

**EFFECTIVENESS OF INTRAVENOUS NALBUPHINE AND MIDAZOLAM
AS PREMEDICATION IN PATIENTS UNDERGOING PERCUTANEOUS
NEPHROLITHOTOMY**

Muhammad Zain Shahzad

Anesthesia Technology, Department of Emerging Allied Health Technologies, Faculty of Allied Health Sciences, The Superior University Lahore, Pakistan

Email: bsat-f21-253@superior.edu.pk

Areeba Nadeem

Anesthesia Technology, Department of Emerging Allied Health Technologies, Faculty of Allied Health Sciences, The Superior University Lahore, Pakistan

Email: areebanadeem755@gmail.com

Kashif Karim

Anesthesia Technology, Department of Emerging Allied Health Technologies
Designation: Lecturer Anesthesia Technology, The Professional Institute of Health Sciences Mardan KPK

Email: kashifkarim84@gmail.com

Zainab Mumtaz

Anesthesia Technology, Department of Emerging Allied Health Technologies, Faculty of Allied Health Sciences, The Superior University Lahore, Pakistan

Email: zainaykhan05@gmail.com

Hussnain Mushtaq

Anesthesia Technology, Department of Emerging Allied Health Technologies, Faculty of Allied Health Sciences, The Superior University Lahore, Pakistan

Designation: Anesthesia Technologist, Maryam Nawaz Hospital, Ghaziabad City

Email: Hussnainm495@gmail.com

Umme Kalsoom

Anesthesia Technology, Department of Emerging Allied Health Technologies, Faculty of Allied Health Sciences, The Superior University Lahore, Pakistan

Email: ummekalsoom048@gmail.com

Ghulam Abbas

Anesthesia Technology, Department of Emerging Allied Health Technologies, Faculty of Allied Health Sciences, The Superior University Lahore, Pakistan

Email: ga6641139@gmail.com

Author Details

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Corresponding E-mail & Author*:

Hussnain Mushtaq

Anesthesia Technology, Department of Emerging Allied Health Technologies, Faculty of Allied Health Sciences, The Superior University Lahore, Pakistan

Designation: Anesthesia Technologist, Maryam Nawaz Hospital, Ghaziabad City

Email: Hussnainm495@gmail.com

Abstract

Background: Patients undergoing percutaneous nephrolithotomy (PCNL) often experience preoperative anxiety, hemodynamic fluctuations, and postoperative pain. Although nalbuphine and midazolam are commonly used individually, evidence regarding their combined use as premedication in PCNL is limited.

Objective: To evaluate the effectiveness of intravenous nalbuphine and midazolam premedication in reducing preoperative anxiety, maintaining hemodynamic stability, reducing postoperative pain in patients undergoing percutaneous nephrolithotomy under general anesthesia.

Methodology: A cross-sectional study was conducted on 50 patients undergoing elective PCNL under general anesthesia at two hospitals of Lahore. Preoperative anxiety (VAS-A), heart rate, blood pressure, and postoperative pain (VAS) were assessed before and after intravenous nalbuphine and midazolam administration. Data were analyzed using descriptive statistics and paired t-tests in SPSS version 27.0.

Results: Premedication with intravenous nalbuphine and midazolam significantly reduced preoperative anxiety ($p < 0.001$) and improved postoperative pain scores

($p < 0.001$). No significant changes were observed in heart rate or blood pressure ($p > 0.05$), indicating good hemodynamic stability.

Conclusion: Intravenous nalbuphine and midazolam are effective and safe premedication combination for patients undergoing PCNL under general anesthesia. It provides significant anxiolysis, satisfactory postoperative analgesia, and maintains stable hemodynamic parameters.

INTRODUCTION

Percutaneous nephrolithotomy is used often to treat large, complex renal stones. Patients undergoing PCNL under general anesthesia, common factors that cause anxiety include preoperative anxiety, sympathetic stimulation during laryngoscopy and intubation, hemodynamic fluctuations and postoperative pain. Nalbuphine is an opioid analgesic/sedative while midazolam is an anxiolytic/amnestic/sedative. A study compared the effectiveness and adverse effects of nalbuphine, midazolam and buprenorphine to be used as premedication. The patients in the study were 200 surgical patients, given one of the drugs under study before going to the operating room. Each of the agents was examined for sedative, anxiolytic, and analgesic effects and adverse reactions. The anxiolysis, amnesia and sedation effects were mainly produced by midazolam while nalbuphine produced both sedation and analgesic effects [1].

The pressor response of the cardiovascular system (CVS) to laryngoscopy and endotracheal intubation has been studied at different doses of intravenous nalbuphine.

Measuring changes in blood pressure and heart rate after airway manipulation during general anesthesia was the basis for this study. Nalbuphine was given prior to the induction to see if it could reduce the sympathetic response that is a side effect of laryngoscopy and intubation. Both doses were reported to have a dose-dependent effect on pressor response attenuation, with the higher dose being reported to have a greater effect. The results allow the use of nalbuphine as pre-treatment before general anesthesia when there is a clinical need to maintain a stable heart rate and blood pressure [2].

The efficacy of intravenous tramadol and intravenous nalbuphine both with midazolam was assessed in patients receiving surgical procedures under spinal anesthesia with regard to the control of post-spinal anesthesia shivering. Comparing intravenous tramadol 0.5 mg/kg with intravenous nalbuphine 0.1 mg/kg for the control of post-spinal anesthesia shivering, in addition to midazolam. The mean times to stop shivering were not statistically different between the two groups, the tramadol group averaged 4.1 minutes, while the nalbuphine group averaged 4.2 minutes. Throughout the observation period, there was no significant difference in heart rate and systolic and diastolic blood pressure. The authors concluded nalbuphine and midazolam would be effective in combination with midazolam and were hemodynamically stable and safely used [3].

The effect of midazolam and nalbuphine was tested on the prevention of emergence agitation in pediatrics under sevoflurane anesthesia. To evaluate the effectivity of postoperative agitation control and adequate recovery and hemodynamic stability with either of the drugs. Both drugs shortened emergence agitation and reduced its intensity when compared to the usual anesthetic care. Both drugs reduced the number and intensity of emergence agitation compared to the usual anesthetic care. In particular, the use of Nalbuphine because of its analgesic and sedative properties was helpful in reducing the postoperative pain, a major source of postoperative agitation. Midazolam and nalbuphine were seen to both improve the quality of emergence from general anesthesia, but in different ways of action in the study [4].

The study aimed to evaluate the heart rate, blood pressure lowering effect of the two drugs in the peri-operative period. Nalbuphine was associated with analgesia and reduction of sympathetic cardiovascular responses, while midazolam primarily caused anxiolysis and sedation. Perioperative hemodynamic stability was reported as satisfactory for both drugs and the clinical effect was dependent on their pharmacological properties. The findings support the idea that a combination of an anxiolytic and an analgesic agent (midazolam and nalbuphine) may have a better effect when used as premedications than either drug individually [5].

Anxiety, hemodynamic changes, as well as postoperative pain are common problems in patients with urolithiasis who have undergone percutaneous nephrolithotomy (PCNL) under general anesthesia, which can negatively impact on the perioperative period. Nalbuphine and midazolam are two drugs that are used in PCNL patients as premedication and are used as single drugs for analgesia and anxiolysis/sedation respectively, although there are limited evidences regarding the combination of the two drugs in PCNL patients. Therefore, the aim of this study is to evaluate the comfortness of the patients, hemodynamic stability, reduction in postoperative pain and the need for

rescue analgesic in the perioperative period following IV nalbuphine and midazolam administration.

LITERATURE REVIEW

Lam et al., (2005) randomly tested intramuscular and intranasal midazolam as premeds in 23 children for dental treatment under intravenous conscious sedation. Sedation, patient cooperation and ease of administration were assessed for both routes, and clinical acceptability was assessed for the latter. Intranasal and IV midazolam were effective when used for pre-operative sedation, but intranasal use was more uncomfortable during drug delivery. Intramuscular use seemed more reliable and was usually well tolerated despite the need to inject. The authors finally found that both routes could be useful to give premedication in children, but the choice should depend on the patient comfort, patient acceptance and clinical situations [7].

Sajedi et al., (2015) performed a randomized clinical trial to evaluate the effect of intravenous midazolam, ketamine and combination of these two drugs on anxiety reduction in children prior to general anesthesia. The treatment groups were assessed for anxiety, sedation, cooperation in separation from parents and acceptance of induction of anesthesia. When used together, midazolam and ketamine were more effective at reducing anxiety than either drug alone and were found to be more effective at providing satisfactory sedation. Cooperation of patients was better without major clinical complications due to the complementary anxiolytic effect of midazolam and sedative effect of ketamine. The authors found that combination of midazolam and ketamine was more effective for premedication of pediatric patients than either drug alone [8].

Kogan et al., (2002) performed a study to assess oral, rectal, intranasal and sublingual premedication with midazolam in young children undergoing surgery. The investigators evaluated when and how well the sedation was achieved, how easy it was to separate from parents, to accept induction of anesthesia and adverse effects. Oral, rectal and sublingual midazolam were effective for achieving the desired sedation preoperatively, and intranasal sedative was less well tolerated due to nasal discomfort and irritation. Route of administration may affect the clinical usefulness of midazolam, as suggested by differences of onset and patient acceptance. The authors found several ways safe and effective, and oral premedication is a feasible and acceptable method for the pediatric population [9].

Lindahl et al., (1990) summarized the clinical experience with midazolam as a premedication drug for anesthesia. Its anxiolytic, sedative and amnesic effects, onset, duration and potential adverse effects were the aspects of its actions examined in the review. Midazolam was found to be effective in decreasing preoperative anxiety, to provide reliable sedation and anterograde amnesia. It had a short half-life and onset of action that were favorable compared to longer acting benzodiazepines, especially for situations where it was necessary to recover in a timely fashion. The review recommended that midazolam is effective as a premedication drug in an appropriate dose, provided there is appropriate monitoring of the respiratory and cardiovascular systems [10].

Hook et al., (1988) performed a randomized double blinded study to evaluate the use of intravenous nalbuphine–midazolam and pentazocine–midazolam for patients

undergoing oral surgery. Intraoperative sedation, analgesia, patient cooperation, recovery and adverse effects were assessed. Both combinations were equally effective for sedation, but the nalbuphine–midazolam combination was effective in providing good analgesia and acceptable operating conditions. The results show that an opioid (analgesic) and midazolam may be used together for their complementary analgesic, anxiolytic and sedative effects. The authors found that nalbuphine and midazolam is an effective clinically acceptable intravenous sedative combination for surgical procedures [11].

METHODOLOGY

This research was a cross sectional study carried out at Sheikh Zayed Hospital and CMA Hospital, Lahore. Total 50 patients who were scheduled for elective PCNL under general anesthesia were enrolled in the study. The non-probability convenience sampling technique was used in determining the participants.

Patients were included (20-73 years) and underwent elective percutaneous nephrolithotomy (PCNL) under general anesthesia of either gender. We enrolled only patients who had ASA physical status I or II, had received intravenous nalbuphine and midazolam as premedication following the study protocol and had signed informed consent. The patients were excluded are patients with known hypersensitivity to nalbuphine or midazolam, significant hepatic, renal, cardiovascular, or respiratory disease, psychiatric or cognitive disease, chronic opioid or sedative use, incomplete clinical records or missing clinical outcome data, emergency PCNL or conversion to another procedure.

Basic demographic data, anxiety level (VAS-A), heart rate, and blood pressure were collected prior to administering the intravenous nalbuphine and midazolam, and 15 minutes after the premedication. Documented in recovery period were post-operative pain scores 2 hours and 6 hours pain scores. Data collected were entered into SPSS version 27.0 and subjected to analysis using a P-value<0.05 as statistically significant.

RESULTS

Table 4.1: Demographic characteristics of the study participants

Descriptive Statistics					
	N	Minimum	Maximum	Mean	Std. Deviation
Weight	50	49	93	69.66	12.437
Age	50	20	73	45.72	13.637
Valid N (listwise)	50				

Interpretation

A total of 50 patients were included in the study. The mean age was 45.72 ± 13.64 years, while the mean body weight was 69.66 ± 12.44 kg, indicating a middle-aged study population.

Table 4.2: Gender distribution of the study participants

Gender					
		Frequency	Percent	Valid Percent	Cumulative Percent
	Female	20	40.0	40.0	40.0
	Male	30	60.0	60.0	100.0
	Total	50	100.0	100.0	

Interpretation

Among the participants, 30 (60%) were males and 20 (40%) were females. This indicates that male patients constituted the majority of the study population.

Table 4.3: Comparison of clinical outcomes before and after premedication using paired t-test

Paired Samples Effect Sizes						
			Standardizer ^a	Point Estimate	95% Confidence Interval	
					Lower	Upper
Pair 1	Anxiety (VAS-A) before premedication - Anxiety (VAS-A) 15 min after premedication	Cohen's d	.778	1.182	.816	1.541
		Hedges' correction	.784	1.173	.810	1.529
Pair 2	Heart Rate (BPM) before premedication - Heart Rate (BPM) 15 min after premedication	Cohen's d	.416	.240	-.042	.520
		Hedges' correction	.420	.238	-.042	.516
Pair 3	B.P before premedication - B.P 15 min after premedication	Cohen's d	1.400	.100	-.178	.377
		Hedges' correction	1.411	.099	-.177	.374
Pair 4	Pain after 2 hours surgery- Pain after 6 hours surgery	Cohen's d	.396	-2.324	-2.856	-1.784
		Hedges' correction	.399	-2.306	-2.834	-1.771

Interpretation

The mean anxiety score decreased significantly after administration of nalbuphine and midazolam ($t = 8.359$, $p < 0.001$). This indicates that the premedication was highly effective in reducing preoperative anxiety. There was no statistically significant difference in heart rate before and after premedication ($t = 1.698$, $p = 0.096$). The findings suggest that premedication maintained stable heart rate without causing significant cardiovascular changes. No statistically significant difference was observed in blood pressure before and after premedication ($t = 0.707$, $p = 0.483$). This demonstrates that the premedication regimen preserved hemodynamic stability. Pain scores differed significantly between 2 and 6 hours after surgery ($t = -16.432$, $p < 0.001$). The findings indicate a significant change in postoperative pain during the

recovery period and shows that mostly patients have no pain after 2 hours and 6 hours of surgery.

Figure 4.1: Distribution of preoperative anxiety (VAS-A) before premedication

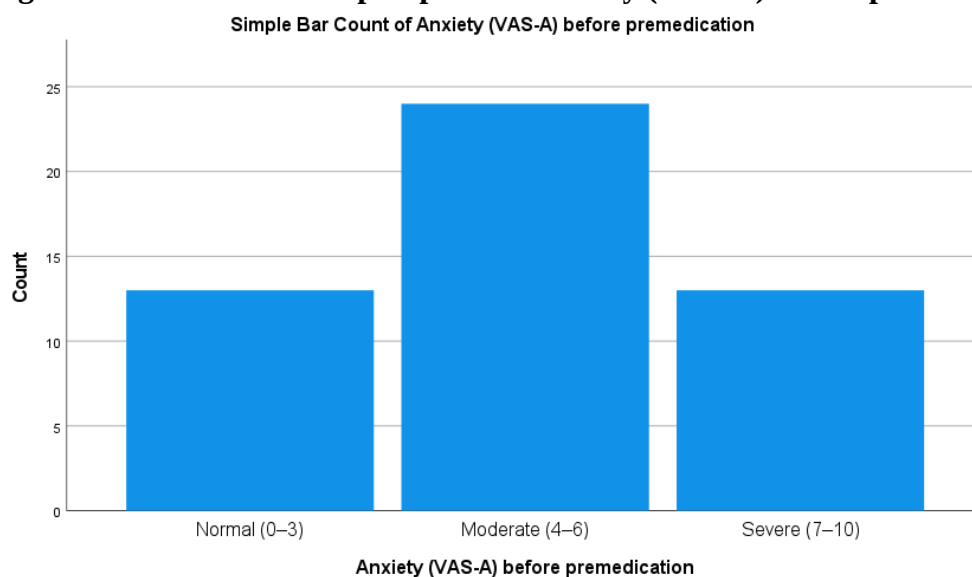


Figure 4.2: Distribution of anxiety (VAS-A) 15 minutes after premedication

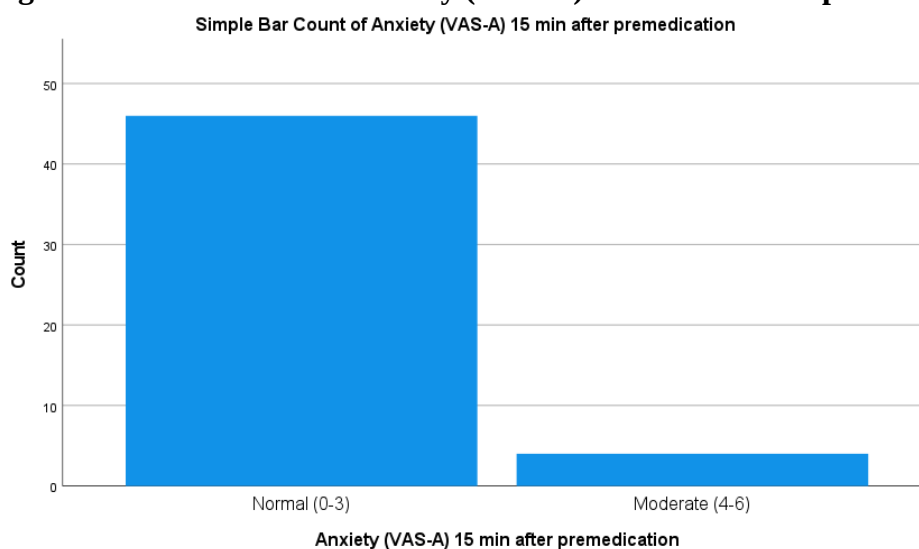
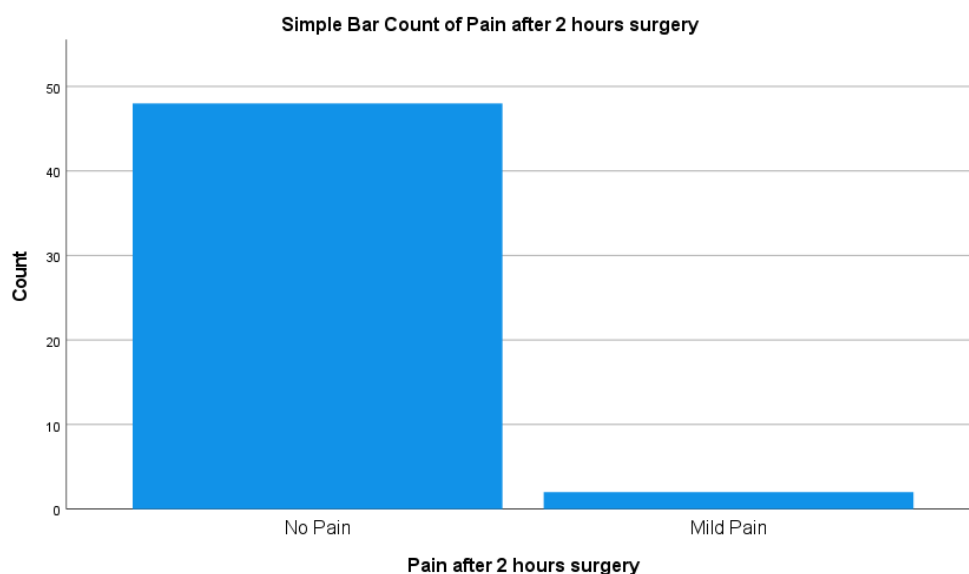
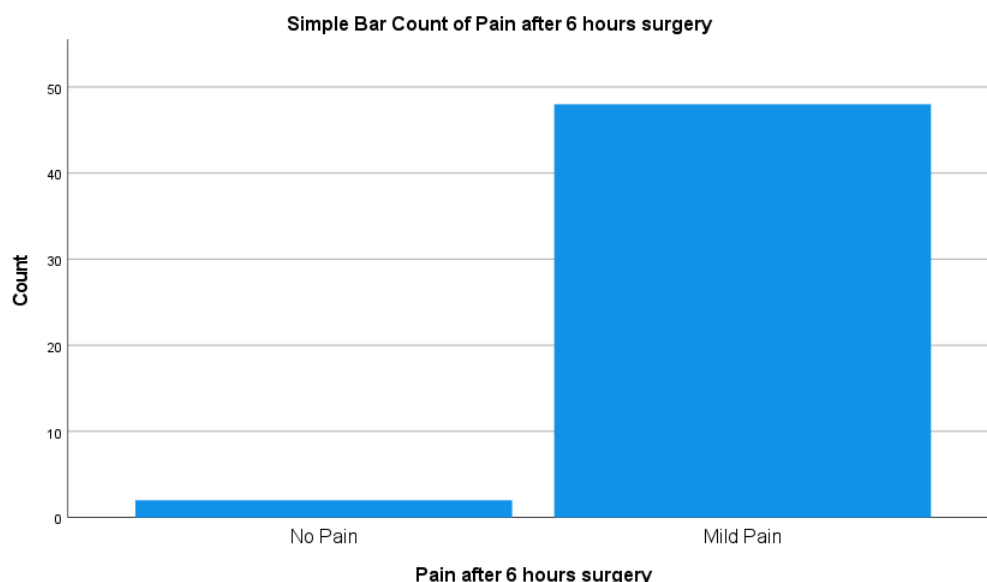


Figure 4.3: Distribution of pain scores 2 hours after surgery**Figure 4.4: Distribution of pain scores 6 hours after surgery****DISCUSSION**

Our study indicated that intravenous administration of nalbuphine and midazolam could effectively reduce preoperative anxiety and stabilize the heart rate and blood pressure. Kim et al. (1997) have compared the efficacy of nalbuphine, midazolam and buprenorphine as premedication agents and found that both nalbuphine and midazolam were effective in providing sedation, anxiolysis and stable hemodynamic parameters with acceptable patient tolerance. Both studies found nalbuphine and midazolam to be effective for preoperative anxiolysis without significant cardiovascular instability and our results are consistent with both of these studies.

In the present study, there was significant improvement in the perioperative level of patient comfort in terms of reduced anxiety and adequate postoperative pain control after using nalbuphine and midazolam as premedications. According to Madem et al. (2024), intravenous tramadol was ineffective in treating shivering following spinal anesthesia and combination of intravenous nalbuphine and midazolam was more effective in controlling shivering and offered better analgesia, sedation, and comfort to patients. Our results are in line with theirs, indicating that nalbuphine and midazolam are effective in having a good perioperative outcome.

The study revealed that nalbuphine and midazolam were effective in reducing anxiety without causing any significant changes in the hemodynamic parameters in the perioperative period. Noor El-Din et al. (2018) compared midazolam and nalbuphine as an emergence agitation prevention in children and found no significant cardiovascular changes and both drugs were effective in improving recovery quality. The conclusions of our study are similar with their results, and nalbuphine and midazolam are safe and effective perioperative drugs, respectively, which have favorable hemodynamic profiles.

The results of our study showed that intravenous nalbuphine and midazolam administration successfully decreased the anxiety of the patients before surgery without affecting the hemodynamic parameters and resulted in an acceptable postoperative comfort. Hook and Lavery (1988) made a comparative study of intravenous nalbuphine–midazolam and pentazocine–midazolam combinations in patients receiving oral surgery. They said that nalbuphine–midazolam combination was effective for sedation and analgesia and resulted in good surgical conditions, and had minimal side effects. Our study results agree with those of Hook and Lavery (1988) who reported that the nalbuphine–midazolam combination was effective and safe for enhancing perioperative patient comfort and cardiovascular stability.

CONCLUSION

The present study concluded that intravenous nalbuphine and midazolam are effective premedication agents for patients undergoing percutaneous nephrolithotomy under general anesthesia. This regimen markedly decreased preoperative anxiety and had a minimal effect on heart rate and blood pressure during the preoperative period. It also gave satisfactory post-operative analgesic effect, and there were significant difference in pain score during recovery. These results suggest that nalbuphine and midazolam provide effective anxiolysis, hemodynamic stability and enhanced perioperative patient comfort. Thus, this premedication regimen is thought to be safe and useful for PCNL under general anesthesia.

RECOMMENDATIONS

- Considering IV nalbuphine and midazolam as an effective premedication combination for reducing preoperative anxiety of patients undergoing PCNL under GA may be considered.
- A larger sample and more healthcare centers should be included in future studies to increase the generalizability of the results.
- Comparative studies need to be carried out to compare the nalbuphine–midazolam combination with other combinations of premedications that are commonly used in the country.
- Further research is needed to evaluate long term postoperative outcomes, patient satisfaction, recovery quality and potential side effects of this premedication regime.

LIMITATIONS

- The sample size (n = 50) was relatively small and might not be representative of the larger population.
- The study was conducted in two hospitals only, so that the results cannot be generalized to other settings.
- There was no control or comparison group to directly compare the efficacy of the nalbuphine–midazolam combination with other premedication drugs.
- Only short-term perioperative outcomes were assessed.

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