Original Research Paper

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Comparison of Oral Midazolam and Diazepam for Anxiety Management in Minor Oral Surgical Procedures: A Randomized Controlled Trial

Abstract:

Purpose: To compare the anxiolytic efficacy, effects on vital signs, retrograde amnesia, and postoperative pain of oral midazolam (7.5 mg) versus oral diazepam (5 mg) in patients undergoing minor oral surgical procedures.Midazolam's potential co-analgesic effect has been explored in previous dental sedation literature.

Materials and Methods : This prospective, randomized, parallel-design controlled trial enrolled 128 patients (64 per group) undergoing various minor oral surgeries at the Department of Oral and Maxillofacial Surgery, Sudha Rustagi College of Dental Sciences and Research, Faridabad. Patients received either 5 mg oral diazepam (Group I) or 7.5 mg oral midazolam (Group II) 30 minutes preoperatively Anxiety levels were assessed using the Corah Dental Anxiety Scale (pre-medication) and the Depression, Anxiety, and Stress Scale (DASS) (post-procedure). Vital signs (blood pressure, heart rate, oxygen saturation) were monitored at four distinct time points: before sedation, 30 minutes post-medication, during the surgical procedure (at 30-minute intervals), and 15 minutes post-procedure Retrograde amnesia was evaluated using a 6-image recall test, and postoperative pain was assessed using a Numerical Rating Scale (NRS). Statistical analysis was performed using SPSS version 21, employing independent t-tests, repeated measures ANOVA, Mann Whitney U test, and Wilcoxon test, with significance set at $p<0.05$.

Results: Both midazolam and diazepam significantly reduced anxiety levels from baseline ($p<0.001$ intragroup for both), with no statistically significant difference between the groups in anxiety reduction ($p=0.939$ intergroup). Oxygen saturation remained stable and within physiological limits in both groups across all time points (all $p>0.05$). Significant intergroup differences were observed in heart rate during surgery ($p=0.045$) and 15 minutes post-surgery ($p=0.005$), with the diazepam group exhibiting a more sustained reduction. Systolic blood pressure showed a more pronounced initial reduction with midazolam, while the diazepam group experienced a significant rebound above baseline post-surgery ($p=0.008$). Retrograde amnesia levels were comparable between the two groups ($p=0.909$). Notably, the midazolam group reported significantly lower mean postoperative pain scores compared to the diazepam group ($p=0.001$).

Conclusions: Both oral midazolam (7.5 mg) and oral diazepam (5 mg) are equally effective in providing anxiolysis for minor oral surgical procedures. Midazolam demonstrated a distinct advantage in reducing postoperative pain, while both drugs maintained stable oxygenation and comparable levels of retrograde amnesia.

Key-words: Oral Midazolam; Diazepam; Dental Anxiety; Minor Oral Surgery; Conscious Sedation; Anxiolysis; Benzodiazepines.

Introduction:

Dental anxiety is a significant concern in minor oral surgical procedures. [1] Benzodiazepines are widely employed for anxiolysis in dental practice due to their sedative, amnestic, and anxiolytic properties, coupled with a low risk of respiratory depression and ease of oral administration, making them suitable for outpatient procedures. [2] Midazolam, a short-acting benzodiazepine, provides rapid anxiolysis, anticonvulsant, and muscle relaxant effects but may induce airway obstruction or cardiovascular depression at higher doses. [3] Diazepam, in contrast, is long-acting, less sedative,

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strongly anxiolytic, rapidly absorbed, and stabilizes cardiovascular function through phosphodiesterase-4 inhibition, whereas midazolam decreases systemic vascular resistance via sympathetic depression. [4] Accurate assessment of dental anxiety using validated scales is therefore critical for optimizing sedative selection and minimizing hemodynamic perturbations. [5] This study aims to compare the anxiolytic efficacy and cardiovascular effects of oral midazolam and diazepam in patients undergoing minor oral surgical procedures, to guide evidence-based selection of preoperative sedation. [5]

Study Design and Ethical Approval:

This investigation was a prospective, randomized, parallel-design controlled trial conducted at the Department of Oral and Maxillofacial Surgery, Sudha Rustagi College of Dental Sciences and Research, Faridabad, Haryana, India. [6]

The study protocol received rigorous review and approval from the Institutional Ethics Committee (Sudha Rustagi College of Dental Sciences & Research). [7] All procedures adhered strictly to the ethical principles outlined in the Declaration of Helsinki and conformed to the Consolidated Standards of Reporting Trials (CONSORT) guidelines for transparent clinical trial reporting. [7]

Sample Size Determination:

The appropriate sample size for this investigation was determined using GPower software (version 3.0). [8] The calculation focused on achieving adequate statistical power to detect meaningful differences in heart rate, which was designated as the primary physiological outcome. [8]

A minimum total sample size of 128 participants was determined to be sufficient, with an equal allocation of 64 participants per group. [9]

Patient Selection:

Inclusion Criteria

Participants were selected based on the following:

Age: 18 to 60 years. [10]

Health Status: Classified as ASA Physical Status I or II (generally healthy or with mild systemic disease). [10]

Procedure Type: Undergoing minor oral surgical procedures, including, but not limited to:

Surgical extractions and impactions

Treatment for periapical pathology and apicectomy

Alveoloplasty and ridge augmentation

Incisional/excisional biopsy of small lesions

Dental implant placement [10]

Exclusion Criteria:

Patients were excluded if they presented with any local or systemic conditions that contraindicate the planned surgery or the study drugs. Specific exclusions included:

Comorbidities: Active cardiac disease, cirrhosis of the liver, chronic kidney disease (CKD), Tuberculosis, Leukemia, immunocompromised status, or any other debilitating medical condition. [11]

Medication Use: Long-term steroid medication or adrenergic antagonists within the 15 days preceding the study. [11]

Other Conditions: Uncontrolled diabetes or pregnancy. [11]

Group Allocation and Intervention Protocols:

A total of 128 participants were randomly allocated into two equal groups (n=64 each) using a parallel-design methodology. [8] The study was conducted as a double-blind trial, ensuring both the patients and the outcome assessors were blinded to the treatment allocation. [6]

Intervention Protocol:

The assigned sedative medication was administered orally 30 minutes prior to the commencement of the surgical procedure for both groups: [6]

Group I (n=64): Received 5mg of oral Diazepam. [12]

Group II (n=64): Received 7.5mg of oral Midazolam. [13]

Surgical Procedures:

The study encompassed a range of minor oral surgical procedures. Prior to all interventions, standard antisepsis protocols were strictly followed, including Povidone Iodine application and 0.2% Chlorhexidine mouthwash. Local anesthesia utilized 2% lignocaine hydrochloride with 1:200,000 adrenaline, specifically tailored to the surgical site. [14]

Key Procedures and Techniques:

Procedure Description and Key Steps

Surgical Impactions:

Managed with mandibular anesthesia (IANB, LNB, LBB), full-thickness flap elevation (Ward's Incision), bone guttering (e.g., 703 burr), tooth sectioning, thorough debridement, irrigation (sterile saline), and primary closure (3-0 braided silk sutures).

Alveoloplasty:

Pre-prosthetic procedure to reshape and smooth the jawbone. Included mucoperiosteal flap elevation, bone reduction

(rongeurs/bone file), copious irrigation, and primary closure (3-0 braided black silk suture).

Ridge Augmentation

Restoration of the alveolar ridge contour, typically post-extraction. Involved placing bone graft material in the socket, covering with soft tissue, and securing with sutures.

Periapical Pathology Surgery

Intervention (Apical Osteotomy, Apicectomy, Root Resection) for failed endodontics. Steps included incision, flap elevation, ostectomy, periapical curettage to remove necrotic tissues, and primary suturing.

Incisional/Excisional Biopsy

Removal of a portion (incisional) or the entirety (excisional) of a lesion for histological examination. Techniques involved wedge or punch biopsies, achieving hemostasis, and primary closure

Dental Implant Placement

Involved a crestal incision, flap elevation, a controlled drilling sequence, implant insertion (torqued), cover screw placement, and closure (3-0 silk sutures). Radiographic confirmation was used during the drilling sequence

Outcome Parameters and Data Collection

The study meticulously collected data on several key outcome parameters to comprehensively evaluate the effects of the two anxiolysis protocols. [15].

1. Anxiety Assessment

Anxiety levels were assessed using two validated scales at distinct time points: [5]

Pre-operative Anxiety: Measured using the Corah Dental Anxiety Scale (Corah DAS), completed before any medication administration. [5]

Post-operative Anxiety: Measured using the Depression, Anxiety, and Stress Scale (DASS) questionnaire, completed approximately 15 minutes after the surgical procedure. [5].

2. Vital Sign Monitoring

The following vital signs were recorded at four distinct time points (Before Sedation, 30 minutes Post-Sedation, During Procedure, 15 minutes Post-Procedure) to capture dynamic physiological responses: [11]

Systolic Blood Pressure (SBP) [11]

Diastolic Blood Pressure (DBP) [11]

Heart Rate (HR) [11]

Oxygen Saturation (SpO2) [14]

3. Pain Assessment:

Postoperative pain was assessed using a Numerical Rating Scale (NRS). [10]

4. Retrograde Amnesia Assessment:

Retrograde amnesia was evaluated using a 6-image recall test with the following protocol: [8]

Pre-Sedation: Three distinct images (an apple, a car, and a swimming scene) were shown to the patient. [8]

Post-Sedation (30 mins): Another three different images (an airplane, a watermelon, and a football game scene) were presented. [8]

After Procedure: Patients were shown all six previously seen images mixed with six new images (total 12). They were asked to identify the previously seen images. [8]

Scoring: A total recall score was recorded, ranging from 0 (no images recalled) to 6 (all 6 images correctly recalled), allowing for comparison of amnesia levels between the groups. [8]

Statistical Analysis:

All collected data were subjected to statistical analysis using the Statistical Package for Social Sciences (SPSS) version 21. [16].

Descriptive Analysis:

Data for all outcome measures (including blood pressure, heart rate, oxygen saturation, anxiety, amnesia, and pain scores) were summarized using descriptive statistics, specifically means and standard deviations. [16].

Inferential Analysis:

Inferential statistical methods were employed to compare groups and assess changes over time:

Independent t-test: Used for intergroup comparisons of continuous variables to assess significant differences between Group I (Diazepam) and Group II (Midazolam) at specific time points. [16]

Repeated Measures ANOVA: Applied for intragroup comparisons over time, enabling the analysis of changes within each group across the four measurement intervals. [16]

Mann-Whitney U Test & Wilcoxon Test: These non-parametric tests were utilized for specific comparisons where data distribution required it, or for ordinal data. [16]

The level of statistical significance for all analyses was set at $p<0.05$. [16].

Results:

The study successfully enrolled 128 participants, with 64 individuals allocated to Group I (Diazepam, 5 mg) and 64 to Group II (Midazolam, 7.5 mg). Baseline demographic characteristics were comparable between the two intervention groups, ensuring that any differences observed in the outcome parameters could be attributed to the drug interventions. [9] Key Intragroup Findings (Change from Baseline) [11]

Heart Rate (HR): Both groups showed a significant decrease in HR after 30 minutes post-medication and during surgery ($p<0.001$). Only Group I maintained a significant, albeit smaller, decrease 15 minutes post-surgery ($p=0.013$). [11]

Systolic Blood Pressure (SBP): Both groups showed highly significant drops in SBP 30 minutes post-medication and during surgery ($p<0.001$). [12]

Diastolic Blood Pressure (DBP): Both groups showed highly significant drops in DBP 30 minutes post-medication and during surgery ($p<0.001$). [12]

Oxygen Saturation (SpO2): Neither group showed a statistically significant change in (SpO2 from baseline across any time point (p-values}> 0.05). [14]

Discussion

Principal Findings

This study compared oral midazolam (7.5 mg) and diazepam (5 mg) for anxiety management in minor oral surgery. Both agents were equally effective in achieving anxiolysis and maintaining stable oxygen saturation (SpO2). [15] Key differences were noted in pain and cardiovascular response. [11].

Core Comparative Outcomes

Outcome Parameter

Midazolam (7.5 mg) vs. Diazepam (5 mg)

Key Finding Anxiolytic Effect

Equivalent ($p=0.939$)

Both drugs were highly effective at reducing anxiety. [15]

Postoperative Pain

Midazolam superior ($p=0.001$)

Midazolam significantly lowered post-operative pain (NRS 1.03) compared to Diazepam (NRS 2.02), suggesting a co-analgesic effect. [10]

Heart Rate (HR)

Diazepam difference sustained

Diazepam led to a more sustained reduction in HR. [12]

Systolic BP (SBP)

Midazolam difference significant

Midazolam caused a greater initial drop in SBP and was better at preventing postoperative SBP rebound. [11]

Retrograde Amnesia

Equivalent ($p=0.909$)

No significant intergroup difference was detected. [8]

Clinical Implications

The findings offer clear guidance for selecting between oral midazolam and diazepam for anxiolysis in minor oral surgery: [16]

Midazolam (7.5 mg) Preference: Should be the preferred agent when postoperative pain control, a faster onset/recovery profile, or a more pronounced initial reduction in Systolic Blood Pressure (SBP) is a clinical priority. [13]

Diazepam (5 mg) Preference: Remains a suitable alternative when the primary goal is a more sustained heart rate reduction or a milder overall hypotensive effect. [12]

Safety: Both agents are confirmed to be safe and effective for anxiety reduction in ASA I/II patients. [16]

Individualization: The final choice must be individualized based on the patient's specific comorbidities (e.g., pre-existing hypertension or tachycardia), the nature of the surgical procedure, and anticipated recovery needs. [16]

The present study compared the anxiolytic efficacy of two commonly prescribed benzodiazepines—oral diazepam (5 mg) and oral midazolam (7.5 mg)—administered as premedication in minor oral surgical procedures. The study population demonstrated excellent baseline comparability, with no significant differences in age (23.02 ± 6.085 vs. 22.44 ± 4.261 years; $p = 0.535$) or gender distribution (71.9% vs. 64.1% female; $p = 0.224$), minimizing potential confounding. The predominance of female participants (68%) aligns with existing literature suggesting higher anxiety prevalence or greater health-seeking behavior among women. [13]

Both diazepam and midazolam demonstrated statistically significant and clinically meaningful reductions in anxiety scores. Group I (diazepam) showed a reduction from 14.31 ± 1.612 to 11.52 ± 1.141, while Group II (midazolam) decreased from 14.48 ± 1.877 to 11.53 ± 1.181, with no significant intergroup difference ($p = 0.939$), indicating equipotent anxiolytic efficacy at the studied doses. [15] The observed ~20% reduction from baseline meets recognized clinical thresholds for effective anxiety management. [5] These findings are in agreement with Araújo et al., who reported satisfactory anxiety reduction using midazolam (7.5–15 mg), clonidine (150 µg), and alprazolam (0.5–0.75 mg). [5]

Both agents maintained excellent oxygen saturation stability throughout all perioperative phases ($p > 0.05$), reflecting favorable respiratory safety profiles. [14] However, notable cardiovascular differences were observed. Diazepam produced a greater and more sustained heart rate reduction intraoperatively (72.28 ± 6.79 vs. 73.80 ± 7.38; $p = 0.045$) and postoperatively (76.56 ± 6.99 vs. 78.91 ± 7.25; $p = 0.005$), likely attributable to its longer half-life and active metabolites. [12] Conversely, midazolam, with a shorter elimination half-life, elicited a more pronounced hypotensive response, reducing systolic blood pressure by - 10.63 mmHg versus - 7.52 mmHg for diazepam ($p < 0.001$), and maintaining lower pressures postoperatively (- 4.46 mmHg vs. +4.62 mmHg rebound; $p = 0.008$). These hemodynamic trends may reflect differences in potency and receptor affinity. [11] The findings partially concur with prior cardiovascular observations with benzodiazepines. [12]

Pain assessment revealed significantly lower mean pain scores in the midazolam group (1.03 ± 0.234) compared with diazepam (2.02 ± 0.128; $p = 0.001$). [10] To date, direct head-to-head published studies comparing postoperative pain outcomes between diazepam and midazolam in minor oral surgery remain limited, underscoring the relevance of these present findings. Retrograde amnesia scores were comparable between groups (5.02 ± 0.678 vs. 5.03 ± 0.854; $p = 0.909$), contrasting with some earlier work that described stronger amnestic effects with midazolam. [8] Both regimens demonstrated excellent safety, with no adverse events observed, consistent with reports of benzodiazepine use for dental sedation in outpatient settings. [16]

Clinically, both 5 mg oral diazepam and 7.5 mg oral midazolam offer equivalent, clinically significant anxiolysis in minor oral surgery. Agent selection may thus be individualized: midazolam may be preferred for patients requiring stronger intraoperative blood pressure control or shorter recovery, while diazepam's prolonged action and greater heart rate stabilization may benefit those with tachycardic tendencies. Both maintain satisfactory safety and amnestic profiles, supporting their use in outpatient oral surgery. [16]

Study Appraisal (Strengths and Limitations)

Strengths:

Robust Design: Conducted as a randomized controlled trial (n=128), ensuring adequate statistical power and minimizing selection bias. [6]

Comprehensive Outcomes: Assessed a broad range of critical parameters, including anxiety, all major vital signs, amnesia, and pain. [15]

Standardization: Utilized validated assessment scales and maintained consistency by having all surgical procedures performed by a single surgeon. [14]

Objectivity: Blinding of patients and outcome assessors enhanced the objectivity of the results. [6]

Limitations:

Subjectivity: Reliance on patient-reported, subjective scales (Corah DAS, DASS, NRS) for measuring anxiety and pain. [5]

Biomarkers: Lacked objective measures of anxiety (e.g., cortisol levels). [16]

Amnesia Focus: Focused on retrograde amnesia; the more clinically relevant anterograde amnesia was not specifically evaluated. [8]

Single-Center Scope: Being a single-center study, the generalizability of the findings may be limited. [6]

Route-specific pharmacokinetic variations (IV, IM, oral) and patient-specific variables (age, weight, comorbidities) were not analyzed, reducing clinical generalizability. [16]

Limited Doses & Recovery: Only specific oral doses were tested, and comprehensive psychomotor recovery or patient satisfaction measures were omitted. [16]

The study successfully enrolled 128 participants, with 64 individuals allocated to Group I (Diazepam, 5 mg) and 64 to Group II (Midazolam, 7.5 mg). Baseline demographic characteristics were comparable between the two intervention groups, ensuring that any differences observed in the outcome parameters could be attributed to the drug interventions.

Table 1: Baseline Demographics and Key Outcomes (Mean \pm SD)

This table summarizes the participant demographics (Age, Gender) and the final single-point outcome measures (Amnesia, Post-Op Pain).

Parameter	Group I (Diazepam, n=64)	Group II (Midazolam, n=64)	Intergroup p-value	Conclusion
Age (years)	23.02 \pm 6.09	22.44 \pm 4.26	0.535	Not Significant
Gender (Female: Male N)	46:18 (71.9\%: 28.1\%)	41:23 (64.1\%: 35.9\%)	0.224	Not Significant
Pre-Op Anxiety (Corah DAS)	14.31 \pm 1.61	14.48 \pm 1.88	0.579	Not Significant
Retrograde Amnesia (Score 0-6)	5.02 \pm 0.68	5.03 \pm 0.85	0.909	Not Significant
Post-Op Pain (NRS Score)	2.02 \pm 0.13	1.03 \pm 0.23	0.001	**Significantly Different**

Table 2: Comparison of Anxiety Scores (Intergroup and Intragroup)

Outcome / Time Point	Group I (Diazepam, n=64) Mean \pm SD	Group II (Midazolam, n=64) Mean \pm SD	Intergroup p-value	Intragroup p-value (Pre vs. Post)
Pre-Op Anxiety (Corah DAS)	14.31 \pm 1.61	14.48 \pm 1.88	0.579	{N/A}
Post-Op Anxiety (DASS)	11.52 \pm 1.14	11.53 \pm 1.18	0.939	{N/A}
Anxiety Reduction (\Delta Mean)	-2.79	-2.95	0.939 (Difference)	<0.001 (Both Groups)

Interpretation: Both groups showed a highly significant reduction in anxiety from pre-op to post-op ($p<0.001$), but the magnitude of the reduction was not significantly different between the Midazolam and Diazepam groups ($p=0.939$ for Post-Op scores).

Table 3: Intergroup Comparison of Vital Signs Across All Time Points (Mean \pm SD)

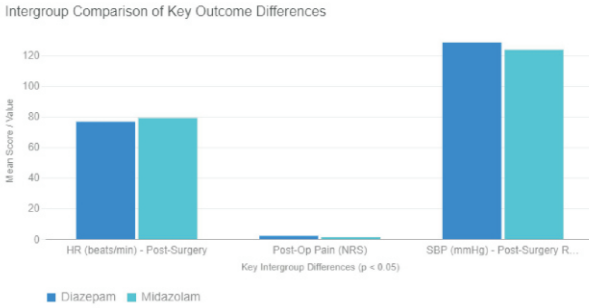
This table consolidates the intergroup results for Heart Rate (HR), Oxygen Saturation (SpO2), Systolic Blood Pressure (SBP), and Diastolic Blood Pressure (DBP).

Vital Sign	Time Point	Group I (Diazepam) Mean \pm SD	Group II (Midazolam) Mean \pm SD	Intergroup p-value
HR (beats/min)	Before Sedation	78.63 \pm 7.25	77.06 \pm 8.58	0.268
	30 mins Post-Medication	72.95 \pm 6.63	73.98 \pm 7.20	0.401
	During Surgery	72.28 \pm 6.79	73.80 \pm 7.38	0.045
	15 mins Post-Surgery	76.56 \pm 6.99	78.91 \pm 7.25	0.005
SBP (mmHg)	Before Sedation	123.66 \pm 14.47	127.94 \pm 12.76	0.078
	30 mins Post-Medication	116.14 \pm 12.46	118.02 \pm 11.66	0.032
	During Surgery	116.50 \pm 13.60	117.31 \pm 12.37	0.724
	15 mins Post-Surgery	128.28 \pm 14.06	123.48 \pm 13.41	0.049
DBP (mmHg)	Before Sedation	78.73 \pm 11.30	79.63 \pm 11.74	0.663
	30 mins Post-Medication	72.63 \pm 8.90	73.28 \pm 9.79	0.692
	During Surgery	71.78 \pm 9.20	72.81 \pm 10.09	0.547
	15 mins Post-Surgery	80.38 \pm 12.06	79.38 \pm 11.71	0.635
SpO_2 (%)	All Time Points	Range: 97.36 { to } 97.63	Range: 97.41{ to } 97.63	Range: 0.339 { to } 1.00

Key Intragroup Findings (Change from Baseline)

- **Heart Rate (HR):** Both groups showed a significant decrease in HR after 30 minutes post-medication and during surgery ($p<0.001$). Only Group I maintained a significant, albeit smaller, decrease 15 minutes post-surgery ($p=0.013$).
- **Systolic Blood Pressure (SBP):** Both groups showed highly significant drops in SBP 30 minutes post-medication and during surgery ($p<0.001$).
- **Diastolic Blood Pressure (DBP):** Both groups showed highly significant drops in DBP 30 minutes post-medication and during surgery ($p<0.001$).

Oxygen Saturation (SpO2): Neither group showed a statistically significant change in (SpO2 from baseline across any time point (p-values}> 0.05



Conclusion:

This study presents a comparative evaluation of oral midazolam (7.5 mg) and oral diazepam (5 mg) as preoperative sedatives in minor oral surgical procedures. Both benzodiazepines produced significant and comparable reductions in preoperative anxiety, confirming their efficacy as reliable agents for anxiolysis. [15] Physiological monitoring showed stable oxygen saturation across groups, with diazepam eliciting a steadier decrease in heart rate, while midazolam induced a more pronounced yet transient reduction in blood pressure. [12][11] These cardiovascular distinctions suggest diazepam may be advantageous in patients susceptible to tachycardia, whereas midazolam could be preferred when controlled hypotension is desirable. [12][13] Both agents also demonstrated similar effects on retrograde amnesia and maintained excellent safety profiles, with no adverse events observed. [8][16] Overall, the findings reinforce the clinical utility of both diazepam and midazolam as safe, effective, and well-tolerated options for managing preoperative anxiety in dental practice. [16]

Future Research Directions:

Future research should aim to expand on these findings through several key avenues. Dose and route optimization studies could explore varying dosages, alternative administration methods such as intravenous delivery, and potential combination regimens to identify synergistic effects. [21] Incorporating objective biomarkers like cortisol levels may enhance the accuracy of anxiolysis assessment, while validated tools for evaluating psychomotor recovery and patient satisfaction would provide a more comprehensive understanding of postoperative outcomes. [18] Further investigation into the mechanisms underlying midazolam's co-analgesic potential could clarify its broader clinical benefits. [10] Additionally, exploring novel combination protocols—such as pairing midazolam with agents like dexmedetomidine—may improve efficacy, hemodynamic

stability, and recovery times. Finally, future trials should include more diverse patient populations, particularly those classified as ASA III, to ensure wider applicability of the results. [21]

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