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Review Article

Clinical implications of midazolam in preoperative anxiety and sedation: a review

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ABSTRACT

Preoperative anxiety, a common reaction to the unfamiliar setting of medical procedures, affects 60-80% of patients and can lead to significant psychological and physiological stress. This stress can exacerbate hemodynamic instability during surgery, complicate anesthetic management, and contribute to adverse postoperative outcomes such as increased pain perception, longer recovery times, and extended hospital stays. Midazolam, a short-acting benzodiazepine, is frequently used to address these issues due to its rapid onset and effective anxiolytic and sedative properties. By acting on GABA-A receptors, midazolam provides relief from preoperative anxiety and facilitates smoother anesthesia induction. However, its use is not without risks, including potential respiratory depression, paradoxical reactions, and oversedation, which may be particularly concerning in vulnerable populations. These concerns have prompted exploration of non-pharmacological approaches, such as cognitive-behavioral therapy and mindfulness-based interventions, which can reduce anxiety without the side effects associated with pharmacological agents. This review aims to critically evaluate the clinical implications of midazolam use for preoperative anxiety and sedation, highlighting its efficacy, safety profile, and the growing interest in alternative non-pharmacological strategies.

Keywords: Preoperative anxiety, Midazolam, Sedation, Anxiolysis, Benzodiazepines

INTRODUCTION

Anxiety during therapeutic or diagnostic medical procedures is a typical reaction to the unfamiliar setting and experience, affecting up to 60-80% of individuals undergoing procedures.[1,2] This anxiety manifests as heightened psychological stress and physiological responses, such as increased heart rate, elevated blood pressure, and elevated cortisol levels. If left unmanaged, these responses can exacerbate hemodynamic instability during surgery, complicating the anesthetic process and raising the likelihood of perioperative complications.

Preoperative anxiety also correlates with adverse postoperative outcomes, including heightened pain perception, increased demand for analgesics, prolonged recovery times, and extended hospital stays.[3] These complications collectively contribute to increased healthcare costs, suboptimal patient experiences, and delayed rehabilitation, underscoring the importance of effectively managing anxiety in the preoperative period.

Anxiety reduction or anxiolysis can be accomplished through both pharmacological and non-pharmacological methods, with or without sedation.[4,5] When anxiolysis is achieved without significantly affecting consciousness, it is referred to as minimal sedation.[6] However, if the medication causes a noticeable reduction in consciousness while the patient remains responsive, it is known as moderate sedation. One extensive survey found that as many as 75% of anesthesiologists in the United States regularly use sedative premedication for healthy adult patients undergoing surgery.[7] Midazolam, a short-acting imidazobenzodiazepine, is one of the most widely utilized agents for preoperative sedation, anxiolysis or both, before diagnostic and therapeutic procedures.[7,8] Acting on gamma-aminobutyric acid (GABAA) receptors in the central nervous system, midazolam exerts profound inhibitory effects on neuronal excitability, leading to sedation, anxiolysis, anterograde amnesia, and muscle relaxation (Figure 1). Its rapid onset of action, achieved through its high lipid solubility at physiological pH, and quick recovery profile make it an ideal candidate for short-term sedation in a variety of surgical procedures.[9] Midazolam is particularly favored for outpatient and day-case surgeries, where rapid recovery and discharge are crucial. Despite its effectiveness, concerns surrounding midazolam's safety profile—such as paradoxical reactions, respiratory depression, and hypotension—have prompted some clinicians to reconsider its widespread use. Furthermore, the increasing advocacy for non-pharmacological interventions to manage preoperative anxiety has ignited debates over whether pharmacological premedication like midazolam is always necessary. This review aims to critically examine the clinical implications of midazolam use in preoperative anxiety and sedation, considering its efficacy, safety, and the broader context of modern anesthetic practice.

METHODS

This study is grounded in an extensive literature search performed on 09 September 2024, across the Medline and Cochrane databases. The search utilized Medical Subject Headings (MeSH) and a combination of related terms available within the databases. To ensure comprehensive coverage and avoid missing relevant research, a manual search was also conducted using Google Scholar, focusing on the reference lists of previously identified papers. We sought information in studies addressing the clinical implications of midazolam for preoperative anxiety and sedation. There were no restrictions placed on publication date, language, participant age, or type of publication.

DISCUSSION

Midazolam's clinical utility in preoperative care is grounded in its ability to alleviate anxiety and provide sedation, essential components for ensuring a seamless anesthesia induction. Its action on GABAA receptors facilitates significant central nervous system inhibition, which translates into effective anxiolysis, sedation, and muscle relaxation. These properties are critical for managing the stress and discomfort patients experience before surgery, which can otherwise complicate the anesthetic process and affect overall surgical outcomes.

As a benzodiazepine, its high lipid solubility allows for rapid crossing of the blood-brain barrier, resulting in a swift onset of action, which is particularly advantageous in surgical environments where both time efficiency and patient comfort are crucial. Its rapid onset allows anesthesiologists to control anxiety in the short window before surgery, ensuring that patients remain calm and stable without significant delays.

Clinical evidence supports midazolam’s efficacy in reducing anxiety before surgery. For instance, Naguib et al research highlights midazolam’s significant role in decreasing preoperative anxiety while improving patient satisfaction.[11] These findings reinforce midazolam's value in providing both sedation and relief from anticipatory anxiety, thus fostering a more controlled surgical experience. Additionally, Bansal et al demonstrated midazolam’s effectiveness in reducing anxiety without inducing adverse hemodynamic effects, highlighting its safety and efficacy across diverse clinical settings.[12] Midazolam's clinical utility in preoperative care is deeply rooted in its unique pharmacological profile, which combines effective anxiolytic and sedative properties with a rapid onset of action.

The primary clinical benefit of midazolam lies in its capacity to alleviate preoperative anxiety, which, if unmanaged, can intensify physiological stress responses such as tachycardia, hypertension, and elevated anesthetic requirements.[13] Elevated anxiety levels in patients awaiting surgery often lead to heightened sympathetic nervous system activity, which complicates anesthetic management and can result in poorer intraoperative outcomes. Midazolam addresses this by enhancing GABAergic inhibition within the central nervous system, promoting relaxation and diminishing these harmful physiological responses. This stabilization of hemodynamics not only facilitates smoother induction of anesthesia but also minimizes the risk of intraoperative complications, such as hemodynamic instability and the need for higher doses of anesthetics.

Numerous clinical research studies have affirmed midazolam’s efficacy in reducing preoperative anxiety. For instance, studies by Bauer et al have shown that midazolam significantly lowers anxiety levels prior to surgery, which contributes to improved patient satisfaction

[8]. This improvement in psychological well-being translates into a more controlled and predictable surgical experience for both patients and healthcare providers. Additionally, midazolam has been found to enhance patient cooperation and comfort, which is crucial for successful anesthesia induction and operative outcomes.

Bansal et al's findings further reinforce the safety profile of midazolam, as their study demonstrated that it effectively reduces anxiety without inducing adverse hemodynamic changes.[12] This makes midazolam a versatile sedative option across a range of clinical scenarios, including patients with underlying cardiovascular concerns. By providing effective anxiolysis without compromising blood pressure or heart rate, midazolam is particularly suited for use in patients where cardiovascular stability is paramount. Moreover, its pharmacokinetic properties, including rapid redistribution and relatively short half-life, allow for quicker recovery, making it ideal for outpatient or ambulatory surgical settings where rapid post-procedure discharge is desirable.

However, the clinical application of midazolam is not without limitations. An updated systematic review by Conway et al. reveals that, despite widespread use for procedural sedation, the evidence supporting midazolam's superiority over placebo remains of low quality.[14] Specifically, midazolam has not consistently demonstrated a significant reduction in anxiety or discomfort when compared to placebo, suggesting that while it can be effective in many contexts, its impact on preoperative anxiety is not universally robust across all patient populations. Additionally, the review found that while midazolam may reduce procedural difficulty and improve patient satisfaction, these outcomes are based on low-quality evidence, highlighting the need for further research to strengthen these findings.

Comparative studies also provide insights into midazolam's clinical efficacy relative to other sedative agents (Table 1). For example, studies comparing midazolam to chloral hydrate in pediatric populations found that midazolam was associated with a higher rate of incomplete procedures.[15-19] Although chloral hydrate poses challenges due to its inconsistent duration of action and limited availability, this data suggests that midazolam may not be the ideal sedative in all contexts, particularly for certain pediatric cases. Furthermore, dexmedetomidine has been shown to potentially offer superior anxiety reduction compared to midazolam in children undergoing laceration repair.[20] This finding prompts further investigation into the efficacy and cost-effectiveness of dexmedetomidine as an alternative to midazolam, particularly in pediatric settings. Moreover, a comparison between intranasal midazolam and ketamine indicated that while midazolam provided higher initial sedation levels, there was no significant difference in the completion rates of procedures.[21] Interestingly, a study by Cao et al compared midazolam with clonidine for preoperative sedation in children, revealing that clonidine provided better sedation, parental separation, and mask acceptance than midazolam.[22] However, midazolam offered superior postoperative analgesia, though with a higher incidence of postoperative shivering. These results suggest that while clonidine may be preferable for sedation, midazolam remains valuable for managing postoperative pain, highlighting the necessity of patient-centered decisions regarding sedative selection and the need for continued research into the comparative advantages of different sedatives.

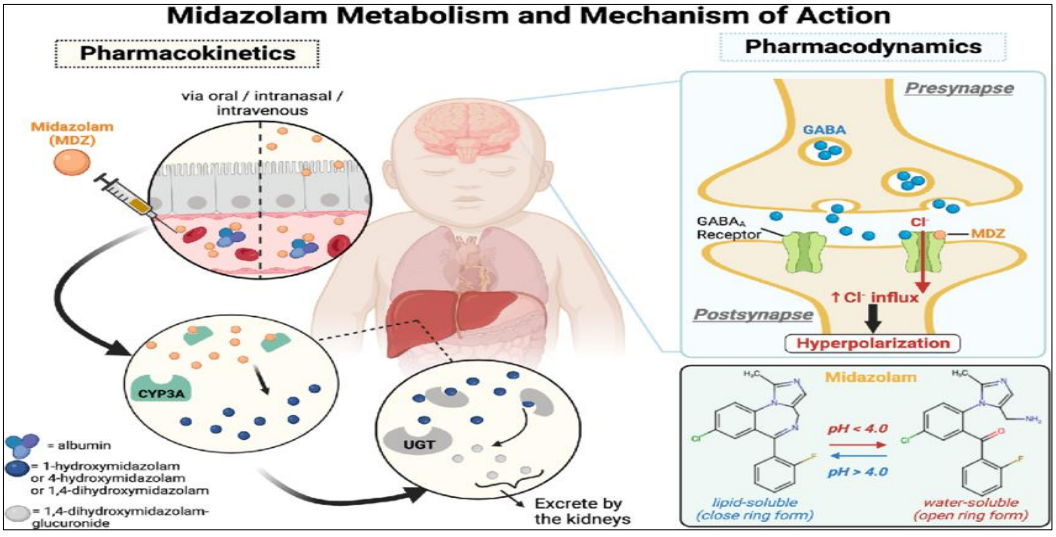

Figure 1: Schematic representation of midazolam metabolism and its mechanism of action. Midazolam (MDZ) can be administered via oral, intranasal, or intravenous routes. Once in the bloodstream, MDZ binds to albumin and is either transported to the brain, where it exerts its effects, or to the liver for conversion into metabolites by CYP3A enzymes, which are eventually excreted by the kidneys. In the brain, MDZ binds allosterically to GABA A receptors, enhancing gamma-aminobutyric acid (GABA) binding and increasing chloride ion (Cl−) influx into the postsynaptic cell. This chloride influx hyperpolarizes the cell by increasing its negative potential (created using Biorender.com).[10]

Table 1: Key findings from the mentioned studies on midazolam and other sedative agents for preoperative anxiety and sedation in pediatric populations.

Study/comparison	Agents compared	Key findings	Advantages	Disadvantages
Meta-analysis: midazolam versus chloral hydrate[14]	Midazolam versus chloral hydrate	Midazolam associated with higher incomplete procedures in pediatric populations. Chloral hydrate had inconsistent action and limited availability	Chloral hydrate: none highlighted due to challenges	Midazolam: inconsistent outcomes in procedure completion
Dexmedetomidine versus midazolam[20]	Dexmedetomidine versus midazolam	Dexmedetomidine showed superior anxiety reduction in children undergoing laceration repair	Dexmedetomidine: better anxiety control in some cases	Midazolam: less effective in anxiety reduction
Intranasal midazolam versus ketamine[21]	Midazolam versus ketamine	Midazolam provided higher initial sedation but no significant difference in procedure completion rates	Midazolam: quick onset of sedation	No significant difference in procedure success
Cao et al (midazolam versus clonidine)[22]	Midazolam (0.5 mg/kg) versus clonidine (2 μg/kg and 4 μg/kg)	Clonidine provided better sedation, parental separation, and mask acceptance. Midazolam resulted in better postoperative analgesia but increased incidence of shivering	Clonidine: superior preoperative sedation; fewer side effects	Midazolam: higher incidence of shivering; better analgesia
Midazolam versus placebo[8]	Midazolam (0.04 mg/kg IV) versus placebo	Midazolam significantly reduced postoperative nausea and increased patient satisfaction compared to placebo. No evidence of retrograde amnesia	Midazolam: Reduced postoperative nausea and vomiting; higher patient satisfaction	No major disadvantages reported compared to placebo

In terms of safety, midazolam presents a range of potential risks that must be carefully managed, particularly in vulnerable populations. Paradoxical reactions, although uncommon, are one of the more concerning adverse effects.[23] These reactions include unexpected agitation, disinhibition, aggression, and even violent behavior, which can be particularly distressing in clinical settings. Such responses are more likely to occur in specific patient groups, including pediatric patients and the elderly, whose central nervous systems may respond unpredictably to benzodiazepines.[24,25] In these populations, the balance between sedation and stimulation is delicate, and midazolam's impact on GABAergic pathways may occasionally produce paradoxical excitement instead of sedation.

One of the most significant risks associated with midazolam is its potential to cause respiratory depression, especially when used in higher doses or combined with other central nervous system depressants, such as opioids.[26] This is particularly hazardous in patients with pre-existing respiratory conditions, including chronic obstructive pulmonary disease (COPD), asthma, or sleep apnea, where respiratory function is already compromised. The risk is heightened in cases where multiple sedative agents are used concurrently during anesthesia, as the cumulative depressive effect on the respiratory system can lead to hypoxia or even respiratory arrest if not promptly managed.

Over sedation is another critical concern, especially in patients with cardiovascular instability.[14] Excessive sedation can lead to hypotension, which in turn may compromise organ perfusion, leading to potentially severe outcomes such as ischemic injury. This is of particular concern in elderly patients or those with underlying cardiovascular diseases, where maintaining stable hemodynamics is essential for reducing perioperative complications.[27] Additionally, over sedation can increase the likelihood of postoperative delirium, cognitive impairment, or prolonged recovery, all of which are detrimental to patient outcomes, particularly in ambulatory or outpatient procedures where rapid recovery is desired.

To mitigate these risks, the benzodiazepine antagonist flumazenil is available as a reversal agent for midazolam.[28,29] Flumazenil competitively inhibits the binding of benzodiazepines to the GABA receptor, effectively reversing sedation and other central nervous system effects caused by midazolam. However, the use of flumazenil is not without its own risks, including the potential for seizures, particularly in patients with a history of long-term benzodiazepine use or in those with underlying seizure disorders.[30] Therefore, the administration of midazolam must be accompanied by careful dosing and vigilant monitoring to ensure that any signs of oversedation or respiratory depression are detected early, allowing for timely intervention. Proper patient selection, individualized dosing based on comorbidities,

and continuous monitoring of vital signs are crucial strategies in minimizing the risks associated with midazolam administration.

In light of the limitations and risks associated with pharmacological agents like midazolam, there is growing interest in non-pharmacological interventions for managing preoperative anxiety. Cognitive-behavioral therapy (CBT), mindfulness-based interventions, and music therapy are emerging as viable alternatives.[31] These strategies offer the advantage of reducing anxiety without the side effects linked to pharmacological agents. However, practical challenges such as the need for specialized training and patient cooperation may limit their widespread adoption in clinical practice. Additionally, the effectiveness of these interventions can vary based on individual patient factors, cultural contexts, and resource availability.

CONCLUSION

In summary, while midazolam remains a widely used and effective agent for preoperative sedation and anxiety management, its clinical implications are complex. The current evidence base reveals both strengths and limitations, highlighting the need for further research to clarify its role in preoperative care. Comparative studies with alternative sedatives and exploration of non-pharmacological approaches may provide valuable insights into optimizing preoperative anxiety management and improving patient outcomes. As the field evolves, a balanced approach that integrates both pharmacological and non-pharmacological strategies will likely offer the most comprehensive solution for managing preoperative anxiety and ensuring effective sedation.

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