Randomized controlled trial assessing the effectiveness of midazolam premedication as an anxiolytic, analgesic, sedative, and hemodynamic stabilizer

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Background: Midazolam premedication is widely used before general anesthesia, but lacks clinical evidence of effectiveness. The present study aimed to evaluate the effectiveness of midazolam premedication following 4 aspects: anxiety reduction, sedation, hemodynamic stabilization, and analgesia.

Methods: In a randomized, single-blind, prospective study, a total of 128 women were allocated to the midazolam premedication group (Group P, n = 64) or the control group (Group N, n = 64). The patients were asked to complete the Beck anxiety inventory (BAI) 2 times: on the day before surgery (BS) and 30 minutes after midazolam premedication (T0). Depth of anesthesia using state entropy (SE), conventional hemodynamic data using heart rate (HR) and mean blood pressure (MBP), and analgesic profiles using surgical pleth index (SPI) were acquired at the following 4 points: T1—pre-induction, T2—prior to intubation, T3—intubation, and T4—20 minutes after intubation.

Results: No change in BAI score was observed between BS and T0 in both groups P and N (median and interquartile range [IQR], Group P: BS—4.5 [2.0–7.0], T0—4.0 [1.0–9.0], $P = .603$; Group N: BS—4.0 [1.0–8.5], T0—3.5 [1.0–6.0], $P = .066$). Midazolam premedication reduced SE at T2–4 (mean difference with 95% confidence interval [95% CI], T2—7.1 [1.6–12.6], $P = .012$; T3—10.4 [6.5–14.4], $P < .001$; T4—9.2 [5.0–13.4], $P < .001$). Midazolam premedication also reduced HR (mean differences [95% CI], T1—7.3 [2.5–12.1], $P = .003$; T3—6.6 [1.1–12.2], $P = .020$) and MBP at T1 and T3 (mean differences [95% CI], T1—7.3 [2.5–12.1], $P = .003$; T3—8.6 [1.3–15.9], $P = .021$), and lowered SPI at T1–3 (mean differences [95% CI]: T1—12.7 [6.1–19.4], $P < .001$; T2—6.0 [0.5–11.5], $P = .033$; T3—7.9 [1.7–14.1], $P = .012$).

Conclusion: Midazolam premedication did not reduce the level of anxiety. However, midazolam premedication reduced the entropy values, stabilized hemodynamics, and provided analgesia during the induction of anesthesia. The purpose of midazolam premedication needs to be reconsidered.

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Abbreviations: 95% CI = 95% confidence interval, ASA-PS = American Society of Anesthesiologists physical status, BAI = Beck anxiety inventory, BS = on the day before surgery, Ce = effect-site concentration, DBP = diastolic blood pressure, Group N = the control group, Group P = the midazolam premedication group, HBI = heart beat interval, HR = heart rate, IQR = interquartile range, MBP = mean blood pressure, NRS = numeric rating scale, PPGA = photoplethysmographic pulse amplitude, *r* = Pearson correlation coefficients, RE = response entropy, RM ANOVA = repeated-measures analysis of variance, SBP = systolic blood pressure, SD = standard deviation, SE = state entropy, SPI = surgical pleth index, STAI = State Trait Anxiety Inventory, T0 = 30 minutes after midazolam premedication, T1 = initial (pre-induction) time points, T2 = prior to intubation, T3 = intubation time, T4 = 20 minutes after intubation.

Trial registration: This study was registered at ClinicalTrials.gov (NCT03325335).

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1 Introduction

Before surgery, most patients experience anxiety,[1] which aggravates hemodynamic instability and increases anesthetic consumption during anesthesia.[2,3] Preoperative anxiety is also related to postoperative outcomes, such as pain, analgesic consumption, recovery time, and length of hospital stay.[4]

Midazolam, an imidazobenzodiazepine, acts on $GABA_A$ receptors to reduce anxiety, leading to sedation, anterograde amnesia, anticonvulsant effects, and centrally produced muscle relaxation.[5] Because it has high lipid solubility at physiological pH, midazolam quickly passes through the blood–brain barrier and has a fast

onset of action. In addition, the rapid redistribution of midazolam leads to a rapid recovery.[6] For these reasons, midazolam is the most popular premedication drug used during anesthesia induction before surgery.[7,8] However, the effect of midazolam premedication remains controversial[7,9] and the drugs' side effects include paradoxical reactions, oversedation, decreased blood pressure, and respiratory depression.[5,10] In this regard, some clinicians question the clinical benefits of benzodiazepine premedication[11,12] and argue that non-pharmacological methods alone are sufficient to reduce preoperative patient anxiety.[11]

In the present study, we aimed to evaluate the effects of midazolam premedication. In particular, we evaluated the anxiolytic, sedative, hemodynamic, and analgesic effects of the drug.

2 Methods

2.1 Subjects

This randomized, prospective, single-blind study was approved by the Institutional Review Board of Pusan National University hospital (ID 1607-003-057). The study was also registered with ClinicalTrials (ID NCT03325335). After obtaining written informed consent, we enrolled a total of 128 female patients aged between 20 and 65 years old. All patients had an American Society of Anesthesiologists physical status (ASA-PS) I or II, and were scheduled for elective thyroidectomy. The exclusion criteria were as follows: central nervous system disorders, major cardiovascular disease, chronic pain disorders, peripheral neuropathy, diabetes mellitus neuropathy, nephropathy, hepatopathy, current prescription of any medication affecting the central nervous system or heart rate (HR), alcohol or drug abuse, pregnancy, and contraindication to midazolam premedication.

2.2 Randomization

All patients were randomly allocated to either the midazolam premedication group (Group P; n = 64) or the control group (Group N; n = 64). The blocked randomization was performed using an internet-based randomizer service (https://www.sealedenvelope.com/simple-randomiser/v1/lists). The patients in Group P received intramuscular midazolam (0.05 mg kg^{-1}) and glycopyrrolate (0.2 mg) 30 minutes before induction of anesthesia, while those in Group N received intramuscular glycopyrrolate (0.2 mg) at the same time.

2.3 Anesthetic management

In the operating room, standard monitoring (electrocardiogram, pulse oximetry, noninvasive blood pressure, and esophageal stethoscope temperature) was performed, and entropy, train of four, and surgical pleth index (SPI) values were also measured. Anesthesia was induced after each of these measurements maintained at a constant value. Target-controlled infusion of propofol (4.0 μg mL^{-1}; effect-site concentration [Ce]) and remifentanil (4 ng mL^{-1}; Ce) was used to induce anesthesia based on the pharmacological models of Marsh and Minto, respectively.[13,14] Intravenous rocuronium (1.0 mg kg^{-1}) was administered for muscle relaxation. After intubation, propofol (3.0 μg mL^{-1}; Ce) and remifentanil (2 ng mL^{-1}; Ce) were infused until 20 minutes after intubation. Normocapnia (end-tidal CO_2: 30–40 mmHg) and normothermia (35.5–37.5 °C) were maintained during surgery. Intravenous ketorolac (30 mg) was administered 30 minutes before the end of the operation to control postoperative pain.

The drop-out indications were recording error and rescue drug use due to hemodynamic instability. The following rescue drugs were used: ephedrine (5–10 mg) for hypotension (20% reduction in systolic blood pressure [SBP] from baseline), atropine (0.5 mg) for bradycardia (HR < 45 bpm), and esmolol (10 mg) for tachycardia (HR > 130 bpm).

2.4 Assessment of outcomes

To assess the anxiolytic effect of midazolam, the patients completed the Beck anxiety inventory (BAI)[15] form twice: on the day before surgery (BS) and 30 minutes after midazolam premedication (T0). The BAI is a self-report questionnaire consisting of 21 questions. The relevance of each item was rated by the participants on a 4-point Likert scale (from 0—"Not at all" to 3—"Severe"). The total score was used to evaluate the patients' anxiety.

To estimate sedation and hemodynamic effects during anesthesia induction, we measured entropy value (state entropy; SE and response entropy; RE), noninvasive blood pressure (systolic; SBP, mean; MBP, and diastolic blood pressure; DBP), and HR (CARESCAPE Monitor B850, GE Healthcare, Milwaukee, WI) at the following 4 time points: T1; initial (pre-induction), T2; prior to intubation, T3; intubation, T4; 20 minutes after intubation. In addition, the total time taken for intubation, from T1 to T3, was recorded.

To evaluate midazolam's analgesic effect, the SPI (CARESCAPE Monitor B850, GE Healthcare, Milwaukee, WI) [16] was recorded during anesthesia at the 4 time points specified above. The patients' postoperative analgesic profiles were assessed using an initial numeric rating scale (NRS) and maximal NRS, as well as by reviewing analgesic consumption. The postoperative analgesic profiles were measured until the patients' *non per os* status was released. The doctor in charge determined whether additional parenteral analgesics should be administered after surgery.

2.5 Statistical analysis

The sample size was determined based on Cohen study.[17] Accordingly, in the present study, 64 subjects per group were required, with an α-value (significance criterion) of 0.05, a β-value (probability of occurring type II error) of 0.2, and a medium effect size (Cohen d) of 0.5. All analyses were performed using IBM SPSS Statistics (version 22; IBM Corporation, Armonk, NY). Continuous variables were presented as mean ± standard deviation (SD), as mean difference with 95% confidence interval (95% CI), or median and interquartile range (IQR). Categorical data were reported as absolute numbers and percentages. After a normality test, normally distributed variables were analyzed using an independent t test, a paired t test, or repeated-measures analysis of variance (RM ANOVA), and non-parametric data were analyzed using the Mann–Whitney U test and the Wilcoxon signed rank test, where appropriate. The differences between categorical variables were analyzed using the chi-square test. Pearson correlation coefficients (r) between the SPI values and other parameters (SBP, MBP, DBP, SE, and RE) were also calculated. A correlation was judged to be weak when $|r| < 0.3$, moderate when $0.3 < |r| < 0.7$, and strong when $|r| > 0.7$. Two-sided P-values <.05 were considered to indicate statistical significance.

3 Results

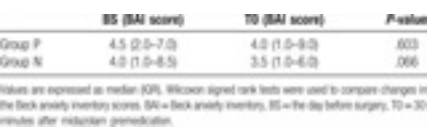
Of the 128 patients enrolled, 16 were excluded, 10 due to hypotensive events, and 6 due to recording errors (Fig. 1). The patients in the 2 groups were comparable in terms of age, height, weight, and ASA-PS. In addition, the 2 groups did not differ in terms of baseline parameters (HR, SBP, MBP, DBP, and BAI scores) at BS (Table 1).

Figure 1

Table 1

3.1 Anxiolytic effect

Midazolam premedication had no anxiolytic effects in preoperative patients. No change in BAI score was observed between BS and T0 in either group (median [IQR], Group P: BS—4.5 [2.0–7.0], T0—4.0 [1.0–9.0], *P* = .603; Group N: BS—4.0 [1.0–8.5], T0—3.5 [1.0–6.0], *P* = .066; Table 2).



	BS (BAI score)	T0 (BAI score)	*P*-value
Group P	4.5 (2.0–7.0)	4.0 (1.0–9.0)	.603
Group N	4.0 (1.0–8.5)	3.5 (1.0–6.0)	.066

Values are expressed as median (IQR). Wilcoxon signed rank tests were used to compare changes in the Beck anxiety inventory scores. BAI = Beck anxiety inventory, BS = the day before surgery, T0 = 30 minutes after midazolam premedication.

Table 2

3.2 Sedative effect

These results are shown in Table 3. RM ANOVA was performed to analyze the interaction between time and group, and Independent *t* tests were used for a comparison of the 2 groups at each measuring point. The mean SE and RE values showed differences over time and between Groups P and N. The SE and RE values of Group P were lower than those of Group N at all measuring points except for T1, i.e., the initial time. The mean differences (95% CI) in RE between Groups P and N at each time point were as follows: T1—0.9 (−0.2–2.1), *P* = .114; T2—7.5 (2.0–13.0), *P* = .008; T3—12.1 (8.0–16.3), *P* < .001; T4—9.7 (5.3–14.1), *P* < .001. The mean differences (95% CI) in SE between Groups P and N at each time point were as follows: T1—0.3 (−1.1–1.6), *P* = .719; T2—7.1 (1.6–12.6), *P* = .012; T3—10.4 (6.5–14.4), *P* < .001; T4—9.2 (5.0–13.4), *P* < .001. Furthermore, the total time taken for intubation was shorter in Group P than in Group N (mean ± SD: 7.0 ± 3.2 vs 8.6 ± 3.2, respectively; *P* = .008).

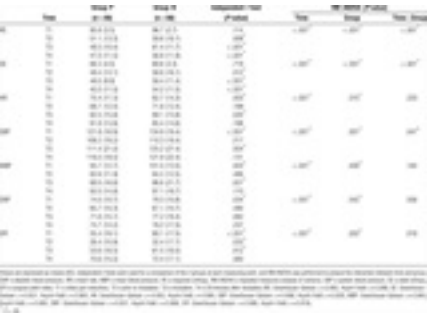


Table 3

3.3 Hemodynamic effect

These results are shown in Table 3. RM ANOVA was performed to analyze the interaction between time and group, and Independent *t* tests were used for a comparison of the 2 groups at each measuring point. The mean values of HR, SBP, and MBP differed over time and between Groups P and N. Specifically, the HR, SBP, and MBP in Group P were all lower than the corresponding values in Group N at T1 and T3. The mean differences (95% CI) at T1 were: HR—7.3 (2.5–12.1), *P* = .003; SBP—13.1 (6.5–19.7), *P* < .001; MBP—7.3 (2.5–12.1), *P* = .003. The mean differences (95% CI) at T3 were: HR—6.6 (1.1–12.2), *P* = .020; SBP—13.8 (4.6–22.9), *P* = .004; MBP—8.6 (1.3–15.9), *P* = .021. While DBP did change over time, it did not differ between the 2 groups except at T1 (RM ANOVA). The DBP values in Group P were lower than those in Group N at T1 (mean difference [95% CI]: 4.4 [0.3–8.4], *P* = .034); however, the groups did not differ at T3 in this regard (mean difference [95% CI]: 5.7 [−0.7–12.1], *P* = .082).

3.4 Analgesic effect

These results are shown in Table 3. The SPI value changed over time and between the 2 groups (RM ANOVA). The SPI value in Group P was lower than that in Group N (mean differences [95% CI]: T1—12.7 [6.1–19.4], $P <$ .001; T2—6.0 [0.5–11.5], $P = .033$; T3—7.9 [1.7–14.1], $P = .012$). Postoperatively, Groups P and N did not differ in terms of initial NRS, maximal NRS, and number of analgesic demand (Table 4).

	Group P	Group N	P-value
Initial NRS (score)	3.0 (2.0–3.0)	3.0 (2.0–4.0)	.887
Maximal NRS (score)	4.0 (2.0–4.0)	3.0 (2.0–4.8)	.799
Analgesic demand (number)	0.5 (0.0–1.0)	0.0 (0.0–1.0)	.137

Values are expressed as median (IQR). Mann–Whitney *U* tests were used for comparisons of the 2 groups. NRS = numeric rating scale.

Table 4

3.5 Correlation between SPI and other parameters

The Pearson correlation coefficients (r) between the SPI and other parameters (SE, RE, HR, SBP, MBP, and DBP) were 0.161, 0.174, 0.550, 0.332, 0.380, and 0.403, respectively ($P <$ .001 in all cases). A moderate correlation between hemodynamic indices (HR, SBP, MBP, and DBP) and the SPI value was found (Table 5).

	Coefficient	P-value
HR, bpm	0.550	<.01*
SBP, mmHg	0.332	<.01*
MBP, mmHg	0.380	<.01*
DBP, mmHg	0.403	<.01*
RE	0.174	<.01*
SE	0.161	<.01*

Pearson correlation coefficients between the SPI values and other parameters (SBP, MBP, DBP, SE, and RE) were calculated. DBP = diastolic blood pressure, HR = heart rate, MBP = mean blood pressure, RE = response entropy, SBP = systolic blood pressure, SE = state entropy, SPI = surgical pleth index.
* $P < .05$.

Table 5

4 Discussion

In the present study, midazolam premedication failed to reduce preoperative anxiety level. However, it did potentiate the degree of sedation during anesthesia. In the midazolam premedication group, hemodynamic parameters and SPI values remained stable during anesthesia induction. However, the postoperative analgesic profiles showed no significant difference between the groups.

Midazolam is widely prescribed as a premedication drug to reduce anxiety and ensure smooth anesthesia induction,[7,8] but the results of earlier studies on midazolam's effect have been controversial. Naguib and Samarkandi[18] reported that midazolam premedication had an anxiolytic and sedative effect before surgery, and that it increased patient satisfaction. Likewise, Bansal et al[19] stated that midazolam premedication reduces patients' anxiety and induces sedation before anesthesia induction, but that it does not cause hemodynamic changes before or after anesthesia induction.

Conversely, a survey-based study of premedication and preoperative anxiety presented different results. According to this study, many patients were administered premedication for anxiolysis, and the most commonly prescribed premedication drug was midazolam. However, the percentage of patients receiving premedication agents and reduction of perceived anxiety were not relevant.[7] Abdul-Latif et al[9] reported that oral midazolam premedication in patients undergoing day-time breast surgery failed to produce preoperative anxiety scores that were lower than those of a control group. However, the authors did observe that midazolam premedication attenuated hemodynamic changes, reduced the induction dose of propofol, and shortened the time required for laryngeal mask airway insertion during anesthesia induction.

In the present study, intramuscular midazolam premedication (0.05 mg kg^{-1}) failed to reduce preoperative anxiety levels, as measured by the BAI score. The BAI is a self-report diagnostic tool that was developed to differentiate anxiety from depression.[15] Previous studies have shown that anxiety and depression are common in patients who are undergoing surgery,[20] and that these 2 conditions are difficult to distinguish clinically, as

both involve psychiatric symptoms.[21] Unlike the State Trait Anxiety Inventory (STAI),[22] a widely used anxiety assessment tool, the BAI does not distinguish between trait anxiety (reflecting a person's intrinsic tendency) and state anxiety (the anxiety of a person at a particular moment in time). Instead, the BAI assesses anxiety based on the patient's feelings during the last week. Accordingly, based on test–retest reliability, Yook and Kim[23] reported that the BAI reflects current state anxiety (i.e., current psychopathology), rather than trait anxiety. In the present study, we used the BAI to measure the degree of actual anxiety while excluding the possibility of preoperative depression. Therefore, to find the most appropriate tool for determining the degree of anxiety in preoperative patients, future researchers should conduct follow-up studies using the visual analog scale, STAI, and BAI.

In the present study, although the sedation effect of midazolam premedication was not evident before anesthesia induction, the entropy value of the premedication group was significantly lower than that of the control group after anesthesia induction. In particular, the entropy value of the premedication group was maintained between 40 and 50, while that of the control group was maintained to between 50 and 60 after anesthesia induction. Furthermore, the time taken to intubation was significantly reduced in the midazolam premedicated patients. Similarly, in a previous study that used a midazolam–propofol combination during anesthesia induction, McClune et al[24] demonstrated, using probit regression analysis, that the drugs had a synergistic effect on the patient's “loss of response to command” reaction. Therefore, the entropy results observed in the present study may have been due to the synergistic effect of propofol, an induction agent, and midazolam, which was used as a premedication drug.

Furthermore, in the midazolam premedication group, we observed a decrease in hemodynamic changes during endotracheal intubation. Anxiety causes sympathetic activation and vagal deactivation in the autonomic nervous system, thereby increasing HR and blood pressure.[25] In this regard, Nishiyama et al[26] reported that adding midazolam during anesthesia induction attenuated intubation-induced increases in blood pressure, HR, cardiac autonomic system responses, and serum epinephrine and norepinephrine concentrations. Hence, while midazolam premedication does not reduce patients’ subjective preoperative anxiety, it may suppress physiological responses during anesthesia induction.

The analgesic effect of midazolam premedication is also unclear. Recent studies have shown that pain and discomfort during nasogastric tube insertion can be significantly alleviated using midazolam premedication.[27] In a study by Kim et al[28] into the effects of midazolam premedication on postoperative recovery, midazolam premedication reduced the pain score at the time of discharge from the post-anesthesia care unit. However, it failed to reduce the analgesic requirement. In contrast, Bauer et al[29] reported that midazolam premedication reduced postoperative nausea, but did not reduce opioid consumption in the operating room and post-anesthesia care unit; it also had no effect on the postoperative pain score measured 24 hours after surgery. In the present study, SPI values were lower in the midazolam premedication group, but postoperative pain scores did not differ between the 2 groups. Therefore, midazolam premedication has no analgesic effect after surgery, but it seems to have an analgesic effect during induction of anesthesia. However, SPI values are of limited use when evaluating the analgesic effect of midazolam during anesthesia induction. It may be that the lower SPI values in the midazolam premedication group reflected reduced HR rather than pain relief. That said, HR correlates with pain intensity,[16] and no current diagnostic tools can accurately measure the degree of pain in anesthetized patients. Therefore, it may be that patients in the midazolam premedication group showed reduced SPI in the present study because they had reduced pain during anesthesia induction. Generally, the SPI is inversely related to the heart beat interval.[16] The SPI values were obtained from the pulse plethysmogram wave as a tool to evaluate the patients’ nociception–antinociception balance during general anesthesia; the induction formula was as follows:

$$\text{SPI} = 100 - (\text{normalized HBI} \times 0.3 + \text{normalized PPGA} \times 0.7) \quad (1)$$

where HBI is the heart beat interval and PPGA is the photoplethysmographic pulse amplitude.

The SPI value is positively correlated with the intensity of surgical stress and negatively correlated with analgesic drug concentration. SPI is also moderately correlated with HR for the reasons outlined above. Therefore, further research is needed to confirm our results and provide a better understanding of the moderate correlation between SPI and other parameters (SE, RE, SBP, MBP, and DBP) observed in our study.

The first limitation of the present study is that we did not control the use of rescue drugs (type, quantity, application time) when measuring postoperative analgesic consumption. After surgery, the doctor in charge determined whether the patients should be administered analgesics. The analgesics received were intravenous ketorolac (30 mg), intramuscular diclofenac (90 mg), or intravenous propacetamol (1000 mg), all of which are non-opioid analgesics. Therefore, more detailed follow-up studies are needed to clarify the effects of midazolam premedication on postoperative pain. The second limitation of this study is that we did not demonstrate the dose–response relationship of midazolam premedication for anxiety, sedation, hemodynamics, and analgesia during the anesthetic induction. Eren et al[30] demonstrated that the anxiolytic and sedative effect increased with increasing dose of midazolam, while there was no change in hemodynamics. In contrast, Sun et al[31] suggested that increasing the dose of midazolam did not affect the level of anxiety and hemodynamics, while sedation was enhanced. These conflicting results suggest that a well-designed dose–response study might be needed.

In conclusion, midazolam premedication does not reduce preoperative anxiety. However, midazolam premedication does increase the sedative effect of anesthetics and shorten anesthetic induction time. Midazolam also helps to maintain hemodynamic stability by reducing the stress response during anesthesia induction. Midazolam premedication has no analgesic effect after surgery, but it does seem to have an analgesic effect during anesthesia induction. Overall, our study indicated that midazolam premedication facilitates a fast, stable, and smooth anesthesia induction process. The purpose of midazolam premedication needs to be reconsidered.

Author contributions

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Revising paper: all authors

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Project administration: Soeun Jeon, Hyeon-Jeong Lee.

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Writing – original draft: Soeun Jeon, Hyeon-Jeong Lee.

Writing – review & editing: Soeun Jeon, Hyeon-Jeong Lee.

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