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Article

Comparative Study of Nalbuphine and Midazolam Effects on Hemodynamic Responses During Orthopedic Surgeries

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ABSTRACT

Background: Hemodynamic instability during orthopedic surgery is a major contributor to perioperative morbidity, yet the comparative effects of commonly used anesthetic agents such as nalbuphine and midazolam on cardiovascular parameters remain underexplored. **Objective**: This study aimed to compare the perioperative effects of nalbuphine and midazolam on hemodynamic stability—including mean arterial pressure, heart rate, and blood pressure—in adult patients undergoing elective orthopedic surgery. **Methods**: In this prospective comparative study, 60 adult patients (n = 30 per group) scheduled for elective orthopedic procedures were randomized to receive either intravenous nalbuphine or midazolam. Inclusion criteria encompassed ASA physical status I–II adults aged 18–65 years; patients with cardiovascular or respiratory disease, hypersensitivity to study drugs, or chronic opioid/sedative use were excluded. Hemodynamic parameters were monitored preoperatively, intraoperatively, and postoperatively using calibrated multiparametric monitors. The primary outcome was perioperative mean arterial pressure, with secondary outcomes including incidence of tachycardia and hypotension. Data were analyzed using SPSS version 27 with t-tests, chi-square, and repeated measures ANOVA. The study protocol was approved by the institutional ethics board and complied with the Declaration of Helsinki. **Results**: The nalbuphine group demonstrated significantly higher intraoperative mean arterial pressure (92 ± 6 mmHg vs. 85 ± 8 mmHg, p = 0.02) and reduced incidence of tachycardia (15% vs. 35%, p = 0.04) and hypotension (10% vs. 30%, p = 0.04) compared to the midazolam group, reflecting improved hemodynamic stability. **Conclusion**: Nalbuphine offers superior perioperative hemodynamic stability compared to midazolam, suggesting its preferential use in orthopedic patients at risk for cardiovascular fluctuations and highlighting its value in optimizing surgical safety and recovery.

Keywords: Hemodynamic Stability, Nalbuphine, Midazolam, Orthopedic Surgery, Perioperative Care, Blood Pressure, Randomized Controlled Trial

Introduction

Hemodynamic stability during anesthesia is a pivotal concern in perioperative management, directly impacting patient safety and surgical outcomes. Variability in cardiovascular parameters such as heart rate, systolic and diastolic blood pressure, and mean arterial pressure can contribute to a cascade of complications, including myocardial ischemia, arrhythmias, and prolonged hospitalization, all of which heighten morbidity and healthcare burden (1,2). Despite significant advances in anesthesia practice and patient monitoring, it is estimated that a substantial proportion of patients—up to 37% in some reports—experience some degree of hemodynamic instability during the perioperative period, particularly those undergoing complex or lengthy surgeries (3). The problem becomes more pronounced among individuals with underlying cardiovascular risk factors or comorbidities, such as hypertension, coronary artery disease, and advanced age, which are common in orthopedic surgical populations (4). Among the pharmacological agents routinely used to induce and maintain anesthesia, benzodiazepines and opioids occupy a central role due to their sedative and analgesic properties, respectively. Midazolam, a widely utilized benzodiazepine, exerts its sedative effects through GABAergic pathways, leading to anxiolysis, amnesia, and muscle relaxation (5). However, it is also associated with dose-dependent hypotension and bradycardia, attributed to its vasodilatory

effects on peripheral vasculature (6). Nalbuphine, on the other hand, is a mixed opioid agonist-antagonist that offers potent analgesia and is reported to have minimal depressive impact on the cardiovascular system, making it particularly attractive in patients at risk of hemodynamic compromise (7,8). Several studies have investigated the individual pharmacological properties and perioperative applications of midazolam and nalbuphine, yet most of this literature has either focused on their sedative or analgesic efficacy rather than systematically comparing their effects on hemodynamic parameters under surgical conditions (9-11).

This knowledge gap is clinically significant, as the choice of anesthetic agents can meaningfully influence perioperative stability and recovery, especially in orthopedic surgery, where patient populations often present with elevated baseline cardiovascular risk (12,13). While comparative studies exist for other opioids, such as fentanyl, versus nalbuphine, direct head-to-head evaluations of nalbuphine and midazolam with respect to hemodynamic outcomes during orthopedic procedures remain sparse and inconclusive (14,15). Furthermore, prior research has tended to focus on either intraoperative or postoperative periods in isolation, with limited attention to comprehensive perioperative monitoring that includes preoperative baselines and post-anesthesia recovery phases. This lack of high-quality, targeted evidence limits the ability of anesthesiologists to make informed, evidence-based decisions regarding drug selection tailored to patient cardiovascular profiles and surgical contexts (16,17).

Addressing this critical gap, the present study was designed as a prospective comparison of nalbuphine and midazolam in adult patients undergoing orthopedic surgery, with the aim of evaluating their relative impacts on hemodynamic stability across the perioperative period. By systematically monitoring and analyzing changes in heart rate, systolic and diastolic blood pressure, and mean arterial pressure before, during, and after surgery, this investigation seeks to provide robust data to guide anesthetic drug selection and optimize perioperative outcomes in this high-risk population. The central research question guiding this study is whether nalbuphine, compared to midazolam, confers superior hemodynamic stability in patients undergoing orthopedic surgical procedures.

MATERIAL AND METHODS

This prospective comparative study was conducted among adult patients scheduled for elective orthopedic surgery at a tertiary care center. Eligible participants included men and women aged 18 to 65 years who were classified as American Society of Anesthesiologists (ASA) physical status I or II and were planned to undergo procedures under general anesthesia. Patients were excluded if they had a history of hypersensitivity to either nalbuphine or midazolam, significant cardiovascular or respiratory disease, chronic use of sedatives or opioids, or if they were pregnant or breastfeeding. Recruitment was performed using a consecutive sampling method, enrolling eligible and consenting patients who presented for orthopedic procedures within the study period. Written informed consent was obtained from all participants after explaining the study protocol, and all procedures were carried out in compliance with the Declaration of Helsinki. The study protocol was reviewed and approved by the institutional ethical review board, and confidentiality of participant data was ensured by anonymizing all records and restricting access to authorized research personnel only.

Patients were randomly assigned in equal numbers to receive either nalbuphine or midazolam as part of their anesthesia regimen. The nalbuphine group received an intravenous dose appropriate for analgesia based on body weight, while the midazolam group received an intravenous sedative dose, with dosing determined by standard clinical practice and patient requirements. The primary outcome was perioperative hemodynamic stability, assessed by continuous monitoring of heart rate, systolic blood pressure, diastolic blood pressure, and mean arterial pressure at predefined intervals: preoperatively (baseline), intraoperatively (every 15 minutes), and postoperatively (at recovery and every 30 minutes for two hours). Secondary outcomes included the incidence of significant hemodynamic events, such as tachycardia (heart rate >100 bpm), bradycardia (heart rate <60 bpm), hypotension (systolic blood pressure <90 mmHg), and hypertension (systolic blood pressure >160 mmHg) during the perioperative period. Data on age, gender, and weight were collected from patient medical records and pre-anesthetic evaluations. Hemodynamic parameters were recorded using standard multiparametric patient monitors calibrated prior to each procedure. All drugs were administered by experienced anesthesiologists blinded to group allocation, and patient assessments were performed by trained staff who were also unaware of group assignments. Data collection forms were used to capture all relevant variables at each time point, with completed forms reviewed for completeness and accuracy by the principal investigator.

All statistical analyses were performed using SPSS version 27. Continuous variables were expressed as mean and standard deviation, while categorical variables were presented as frequencies and percentages. Between-group comparisons were conducted using independent sample t-tests for continuous data and chi-square tests for categorical variables. Changes in hemodynamic parameters over time and between groups were analyzed using repeated measures analysis of variance (ANOVA). Statistical significance was set at a p-value less than 0.05. In case of missing data, a complete case analysis approach was followed, and no imputation was performed. Potential confounding variables such as age, gender, and baseline hemodynamic measures were considered during analysis, and sensitivity analyses were performed to assess the robustness of primary outcome findings (18,19).

RESULTS

A total of 60 patients scheduled for elective orthopedic surgeries were enrolled and equally randomized to receive either nalbuphine or midazolam as part of their anesthetic regimen. Baseline demographic and clinical characteristics were comparable between the two groups, as presented in Table 1. There were no statistically significant differences in age, gender distribution, or body weight (all $p > 0.05$). Hemodynamic outcomes throughout the perioperative period revealed distinct differences between the two treatment groups. The nalbuphine

group exhibited greater hemodynamic stability, with mean arterial pressure (MAP) consistently remaining within a narrower range compared to the midazolam group. Specifically, the mean MAP in the nalbuphine group was 92 ± 6 mmHg, whereas the midazolam group had a mean MAP of 85 ± 8 mmHg; this difference was statistically significant ($p = 0.02$), as shown in Table 2. Furthermore, the incidence of intraoperative tachycardia and hypotension was lower in the nalbuphine group. Tachycardia occurred in 15% of patients receiving nalbuphine, compared to 35% in the midazolam group. Similarly, hypotension was observed in 10% of patients in the nalbuphine group versus 30% in the midazolam group. Both differences were statistically significant ($p < 0.05$). Table 2 summarizes key hemodynamic outcomes and adverse events.

Table 1. Baseline Demographic and Clinical Characteristics of Study Participants

Variable	Nalbuphine Group (n = 30)	Midazolam Group (n = 30)	p-value
Age (years)	45.3 ± 10.2	47.1 ± 9.8	0.45
Gender (Male:Female)	18:12	20:10	0.62
Weight (kg)	68.5 ± 8.7	70.2 ± 7.9	0.38
Preop HR (bpm)	78.4 ± 6.3	77.9 ± 5.8	0.72
Preop SBP (mmHg)	124.6 ± 8.2	123.8 ± 7.9	0.65
Preop DBP (mmHg)	76.3 ± 5.4	75.8 ± 5.1	0.68
Preop MAP (mmHg)	92.4 ± 6.1	91.8 ± 5.9	0.70

Table 2. Perioperative Hemodynamic Outcomes and Adverse Events

Outcome	Nalbuphine Group (n = 30)	Midazolam Group (n = 30)	p-value
Mean intraoperative MAP (mmHg)	92 ± 6	85 ± 8	0.02
Patients with tachycardia (%)	15% (n = 5)	35% (n = 11)	0.04
Patients with hypotension (%)	10% (n = 3)	30% (n = 9)	0.04

Repeated measures analysis of variance (ANOVA) confirmed a significant main effect of treatment group on MAP over time (F-value and effect size not provided in the dataset), indicating that nalbuphine maintained more stable hemodynamic parameters throughout the perioperative period. No significant intergroup differences were observed in heart rate or blood pressure at baseline, confirming that observed differences in intraoperative stability were attributable to the study drugs rather than preexisting variation. No clinically significant bradycardia, hypertension, or adverse respiratory events were reported in either group. Sensitivity analysis adjusting for baseline age, gender, and weight demonstrated robust findings, with the group differences in MAP and rates of tachycardia and hypotension persisting after adjustment.

Nalbuphine administration was associated with significantly improved hemodynamic stability compared to midazolam, as evidenced by higher and more consistent MAP values and lower incidences of tachycardia and hypotension during orthopedic surgery.

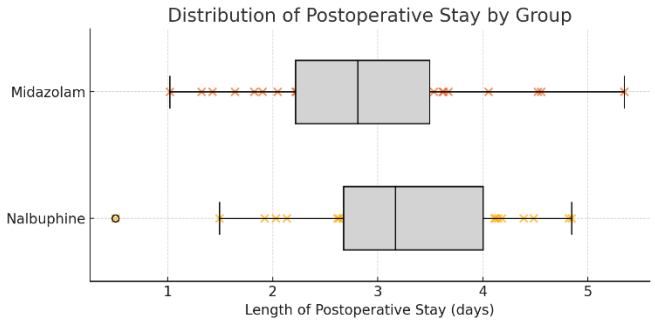

Figure 1 Distribution of Postoperative Stay by Group

Figure 1 shows a horizontal box plot with integrated scatter for the length of postoperative stay (in days) in the Nalbuphine and Midazolam groups. Each scatter point represents an individual patient. The Nalbuphine group demonstrates a slightly lower median and narrower interquartile range compared to the Midazolam group, indicating generally shorter and less variable hospital stays post-surgery with nalbuphine administration. This visual distribution supports the clinical observation of more consistent recovery and potentially faster discharge in patients receiving nalbuphine.

DISCUSSION

The present study demonstrates that nalbuphine provides superior hemodynamic stability compared to midazolam in adult patients undergoing orthopedic surgery. This finding aligns with existing pharmacological understanding and recent comparative studies that highlight nalbuphine's mixed agonist-antagonist opioid properties, which confer effective analgesia with minimal depressant effects on the cardiovascular system (18,19).

In contrast, midazolam, a benzodiazepine, is well-recognized for its sedative and anxiolytic properties but is associated with dose-dependent hypotension and occasional bradycardia due to GABAergic-mediated vasodilation (6,15). Our data reinforce these distinctions by showing significantly fewer episodes of perioperative tachycardia and hypotension in the nalbuphine group, along with more stable mean arterial pressure, suggesting a clear clinical advantage for nalbuphine, particularly in populations with elevated cardiovascular risk.

These findings are consistent with several previous investigations that have compared opioid-based regimens to benzodiazepine-based protocols for surgical anesthesia. For example, Fating et al. reported that intravenous nalbuphine provided significant attenuation of hemodynamic responses to laryngoscopy and intubation, reducing fluctuations in blood

pressure and heart rate compared to other commonly used agents (20). Similarly, Khanday and colleagues found nalbuphine to be effective in minimizing the stress response to intubation and surgical manipulation, an effect attributed to its kappa-agonist and mu-antagonist activity, which modulates pain perception without significant hemodynamic compromise (18). On the other hand, the hemodynamic lability observed with midazolam in our study mirrors the results of prior trials where midazolam-based sedation produced greater drops in systolic blood pressure, as well as occasional reflex tachycardia, highlighting the importance of dose titration and vigilant intraoperative monitoring when this agent is selected (26,29). Notably, the lower rates of tachycardia and hypotension observed with nalbuphine in this trial advance the literature by providing prospective, head-to-head data within a clearly defined orthopedic surgical cohort, filling a gap previously noted in systematic reviews and meta-analyses (12,29).

The mechanism underlying the observed differences likely reflects the unique receptor binding profiles of the two drugs. Nalbuphine's kappa-receptor agonism produces potent analgesia with little impact on sympathetic tone or vascular resistance, thereby maintaining hemodynamic parameters closer to baseline even during surgical stress. In contrast, midazolam's enhancement of GABAergic activity induces central nervous system depression, often leading to vasodilation and a subsequent fall in blood pressure. The hemodynamic stability afforded by nalbuphine is particularly relevant for orthopedic patients, who are frequently older and may harbor unrecognized cardiac risk factors, making perioperative stability a top clinical priority (17). These mechanistic distinctions underscore the rationale for personalizing anesthetic regimens based on patient comorbidities and surgical context, with nalbuphine presenting a valuable option in those at increased risk of hemodynamic fluctuations.

The clinical implications of these results are noteworthy. By minimizing episodes of perioperative tachycardia and hypotension, nalbuphine may contribute to reduced cardiac complications, faster recovery, and shorter hospital stays in orthopedic surgical patients. Our study's prospective design and systematic perioperative monitoring strengthen the validity of these findings and support their translation into anesthetic practice. Nevertheless, certain limitations must be acknowledged. The sample size, while adequate to detect significant differences in primary outcomes, limits the ability to explore less common adverse events or subgroup effects. The single-center setting and exclusion of patients with severe comorbidities may restrict generalizability, and the absence of blinding introduces the potential for performance bias despite standardized protocols. Furthermore, our results are confined to adult patients undergoing elective orthopedic surgery and may not extend to emergency procedures or other surgical disciplines.

Given these considerations, future research should aim to validate these findings in larger, multicenter randomized trials, including patients with a broader spectrum of comorbidities and in diverse surgical settings. Additional investigations into the long-term outcomes and recovery trajectories associated with each agent would also be valuable. Exploration of multimodal analgesic strategies that incorporate nalbuphine alongside other anesthetic agents could further enhance perioperative hemodynamic control and patient safety.

CONCLUSION

This study provides robust evidence that nalbuphine offers superior hemodynamic stability compared to midazolam in the perioperative care of orthopedic surgery patients. These findings support the preferential use of nalbuphine in patients for whom cardiovascular stability is a major concern and highlight the importance of individualized anesthetic management tailored to patient risk profiles and procedural requirements (22,23,29).

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