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Original Research Article

Effect of Midazolam as Premedication in Patients Undergoing Breast Conservation Surgery

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Abstract:
Background: Anxiety before surgery is prevalent in women with breast cancer, which can become a source of unfavorable outcomes in the perioperative setting. While benzodiazepines are common medications administered in pharmacological anxiolysis, their efficacy is questionable in adult surgical patients.***Objective***: To investigate whether intravenous midazolam (0.05 mg/kg) premedication can suppress the preoperative state of anxiety as assessed by the Amsterdam Preoperative Anxiety and Information Scale (APAIS) and enhance postoperative satisfaction as measured by the Leiden Perioperative Patient Satisfaction questionnaire (LPPSq) in female patients with breast conserving surgical procedures. ***Methods***: In this single-blind randomized controlled clinical study, 124 female participants scheduled to undergo breast conservation surgery received intravenous midazolam (62) or a saline placebo (62) before anesthetic induction after random allocation to treatment groups. Anxiety was measured using the APAIS before and after the administration of the medication. The LPPSq study for postoperative satisfaction was performed on the day of surgery or the first postoperative day. The study used the independent t-test and chi-square test for analysis with a significance threshold of $p < 0.05$. ***Results***: The demographic and clinical factors, and APAIS scores at baseline, were not significantly different among the groups ($p > 0.05$). The APAIS scores following premedication were found to be lower in the midazolam group than the placebo group (baseline scores: 9.5 ± 2.5 vs. 13.8 ± 2.9; $p < 0.001$). None of the patients in the midazolam group had scores for very high anxiety levels, whereas 9 (14.5%) of patients receiving the placebo had scores for high anxiety levels ($p = 0.005$). The mean LPPSq scores were also higher among patients of the midazolam group (85.2 ± 8.4 vs. 78.0 ± 10.1; $p < 0.001$), and more patients expressed satisfaction. There were no adverse events reported. ***Conclusion***: Premedication with midazolam is efficacious in reducing preoperative anxiety and increasing patient satisfaction after breast-conserving surgery in women. The results establish its selective usage as an anxiolytic agent, but caution is recommended while administering it, particularly in the elderly or fragile population.

Keywords: Midazolam; Perioperative Anxiety; Breast-Conserving Surgery; Anesthetic Premedication; Patient Satisfaction; Anxiolysis

INTRODUCTION

Preoperative anxiety is widely established and has a significant influence on surgical outcomes. According to meta-analyses, around 60-80% of adult surgical patients experience clinically significant anxiety before their procedures [1, 2]. This anxiety can be exacerbated during breast cancer surgery, when psychological distress arises not only from the

upcoming surgical experience but also from disease-related concerns such as fear of cancer recurrence, changed body image, and loss of femininity [3]. Fear of anesthesia, postoperative discomfort, and uncertainty about the results all contribute to the overall preoperative emotional load.

Elevated anxiety has been associated with numerous adverse perioperative outcomes. Some of the adverse outcomes are longer hospital stays, increased postoperative pain perception, delayed anesthesia recovery, and increased anesthetic and analgesic medication requirements [4, 5]. One of the main objectives of contemporary perioperative treatment is the efficient management of preoperative anxiety due to its substantial influence on both physiological and psychological outcomes.

Benzodiazepines, particularly midazolam, remain the most often used drugs to treat anxiety. Midazolam is a short-acting benzodiazepine that has sedative, amnestic, and anxiolytic effects via acting on the GABA receptor complex. It is perfect for preoperative use, especially in ambulatory and short-stay surgical settings, due to its rapid onset and short duration of action [6].

However, the efficiency of systematic benzodiazepine premedication has been questioned in recent years. Several randomized controlled trials and systematic reviews have shown conflicting conclusions. In a large randomized controlled trial of elderly surgical patients, van Vlymen et al. reported that low-dose oral midazolam did not substantially improve patient satisfaction and was associated with delayed psychomotor recovery [7]. Similarly, Dahlem et al. found that midazolam had minimal influence on postoperative recovery patterns, except for a quicker anesthetic induction [8]. Other studies, however, have shown that midazolam effectively reduces anxiety and enhances patient satisfaction, especially in cases with high baseline anxiety levels [9, 10].

This discrepancy in outcomes suggests that midazolam's effectiveness may be context-dependent, influenced by factors such as patient age, baseline anxiety, dose method, and kind of procedure [11]. Concerns over the adverse effects of benzodiazepines in certain populations are also growing. Well-known side effects include oversedation, respiratory depression, and surgical delirium, particularly in older patients [12]. Because of this, worldwide anesthetic guidelines recommend a more tailored strategy rather than the usual use of benzodiazepines in older adults [13].

Alternative anxiolytic approaches have gained popularity. While dexmedetomidine, a selective alpha-2 agonist, offers strong anxiolysis and analgesia with reduced respiratory depression, albeit with a slower onset and a risk of bradycardia [14], melatonin has been demonstrated to reduce anxiety with a more favorable cognitive side effect profile [15]. Non-pharmacological treatments, such as cognitive-behavioral therapy, guided imagery, and music therapy, are becoming increasingly recognized as useful adjuncts or alternatives [16].

Despite these developments, midazolam is still widely used in clinical practice, particularly where quick and consistent anxiolysis is required. The emotional impact of breast-conserving surgery (lumpectomy) might worsen preoperative anxiety. However, there is a scarcity of high-quality RCTs, especially addressing anxiolytic premedication in this cohort.

To close this gap, we undertook a prospective, single-blind, randomized controlled experiment to see if intravenous midazolam premedication (0.05 mg/kg) decreases preoperative anxiety and increases patient satisfaction in women undergoing breast-conserving surgery. Anxiety was examined using the Amsterdam Preoperative Anxiety and Information Scale (APAIS), a validated tool for surgical patients, and satisfaction with anesthetic care was analyzed using the Leiden Perioperative Patient Satisfaction Questionnaire (LPPSq). We hypothesized a priori that midazolam would reduce preoperative anxiety and increase patient satisfaction without serious adverse effects.

METHODOLOGY:

Study Design and Participants

This prospective single-blind RCT included adult female patients (ages 18-70) scheduled for breast conservation surgery at Shaukat Khanum Memorial Cancer Hospital in Lahore between August 2023 and February 2024. Ethical approval and informed consent were obtained. The RCT was prospectively registered at ClinicalTrials.gov under registration number NCT07184125 (ttps://share.google/IH5np8CTSZyyoSWlm) and followed CONSORT guidelines (Supplementary material) . The main inclusion criteria were proven breast cancer requiring lumpectomy, ASA physical status I-III, and no contraindications to midazolam. Exclusion criteria included persistent benzodiazepine usage, allergic reactions to study medicines, severe hepatic or renal illness, and significant cognitive impairment (Mini-Mental Status Exam <24). Pregnant or lactating women were also excluded.

To detect a mean APAIS difference of ≥2 points (SD ~3) with 80% power and α=0.05, we estimated a sample size of 60 in each group (total 120). We enrolled 124 patients (62 per group) to account for dropouts.

Randomization and blinding

A biostatistician created a random allocation

sequence (1:1) in blocks of ten. The allocations were sealed in opaque envelopes. On the morning of surgery, an anesthesia practitioner who was not involved in the treatment opened the envelope and prepared the study medicine. Patients were randomly allocated to receive intravenous midazolam 0.05 mg/kg (diluted to 5 mL) or 5 mL of normal saline. The anesthesiologist, patient, and data collectors were not aware of the group assignment.

Anesthesia protocol

When the patients arrived in the preoperative holding area, their baseline anxiety was assessed. Premedication (midazolam or placebo) was then given 30 min before induction. Standard monitors (ECG, pulse oximetry, NIBP, and temperature) were used. Anesthesia was induced with IV propofol (2 mg/kg) and fentanyl (1-2 μg/kg), and intubation was aided using a non-depolarizing muscle relaxant as usual. Maintenance consisted of sevoflurane in air/O_2 and opioids (fentanyl or remifentanil) as needed for analgesia. Before incision, all patients were given standard antiemetic prophylaxis (ondansetron and dexamethasone). Intraoperative treatment (fluid, ventilation, and analgesics) was standardized and consistent between groups. Following surgery, patients were extubated in the OR and moved to the PACU for recuperation.

Outcome Measures

Anxiety: Preoperative anxiety was assessed using the Amsterdam Preoperative Anxiety and Information Scale (APAIS) [17], a validated 6-item instrument with two subscales: anxiety about anesthesia and anxiety about operation. Each item is scored 1-5 (higher means greater anxiety), resulting in a total anxiety score (range 4-20). The APAIS was delivered twice: once at pre-op (before premedication) and again soon before entering the OR (30 minutes after premedication). The major anxiety outcome was the post-premedication APAIS total score.

Satisfaction: On the first postoperative day, patient satisfaction was assessed using the LPPSq. This tool has been widely used to quantify patient satisfaction with good reliability and validity [18-20]. The LPPSq is a 20-item questionnaire divided into three areas (information/communication, fear/concern, and staff relationship), with higher scores indicating better satisfaction. We calculated total satisfaction and categorized replies. Patients who stated that they were "very satisfied" or "somewhat satisfied" were classed as satisfied, in line with previous studies. We present satisfaction percentages and average LPPSq scores.

Statistical analysis

Baseline characteristics were compared using t-tests or chi-squares as needed. Anxiety scores (APAIS) were compared using an unpaired t-test (or Mann-Whitney U if not normal). Similarly, the satisfaction scores (LPPSq) were compared. The chi-square test was used to compare proportions (for example, satisfied versus dissatisfied). Statistical significance was determined at $p < 0.05$. We also provide 95% confidence intervals (CIs) for group differences. The analyses were done using SPSS v.25 (IBM) and R v.4.2.

RESULTS

Baseline characteristics

124 patients were randomized (62 midazolam, 62 placebo). All completed the study. Groups were similar in age (mean 49±8 vs. 50±9 years, p= 0.55), BMI, ASA status, cancer stage, and type of breast conservation procedure (Table 1). Baseline APAIS anxiety scores did not differ significantly (midazolam 15.0±3.0 vs. placebo 15.3±3.2; p= 0.72), indicating comparable premedication anxiety. Other perioperative variables (baseline blood pressure, heart rate, previous anesthesia history) were also balanced (p>0.1 for all comparisons).

Anxiety outcomes (APAIS)

The primary outcome, pre-induction APAIS total score, was significantly lower in the midazolam group. Post-premedication APAIS was 9.5 ± 2.5 in the midazolam group versus 13.8 ± 2.9 in the placebo group (mean difference −4.3, 95% CI −5.3 to −3.3; p<0.001). This indicates a substantial anxiolytic effect.

Sub-scores for anesthesia-related anxiety and surgery-related anxiety were both significantly reduced by midazolam (p<0.001 for each domain). No patient (0%) in the midazolam group had very high anxiety (score ≥16) pre-induction, compared to 9 (14.5%) patients in the placebo group (p=0.005).

Intraoperative hemodynamic variables (heart rate, blood pressure) were similar between groups. No adverse events (over-sedation, hypoxia) occurred in either group during the preoperative period.

Figure 1 (embedded below) shows group mean APAIS scores with SD error bars. The anxiety reduction was clinically and statistically significant.

Patient satisfaction (LPPSq)

Overall satisfaction was greater in the midazolam group. The LPPSq assessed 53 patients (85.5%) in the midazolam group as being very or somewhat satisfied compared with 38 patients (61.3%) in the placebo group [absolute difference +24.2%, 95% CI 10.1–38.3%, p = 0.005]. The mean LPPSq score was also significantly higher for the midazolam group (85.2 ± 8.4) than for the placebo group (78.0 ± 10.1, p < 0.001). As a result, there is increased satisfaction in all three LPPSq domains: Information, Care, and Confidence in the midazolam group (p < 0.01 for each domain).

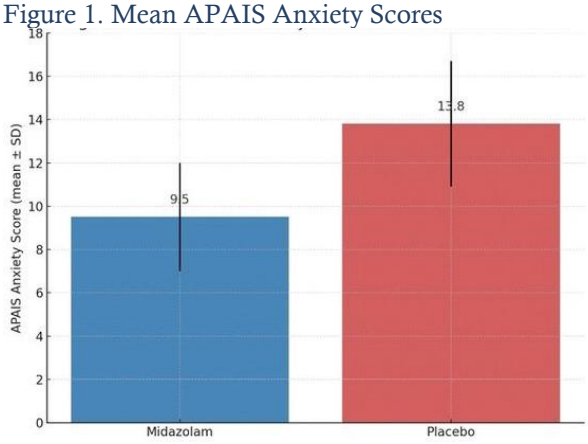
As presented in Table 2, the percentage of patients who were completely satisfied was higher for the midazolam group (37 patients [59.7%]) than for the placebo group (19 patients [30.6%]), while neutral or dissatisfied responses were less common (12 patients [19.4%] vs. 24 patients [38.7%], respectively).

Table 1. Baseline Demographic and Clinical Characteristics (n=124)

Data are presented as mean ± SD or n (%). p-values by t-test or chi-square test.

Characteristic	Midazolam (n=62)	Placebo (n=62)	p-value
Age (years)	49.2 ± 7.8	50.1 ± 9.0	0.55
BMI (kg/m²)	27.5 ± 4.2	28.1 ± 4.5	0.40
ASA I / II (n)	20 (32.3%)	18 (29.0%)	0.68
Stage I / II cancer (n)	35 (56.5%)	32 (51.6%)	0.53
Surgery time (min)	85 ± 15	87 ± 14	0.47
Baseline APAIS score	15 ± 3	15 ± 3.2	0.72

Figure 1. Mean APAIS Anxiety Scores



Mean ± SD anxiety scores in the midazolam vs. placebo groups. Patients receiving midazolam had significantly lower preoperative anxiety ($p < 0.001$).

Category	Midazolam (n=62)	Placebo (n=62)	p-value
Neutral / Dissatisfied (n, %)	7 (11.0%)	24 (39.0%)	0.001

(Chi-square or Fisher's exact test for categorical data.)

Figure 2. Patient Satisfaction (LPPSq)

Pie charts show the proportion of patients reporting "completely satisfied," "satisfied," and "neutral/dissatisfied" in each group.

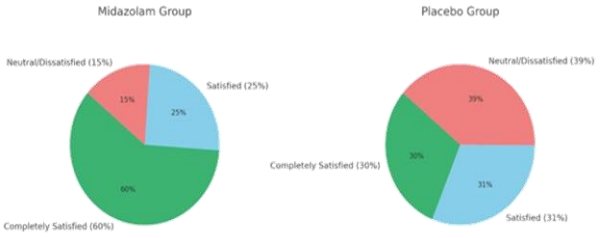


Table 2. Patient Satisfaction (LPPSq) Scores and Categories

Outcome	**Midazolam (n=62)**	**Placebo (n=62)**	**p-value**
Mean LPPSq score (0–100)	85.2 ± 8.4	78.0 ± 10.1	<0.001
Very satisfied (n, %)	37 (60.0%)	19 (31.0%)	0.003
Satisfied (n, %)	18 (29.0%)	19 (31.0%)	0.82

DISCUSSION

This single-blind RCT demonstrated the efficacy of IV midazolam (0.05 mg/kg), significantly reducing preoperative anxiety as determined by APAIS scores and overall patient satisfaction compared to the placebo group among women who had undergone breast-sparing surgeries. Additionally, the midazolam infusion increased the probability of satisfaction and decreased the fraction of patients who were highly anxious without severe adverse outcomes.

Moreover, our result that midazolam causes considerable relief in preoperative anxiety corresponds to several clinical trials as well as systematic reviews that have established the efficacy of midazolam in relieving anxiety. A clinical trial on adult women undergoing general anesthesia resulted in the improvement of patient satisfaction (and thereby the alleviation of anxiety relative to the placebo) by 21% (OR 3.56, 95% CI 1.46-8.70), with greater alleviation of anxiety in more anxious patients (APAIS ≥ 11), much like the initial anxiety level in the subject cohorts.[21] Midazolam had been found effective in most well-designed trials on pediatric patients by the systematic review of the literature by Cox et al., 2025, despite the obvious differences in environment present in pediatric patients relative to adults [22]. The anatomy of anxiety on all age groups consolidates the efficacious GABA antagonism exhibited by midazolam on our adult surgical cohorts.

Nevertheless, there have been some doubts raised by observational trials and those that have not been randomized concerning the common anxiolytic effect of preoperative benzodiazepine administration. For instance, Bucx et al. reported that the administration of anxiolytic-sedative drugs such as midazolam was popular but not evidenced to influence perceived preoperative anxiety [23]. Such observations and differences may be explained by the differences that exist during clinical trials (like the current study) and those which are evident in actual practice.

Our findings of improved satisfaction with midazolam are consistent with those from other trials. Sun et al. reported that intramuscular midazolam administration during general anesthesia increased satisfaction with care among midazolam users, particularly those with higher state anxiety, supporting our finding of increased engagement with information and care [24]. Other RCTs provided evidence consistent with benefits from midazolam administration extending, aside from anxiolysis, to reduced rates of postoperative nausea and vomiting and increased willingness to recommend care, again consistent with our finding. In an ambulatory surgery trial, IV midazolam reduced rates of postoperative nausea and significantly increased the number of patients willing to recommend anesthetic care (85% vs. 42%, $p < 0.001$) [25].

These benefits, notwithstanding, improved satisfaction with the anesthetic procedure is likely related. Concerns may exist because of the potential for oversedation, prolonged recovery times, and respiratory depression in the case of benzodiazepines. As for our research, there were no significant side effects. This agrees with other broader cohort analyses in observing a lack of association for midazolam premedication and the ensuing mortality of patients, though possibly decreasing pre-induction hemodynamic stress, such as systolic blood pressure, in the process.[26] There exist certain RCTs focused on recovery that failed to show benefit in overall quality of recovery for the patient in the use of midazolam, particularly in significant procedures like laparotomy, indicating the efficacy in the alleviation of anxiety does not always significantly impact measurable recovery endpoints.[27]

The anxiolytic effect of midazolam is mediated through its ability to enhance the activity of the GABA_A receptor, resulting in sedative and amnestic effects with a reduction in anticipatory anxiety.[28] The mechanism of action of this drug would be reflected in the study as lower APAIS scores and increased subjective satisfaction, especially in a surgical environment where disease-related anxieties, such as those with breast cancers, may be compounded with stress from the procedure. The APAIS, a valid and sensitive instrument measuring surgery- and anesthesia-related anxiety, would allow the detection of subjective changes, which could be otherwise subtle. Additionally, our method would allow adequate time for the drug to be effective (30 minutes post-dose administration) prior to induction. Most importantly, our study would show no adverse outcomes in the midazolam group, such as oversedation, pulmonary damage, and mental deterioration. This would emphasize the safety of 0.05 mg/kg IVmidazolam when appropriately used.

Clinical implications

The limited use of midazolam in patients undergoing breast surgery who experience preoperative anxiety is supported by our findings. Anxiolytic premedication promotes emotional well-being and contentment, which is consistent with modern, patient-centered perioperative treatment. However, aged or weak patients should exercise caution because benzodiazepines have been linked to delirium and cognitive dysfunction. Melatonin, gabapentinoids, or non-pharmacological approaches (e.g., music therapy, preoperative counseling) may be more appropriate in these groups.

Limitations

This was a single-center study, which may limit its applicability. Only ASA I-III female patients receiving elective breast conservation surgery were enrolled, our findings may not apply to male, geriatric, or high-risk populations. While our midazolam dose was typical, clinical practice varies, and lower or higher doses may elicit different outcomes. Furthermore, we only measured pleasure on postoperative day one, which may not accurately reflect long-term emotional or psychological effects. Finally, LPPSq, while verified, has subjective satisfaction thresholds, and other instruments may produce different results.

CONCLUSION:

Midazolam, when given as a premedication intravenously at 0.05 mg/kg, significantly reduces preoperative anxiety and enhances satisfaction in women having breast-conserving surgery. In our study, significant benefits were discovered with no sedative-related adverse effects. Anxiolytic pre-medication should be taken into consideration due to the high prevalence of anxiety in this group, particularly if the baseline anxiety is moderate to severe. More research is needed to investigate dosage optimization, comparative efficacy to newer pharmaceuticals such as dexmedetomidine or melatonin, and long-term outcomes.

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Conflicts of Interest

The authors have declared no conflicts of interest.

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