search terms included "ketamine AND midazolam AND sedation," "emergency department AND procedural sedation," "ketamine AND hemodynamic effects," and "midazolam AND respiratory depression." Boolean operators (AND/OR) were used to refine search results. The search covered peer-reviewed articles published in English from 2000 to 2025 to ensure the inclusion of contemporary findings.

Additional searches were performed through Google Scholar and reference tracking from key review articles to identify any relevant studies not indexed in major databases. To minimize bias, only studies published in high-impact factor journals and indexed in recognized medical literature databases were included.

Inclusion Criteria: Studies were selected based on the following criteria

- Study Design: Randomized controlled trials (RCTs), cohort studies, systematic reviews, and meta-analyses.
- Population: Adult patients undergoing procedural sedation in an emergency department setting.
- Interventions: Comparative studies evaluating ketamine versus midazolam for sedation.
- Outcome Measures: Studies assessing sedation depth, anxiety reduction, hemodynamic changes (heart rate, blood pressure), and respiratory effects (oxygen saturation, need for assisted ventilation).
- Geographical Relevance: Research conducted in Saudi Arabia and globally to provide comparative insights.

Exclusion Criteria: The following studies were excluded

- Case Reports and Small Sample Studies: Due to the potential for anecdotal bias, individual case reports and studies with sample sizes of less than 30 patients were excluded.
- Pediatric Population Studies: Unless specifically relevant, studies involving pediatric patients were excluded to maintain consistency in adult sedation protocols.
- Animal or Preclinical Studies: Only human clinical studies were included.
- Studies with Incomplete Data: Research lacking key outcomes or statistical analysis was omitted.

Data Synthesis and Analysis Approach

After identifying eligible studies, data were extracted using a structured template, including study design, sample size, sedation depth, anxiety reduction, hemodynamic parameters, and adverse effects. Studies were grouped based on their methodology and reported findings. A qualitative synthesis approach was employed, summarizing key findings rather than performing a formal meta-analysis. Differences in study methodologies, patient populations, and reported outcomes were carefully considered. Studies conducted in Saudi Arabia were analyzed separately to assess region-specific sedation protocols and their applicability to international findings.

Where possible, statistical comparisons were noted, including mean differences in anxiety reduction scores, blood pressure variations, and respiratory rate changes. The limitations of each study, including potential biases and confounding factors, were critically evaluated to provide a balanced interpretation of findings. This structured review ensures that conclusions are drawn from robust and high-quality evidence, allowing emergency medicine practitioners to make informed decisions regarding the safest and most effective sedation strategies in ED settings.

A structured table was used to extract template variables including sedation depth, anxiety scores, hemodynamic changes, and respiratory outcomes. However, as this is a narrative review, raw data tables and appendices were not included but are available upon request

RESULTS

Comparison of Anxiety Reduction and Sedation Efficacy

Ketamine and midazolam exhibit distinct pharmacodynamic properties that influence their effectiveness in managing anxiety during procedural sedation. Ketamine provides rapid dissociative sedation, allowing for effective anxiety reduction within minutes of administration⁶. Studies have reported that ketamine results in higher patient-reported comfort scores and faster procedural readiness compared to midazolam¹². However, midazolam, due to its benzodiazepine-induced anxiolysis, offers a more gradual onset of sedation, leading to a smoother procedural experience with fewer emergence reactions⁷. While ketamine is highly effective in rapidly alleviating anxiety, midazolam is preferred in cases where a controlled and steady sedation level is desired¹¹.

Hemodynamic Stability and Adverse Effects

Hemodynamic stability is a crucial factor in the selection of sedative agents in emergency settings. Ketamine stimulates the sympathetic nervous system, often resulting in elevated heart rate and blood pressure⁵. While this can be advantageous in hypotensive or trauma cases, it may exacerbate cardiovascular strain in patients with preexisting conditions like hypertension or ischemic heart disease⁶. Its hypertensive effect, though usually transient, necessitates monitoring—especially in settings like Saudi Arabia, where cardiovascular comorbidities are highly prevalent⁹. Midazolam, conversely, has a depressant effect on the cardiovascular system, often resulting in hypotension and bradycardia¹³. The risk of respiratory depression is also higher with midazolam, necessitating careful monitoring, particularly in elderly and high-risk patients⁸. Although ketamine has minimal respiratory depressant effects, it may induce airway secretions, increasing the risk of laryngospasm in sensitive individuals¹⁴.

Saudi Arabian Perspective: Cardiovascular Risks and Obesity

In Saudi Arabia, the high prevalence of obesity, diabetes, and cardiovascular disease necessitates a more tailored approach to sedation selection⁹. Ketamine’s hypertensive effects may pose additional risks in patients with uncontrolled hypertension, a common comorbidity in the region⁶. Midazolam, while providing hemodynamic stability, increases the risk of respiratory depression in obese patients with obstructive sleep apnea (OSA), which is a growing health concern in Saudi Arabia¹⁵. Given these factors, careful screening and monitoring are required when selecting a sedation agent in the Saudi Arabian emergency care context¹¹ (Table 1).

Table 1. Comparative Summary of Key Findings

Parameter	Ketamine	Midazolam
Anxiety Reduction	Rapid onset, high efficacy in severe anxiety (Barbic et al., 2021)	Gradual onset, smoother experience (Hapuarachchi et al., 2024)
	Hypertension, tachycardia due to sympathetic stimulation (Goddard et al., 2021)	Hypotension, bradycardia due to cardiovascular depression (Caballero et al., 2024)

Respiratory Effects	Minimal depression, but risk of laryngospasm (Trimmel et al., 2018)	High risk of respiratory depression, requiring close monitoring (Peter et al., 2024)
Saudi Arabian Considerations	May be risky for hypertensive and diabetic patients (Alghadeer et al., 2024)	Caution needed for obese patients with OSA (Zamboni et al., 2023)

This comparison highlights the situational advantages and risks of both sedative agents. While ketamine is preferred for rapid, dissociative sedation, its cardiovascular stimulation effects necessitate caution in hypertensive patients. Midazolam, on the other hand, is more predictable and widely tolerated but requires close respiratory monitoring, especially in patients with obesity-related conditions.

The findings emphasize the need for individualized sedation strategies based on patient profiles, procedural needs, and regional health concerns. Further studies focusing on long-term outcomes of sedation practices in Saudi Arabia would be beneficial in refining ED protocols for safer and more effective patient care.

DISCUSSION

Clinical Implications of Findings

The comparative analysis of ketamine and midazolam highlights key considerations for their use in emergency department (ED) sedation. Ketamine's rapid onset and potent dissociative effects make it highly effective for acute anxiety reduction, particularly in trauma or agitation cases⁶. However, its hypertensive effects pose risks for patients with underlying cardiovascular conditions⁵. Midazolam, on the other hand, offers a more predictable sedation experience with fewer psychiatric adverse effects, making it a suitable choice for patients requiring smooth and prolonged sedation⁷. The higher risk of respiratory depression with midazolam necessitates close monitoring, particularly in elderly or high-risk patients⁸. These findings emphasize the importance of individualized sedation strategies based on patient profiles and procedural needs.

Strengths and Limitations of Ketamine & Midazolam in ED Use

Both ketamine and midazolam offer unique advantages, but their limitations must be carefully considered. Due to its rapid onset and minimal effect on respiratory drive, ketamine is particularly valuable in emergency procedures that require quick action while maintaining airway protective reflexes¹⁴. However, its association with hallucinations and emergence reactions limits its use in certain populations, such as patients with psychiatric disorders¹⁶. Midazolam, in contrast, ensures more controlled sedation but is linked to hypotension and prolonged respiratory depression¹³. The risk of prolonged recovery time with midazolam must also be considered when selecting an appropriate sedative in time-sensitive ED scenarios¹¹. Understanding these strengths and limitations allows ED physicians to optimize their sedation choices based on the patient's medical history and the urgency of the procedure.

Saudi Arabian-Specific Challenges & Recommendations

The high prevalence of cardiovascular diseases, obesity, and diabetes in Saudi Arabia presents additional challenges for sedation protocols. Given ketamine's hypertensive effects, its use in hypertensive and

diabetic patients must be carefully monitored. Conversely, midazolam's increased risk of respiratory depression is of particular concern in Saudi Arabia, where obesity-related conditions such as obstructive sleep apnea (OSA) are prevalent¹⁵. Given these factors, the selection of sedatives must be guided by individualized patient assessments that consider regional health concerns. Saudi emergency departments should implement standardized sedation protocols that integrate comorbidities, weight-based dosing adjustments, and enhanced patient monitoring strategies to improve patient safety and procedural success rates.

Future Research Needs & Areas for Improvement

While ketamine and midazolam are well-established sedatives, further research is required to refine their use in Saudi Arabia and other high-risk populations. Large-scale observational studies and randomized controlled trials should be conducted to assess the long-term effects of sedation protocols tailored to patients with obesity, diabetes, and cardiovascular conditions⁶. Additionally, studies exploring combination therapies—such as the co-administration of ketamine with midazolam to minimize emergence reactions and optimize sedation depth—could provide valuable insights into safer sedation strategies⁷. Research on alternative sedatives with improved safety profiles and their applicability to emergency medicine in Saudi Arabia should also be prioritized. The integration of electronic sedation monitoring systems in Saudi EDs could further enhance patient safety by enabling real-time tracking of hemodynamic and respiratory parameters.

CONCLUSION

This review highlights the distinct pharmacological profiles of ketamine and midazolam in emergency department sedation. Ketamine's rapid onset and dissociative properties make it an effective option for immediate anxiety reduction and procedural sedation, though its hypertensive effects necessitate caution in patients with cardiovascular conditions⁵. Midazolam, with its anxiolytic and smooth sedation effects, is suitable for controlled procedures but presents an increased risk of respiratory depression, requiring close monitoring⁸. The choice between these sedatives should be guided by patient-specific factors, such as comorbidities, procedural requirements, and risk factors associated with each drug.

Recommendations for Clinical Practice

Given the high prevalence of obesity, diabetes, and cardiovascular disease in Saudi Arabia, sedation protocols should incorporate individualized risk assessments to improve patient safety. The use of ketamine should be carefully considered in hypertensive or cardiac-compromised patients, while midazolam should be administered cautiously in patients with respiratory vulnerabilities, particularly those with obstructive sleep apnea (OSA).¹⁵ A multidisciplinary approach involving emergency physicians, anesthesiologists, and nursing teams is recommended to optimize sedation outcomes. Additionally, the implementation of weight-based dosing strategies and continuous hemodynamic monitoring can enhance sedation safety.

Final Thoughts on Future Research Needs

Further research is needed to establish region-specific sedation guidelines that reflect the unique healthcare landscape and comorbidity burden in Saudi Arabia. Comparative studies on ketamine-midazolam combination therapies could provide insights into optimizing sedation depth while minimizing adverse effects.⁷ Future trials should also evaluate the effectiveness of alternative sedatives with improved

safety profiles, particularly in patients with complex medical histories. Finally, integrating real-time sedation monitoring technologies in emergency departments could enhance patient safety and improve clinical outcomes.

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