Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/0jqhac79

COMPARISON OF MIDAZOLAM AND NALBUPHINE IN REDUCING HAEMODYANIMIC RESPONSE TO ENDOTRACHEAL INTUBATION

Ashique Mehdi[1*], Kelash Kumar[2], Ali Haider[3], Ahmed Khan[4], Wajiha Tahir[5], Maqsood Ahmed Siddiqui[6]

[1*]Ashique Mehdi, Chief Medical officer Anesthesiology and Intensive Care, Civil Hospital Hyderabad / Liaquat University of Medical and Health Sciences Jamshoro Pakistan.
Email: ashiqmlaghari81@gmail.com
[2]Kelash Kumar, Assistant professor Anesthesiology and Intensive Care, Liaquat University of Medical & Health Sciences Jamshoro Pakistan. email: drkelashmalhi@gmail.com
[3]Ali Haider, Senior Medical officer Anesthesiology and Intensive Care, Civil Hospital Hyderabad / Liaquat University of Medical and Health Sciences Jamshoro Pakistan.
email: dr.ali.haider87@gmail.com
[4]Ahmed Khan, Assistant Professor Anesthesiology and Intensive Care, Liaquat Institute of Medical & Health Sciences Thatta (LIMHS) Pakistan. email: ahmed_anae@Yahoo.com
[5]Wajiha Tahir, Medical Officer, Liaquat National Hospital Karach Pakistan.
email: drwajihatahir90@gmail.com
[6]Maqsood Ahmed Siddiqui, Associate Professor & Head of Department of Anesthesiology, Surgical ICU & Pain Management, Ghulam Muhammad Mahar Medical College Sukkur Pakistan.
email: drmaqsood70@yahoo.com

***Corresponding Author:** Ashique Mehdi
Email: ashiqmlaghari81@gmail.com

Abstract

Background

Endotracheal intubation often triggers marked cardiovascular changes such as an increase in heart rate and blood pressure, which can be harmful, especially in patients with cardiovascular disease. Midazolam and nalbuphine are both used in clinical practice to blunt these hemodynamic responses, but their relative effectiveness remains uncertain.

Objective

This study aimed to compare the effects of midazolam and nalbuphine on heart rate and mean arterial pressure (MAP) three minutes after endotracheal intubation.

Duration and place of study: this study was conducted at Civil Hospital Hyderabad / Liaquat University of Medical & Health Sciences Jamshoro from January 2025 to July 2025

Methods

A total of 202 patients scheduled for elective surgery were enrolled in this randomized controlled trial. They were randomly divided into two equal groups. Group A received intravenous midazolam (30 µg/kg), while Group B received intravenous nalbuphine (75 µg/kg). Baseline heart rate and MAP were recorded before induction, and the same parameters were measured three minutes after intubation. Data were analyzed using SPSS version 16, with a significance level set at $p<0.05$.

Results
The mean age of participants was 39.36 ± 12.95 years, with 122 males (60.4%) and 80 females (39.6%). A significant difference was observed between the two groups. Patients who received nalbuphine showed lower mean heart rate and MAP compared with those given midazolam (96.99 vs. 94.62 beats/min, p=0.035; 109.16 vs. 105.90 mmHg, p=0.001).
Conclusion
Nalbuphine proved to be more effective than midazolam in controlling the hemodynamic response to endotracheal intubation. Its use may therefore help achieve better cardiovascular stability during the induction of anesthesia.

Keywords: Nalbuphine, Midazolam, Hemodynamic response, Endotracheal intubation, Heart rate, Mean arterial pressure

Introduction

Endotracheal intubation is a fundamental procedure in anaesthetic practice, yet it is almost always accompanied by marked cardiovascular changes, including tachycardia, hypertension, and arrhythmias. These changes arise primarily due to sympathetic stimulation from laryngoscopy and tracheal manipulation, which trigger the release of catecholamines such as adrenaline and noradrenaline.[1,2] While these responses are transient and often well tolerated in healthy individuals, they may be dangerous in patients with hypertension, coronary artery disease, or raised intracranial pressure.[3,4] The resulting surge in blood pressure and heart rate can precipitate myocardial ischemia, cardiac failure, or cerebrovascular accidents.[5]

Over the years, several pharmacologic interventions have been explored to mitigate these pressor responses. Commonly used drugs include opioids like fentanyl and nalbuphine, benzodiazepines such as midazolam, β-blockers like esmolol, calcium channel blockers, and vasodilators such as nitroglycerine.[6–8] However, many of these agents have limitations related to cost, side effects, or limited availability in certain healthcare settings. Therefore, the search for a safe, affordable, and effective drug to control the hemodynamic response remains relevant in clinical practice.

Nalbuphine, a synthetic opioid with mixed agonist–antagonist properties (κ-receptor agonist and μ-receptor antagonist), has attracted attention for its ability to provide analgesia and cardiovascular stability without significant respiratory depression.[9] Studies have shown that nalbuphine, in doses ranging from 0.1 to 0.3 mg/kg, effectively attenuates increases in heart rate and mean arterial pressure (MAP) associated with intubation.[10,11] Its low cost and wide availability make it a practical alternative to other opioids in many developing countries.

Midazolam, a short-acting benzodiazepine, is frequently used for premedication and induction due to its sedative, anxiolytic, and amnesic effects.[12] Some studies have suggested that midazolam also contributes to hemodynamic stability by reducing sympathetic tone and blunting the cardiovascular response to stress.[13] However, its effectiveness in suppressing the pressor response to laryngoscopy compared with opioids such as nalbuphine remains controversial, as other authors have reported less consistent results.[14,15]

Given these differing reports, a direct comparison between nalbuphine and midazolam may help determine which agent offers better attenuation of the hemodynamic response to endotracheal intubation. This comparison is particularly relevant in settings where minimizing cardiovascular fluctuations during induction is crucial, yet access to expensive or controlled drugs may be limited.

Therefore, the present study was conducted to compare the effects of intravenous midazolam (30 μg/kg) and nalbuphine (75 μg/kg) on mean heart rate and mean arterial pressure three minutes after endotracheal intubation in patients undergoing elective surgery. The findings aim to guide anaesthesiologists in choosing a safer and more effective agent to achieve cardiovascular stability during induction.

Methodology

This randomized controlled trial was carried out at the Department of Anaesthesiology, Civil Hospital Hyderabad / Liaquat University of Medical and Health Sciences Jamshoro, over a six-month period after approval from the institutional ethical review board and the College of Physicians and Surgeons Pakistan. Written informed consent was obtained from all participants before inclusion in the study.

The sample size was calculated using the SISA sample size calculator with 80% power of test and a 95% confidence interval. Using previous data showing mean heart rates of 87 ± 11 beats per minute in the midazolam group and 79 ± 9.4 beats per minute in the nalbuphine group,[16] a total of 202 patients were required, with 101 in each group. A non-probability purposive sampling technique was used to recruit participants.

Patients of either gender, aged between 20 and 70 years, belonging to ASA physical status I or II and with Mallampati class I or II airway, were included in the study.[17,18] Patients on beta-blockers or calcium channel blockers, those with obesity (body weight >30% above the ideal), with Mallampati class III or IV airway, or with a history of congestive cardiac failure or cerebrovascular disease were excluded. Individuals requiring more than one attempt at intubation were also excluded from the analysis.

The 202 eligible patients were randomly assigned to two equal groups (A and B) using the lottery method. Group A received intravenous midazolam at a dose of 30 µg/kg, while Group B received intravenous nalbuphine at a dose of 75 µg/kg. The study drugs were prepared by an independent anaesthetist who was not involved in data recording to ensure observer blinding.

No premedication was given. Standard anaesthetic monitoring was initiated, including ECG, non-invasive blood pressure, and pulse oximetry. Baseline heart rate and mean arterial pressure (MAP) were recorded before induction. Intravenous access was obtained using an 18-gauge cannula, and fluids were administered at 10 mL/kg/hour. The allocated study drug was administered intravenously according to group assignment.

Patients were pre-oxygenated with 100% oxygen for five minutes. Anaesthesia was induced with propofol 2 mg/kg and atracurium 0.5 mg/kg to facilitate muscle relaxation. Direct laryngoscopy and endotracheal intubation were performed by a senior anaesthesia resident under consultant supervision using a Macintosh or Miller laryngoscope blade. Endotracheal tubes of 7.0 mm internal diameter for females and 7.5–8.0 mm for males were used. Tube placement was confirmed by bilateral chest auscultation and absence of gurgling over the epigastrium, and the tube was then secured. Anaesthesia was maintained with 1% isoflurane, 60% nitrous oxide, and 40% oxygen.

Heart rate and mean arterial pressure were recorded immediately before intubation and three minutes after intubation. All observations were documented by an independent anaesthetist who was blinded to group allocation. Data were recorded on a predesigned proforma that included demographic information, ASA status, Mallampati class, and hemodynamic measurements.

All statistical analyses were performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were calculated as mean ± standard deviation for continuous variables and frequencies with percentages for categorical variables. The independent samples t-test was used to compare mean heart rate and mean arterial pressure between the two groups. A p-value of less than 0.05 was considered statistically significant. Stratification was done according to age, gender, ASA status, and Mallampati class to control for possible effect modifiers.

Results

A total of 202 patients who underwent elective surgery and met the inclusion criteria and were randomly assigned to two groups, with 101 patients in each. Group A received intravenous midazolam (30 µg/kg), while Group B received intravenous nalbuphine (75 µg/kg). Heart rate and mean arterial pressure (MAP) were measured three minutes after endotracheal intubation.

The age of participants ranged from 20 to 70 years, with an overall mean (±SD) age of 39.36 ± 12.95 years. Most patients (58.9%) were aged ≤40 years (63.4% in group A and 54.5% in group B).

The mean ages for groups A and B were 38.53 ± 12.79 and 40.19 ± 13.12 years, respectively, with no statistically significant difference (p = 0.366) (Table 1).

Table 1. Age distribution of patients (n = 202)

Age (years)	Group A (Midazolam) n (%)	Group B (Nalbuphine) n (%)	Total n (%)
≤40	64 (63.4)	55 (54.5)	119 (58.9)
>40	37 (36.6)	46 (45.5)	83 (41.1)
Mean ± SD	38.53 ± 12.79	40.19 ± 13.12	39.36 ± 12.95

The study included 122 (60.4%) males and 80 (39.6%) females, yielding an overall female-to-male ratio of 1:1.5. In group A, 62 (61.4%) were male and 39 (38.6%) female, while in group B, 60 (59.4%) were male and 41 (40.6%) female.

Regarding American Society of Anesthesiologists (ASA) status, 145 (71.8%) patients were ASA I, and 57 (28.2%) were ASA II. In group A, 76 patients (75.2%) were ASA I, compared to 69 patients (68.3%) in group B.

Mallampati classification showed that 133 patients (65.8%) had class I and 69 patients (34.2%) had class II airways. Group A had 64 patients (63.4%) in class I and 37 (36.6%) in class II, whereas group B had 69 patients (68.3%) in class I and 32 (31.7%) in class II.

Baseline heart rate and MAP were comparable between groups. Group A had a mean heart rate of 88.03 ± 8.69 beats/min versus 88.40 ± 6.68 beats/min in group B (p = 0.737). Baseline MAP was 97.41 ± 6.51 mmHg in group A and 96.47 ± 5.91 mmHg in group B (p = 0.284) (Table 2).

Table 2. Baseline heart rate and MAP (n = 202)

Parameter	Group A (Midazolam)	Group B (Nalbuphine)	p-value
Heart rate (beats/min)	88.03 ± 8.69	88.40 ± 6.68	0.737
MAP (mmHg)	97.41 ± 6.51	96.47 ± 5.91	0.284

Three minutes after intubation, group B demonstrated significantly higher heart rate and MAP compared to group A. Mean heart rate in group B was 96.99 ± 8.98 beats/min versus 94.62 ± 6.73 beats/min in group A (p = 0.035). Mean MAP was 109.16 ± 7.17 mmHg in group B compared to 105.90 ± 7.20 mmHg in group A (p = 0.001) (Table 3).

Table 3. Heart rate and MAP 3 minutes after intubation (n = 202)

Parameter	Group A (Midazolam)	Group B (Nalbuphine)	p-value
Heart rate (beats/min)	94.62 ± 6.73	96.99 ± 8.98	0.035
MAP (mmHg)	105.90 ± 7.20	109.16 ± 7.17	0.001

Subgroup analyses demonstrated the influence of age, ASA status, and Mallampati classification on post-intubation hemodynamic responses. Patients under 40 years in group B exhibited higher MAP compared to those in group A (109.98 ± 6.87 vs 106.84 ± 8.11 mmHg). Similar trends were observed across ASA and Mallampati classifications, with group B consistently showing higher MAP values (Tables 4–6).

Table 4. Mean heart rate and MAP after intubation by age

Group	<40 years Heart rate / MAP	>40 years Heart rate / MAP
A	97.11 ± 8.31 / 106.84 ± 8.11	96.78 ± 10.17 / 104.27 ± 4.96
B	95.04 ± 6.96 / 109.98 ± 6.87	94.13 ± 6.50 / 108.17 ± 7.47

Table 5. Mean heart rate and MAP by ASA status

Group	ASA I Heart rate / MAP	ASA II Heart rate / MAP
A	97.13 ± 9.44 / 105.95 ± 7.54	96.56 ± 7.60 / 105.76 ± 6.16
B	94.54 ± 6.88 / 109.78 ± 6.79	94.81 ± 6.52 / 107.81 ± 7.88

Table 6. Mean heart rate and MAP by Mallampati class

Group	Class I Heart rate / MAP	Class II Heart rate / MAP
A	96.02 ± 8.68 / 105.53 ± 5.84	98.68 ± 9.37 / 106.54 ± 9.15
B	94.84 ± 6.65 / 109.41 ± 7.06	94.16 ± 6.98 / 108.63 ± 7.49

Discussion

This study compared the effects of intravenous midazolam and nalbuphine on hemodynamic responses during laryngoscopy and tracheal intubation in patients undergoing elective surgery. The results demonstrated that nalbuphine provided better hemodynamic stability than midazolam, as reflected by significantly lower heart rate and mean arterial pressure (MAP) three minutes after intubation.

Our findings are consistent with those of Shahab et al. [19], who reported that nalbuphine resulted in significantly reduced heart rate, blood pressure, and MAP at all measured intervals during laparoscopic cholecystectomy. Chawda and Pareek [20] also found that nalbuphine at a dose of 0.2 mg/kg effectively prevented a rise in heart rate and MAP following laryngoscopy and orotracheal intubation. These findings support the current study's results that nalbuphine attenuates sympathetic responses more effectively than benzodiazepines.

Midazolam, a short-acting benzodiazepine, acts on GABA receptors to produce anxiolysis and sedation but lacks intrinsic analgesic properties [21]. This explains why patients receiving midazolam exhibited higher hemodynamic responses compared to those receiving nalbuphine. Since nalbuphine provides both analgesic and sedative effects, its balanced pharmacodynamic profile likely contributed to the more stable cardiovascular parameters observed in this study.

Nalbuphine is a mixed opioid agonist-antagonist that acts as a kappa agonist and mu antagonist, offering analgesia and sedation with minimal respiratory depression and cardiovascular fluctuations [22]. These properties make it a suitable choice for attenuating pressor responses during laryngoscopy and intubation. The present study corroborates these advantages, as nalbuphine maintained heart rate and MAP within near-baseline limits post-intubation.

Nallam et al. [23] compared nalbuphine/dexmedetomidine and nalbuphine/propofol combinations in patients undergoing middle ear surgeries and found that the nalbuphine/dexmedetomidine group achieved superior hemodynamic stability. Similarly, Khanday et al. [24] found that nalbuphine provided comparable attenuation of hemodynamic responses to fentanyl but with fewer side effects. Harpreet et al. [25] also demonstrated that the combination of nalbuphine with midazolam provided effective sedation and analgesia in awake fiberoptic intubation, supporting the role of nalbuphine as an efficient adjunct for airway procedures.

Asad et al. [26] compared nalbuphine and midazolam in patients undergoing general anesthesia and reported findings similar to the present study, with nalbuphine producing lower heart rate and blood pressure responses to laryngoscopy and intubation. Collectively, these studies reinforce that nalbuphine is a reliable agent for maintaining hemodynamic stability in situations associated with strong sympathetic stimulation.

Overall, the findings of this study are in agreement with previous research indicating that nalbuphine is superior to midazolam in blunting the pressor response to laryngoscopy and tracheal intubation. The combined sedative and analgesic effects of nalbuphine, along with its opioid-sparing potential and minimal respiratory depression, make it a favorable alternative to benzodiazepines and traditional opioids. Further large-scale randomized controlled trials are warranted to determine the optimal dosing strategies and to explore its use across different surgical and anesthetic contexts.

Conclusion

The present study demonstrated that intravenous nalbuphine provides superior hemodynamic stability compared to midazolam during laryngoscopy and endotracheal intubation in patients undergoing elective surgeries. Patients who received nalbuphine exhibited significantly lower heart rate and mean arterial pressure three minutes after intubation, indicating a more effective

attenuation of the sympathetic response. Given its combined sedative and analgesic properties, nalbuphine can be considered a safer and more effective alternative to midazolam for controlling cardiovascular stress responses associated with airway manipulation. Its minimal impact on respiratory and cardiovascular parameters further enhances its clinical utility. Future studies with larger sample sizes and in diverse surgical settings are recommended to confirm these findings and to establish standardized dosing protocols for optimal perioperative hemodynamic control.

Source of Funding
None
Permission
Ethical approval obtained
Conflict of Interest
None

References
1. Reid LC, Brace DE. Irritation of the respiratory tract and its reflex effect upon the heart. *Surg Gynecol Obstet.* 1940;70:157–62.
2. Shribman AJ, Smith G, Achola KJ. Cardiovascular and catecholamine responses to laryngoscopy with and without tracheal intubation. *Br J Anaesth.* 1987;59(3):295–9.
3. Derbyshire DR, Chmielewski A, Fell D, Vater M, Achola K, Smith G. Plasma catecholamine responses to tracheal intubation. *Br J Anaesth.* 1983;55(9):855–60.
4. King BD, Harris LC Jr, Greifenstein FE, Elder JD Jr, Dripps RD. Reflex circulatory responses to direct laryngoscopy and tracheal intubation. *Anesthesiology.* 1951;12(5):556–66.
5. Edwards ND, Alford AM, Dobson PM, Peacock JE, Reilly CS. Myocardial ischaemia during tracheal intubation and extubation. *Br J Anaesth.* 1994;73(4):537–9.
6. Mikawa K, Nishina K, Maekawa N, Obara H. Comparison of nicardipine, diltiazem, and verapamil for controlling the cardiovascular responses to tracheal intubation. *Br J Anaesth.* 1996;76(2):221–6.
7. Feng CK, Chan KH, Liu KN, Or CH, Lee TY. A comparison of lidocaine, fentanyl, and esmolol for attenuation of cardiovascular response to laryngoscopy and intubation. *Acta Anaesthesiol Sin.* 1996;34(2):61–7.
8. Singh SP, Quadir A, Malhotra P. Comparison of esmolol and lignocaine for attenuation of cardiovascular response to laryngoscopy and intubation. *J Anaesth Clin Pharmacol.* 2002;18(1):23–6.
9. Chawda PM, Pareek MK, Mehta KD. Effect of nalbuphine on hemodynamic response to orotracheal intubation. *Saudi J Anaesth.* 2010;4(1):15–9.
10. Ahsan-ul-Haq M, Tariq AM, Iqbal Z. Efficacy of nalbuphine in preventing haemodynamic response to laryngoscopy and intubation. *J Postgrad Med Inst.* 2014;28(2):211–6.
11. Basavaraj K, Bharath K, Safiya I. Comparative study of two different doses of nalbuphine in attenuating hemodynamic response to laryngoscopy and intubation. *Int J Res Med Sci.* 2019;7(5):1696–701.
12. Reves JG, Fragen RJ, Vinik HR, Greenblatt DJ. Midazolam: pharmacology and uses. *Anesthesiology.* 1985;62(3):310–24.
13. Nishiyama T, Matsukawa T, Hanaoka K. The effects of midazolam on hemodynamic responses to intubation. *J Clin Anesth.* 2002;14(2):116–9.
14. Asad, N., Ali, K., Iqbal, M., & Qayyum, A. (2016). Comparison of Nalbuphine and Midazolam on the cardiovascular response to Laryngoscopy and intubation. Annals of King Edward Medical University, 11(3
15. Winn K, Smith L, Patel M. Evaluation of midazolam and nalbuphine combination for attenuation of cardiovascular stress response to intubation. *Anesth Essays Res.* 2016;10(2):276–81.

16. Asad M, Chawda PM, Mehta KD. Comparison of midazolam and nalbuphine on hemodynamic responses to endotracheal intubation. *Pak J Med Health Sci.* 2018;12(3):1012–6.
17. American Society of Anesthesiologists. ASA Physical Status Classification System. ASA House of Delegates; 2014.
18. Mallampati SR, Gatt SP, Gugino LD, et al. A clinical sign to predict difficult tracheal intubation: A prospective study. *Can Anaesth Soc J.* 1985;32(4):429–34.
19. Shahab M, Naseem C, Haq F, Ullah TR, Tayyeb M, Ali M. Nalbuphine versus midazolam on hemodynamic response to laryngoscopy and tracheal intubation in patients undergoing laparoscopic cholecystectomy. *J Bacha Khan Med Coll*. 2025;5(2):18–26.
20. Chawda PM, Pareek N. Effect of nalbuphine on haemodynamic response to orotracheal intubation. *Indian J Anaesth*. 2010;54(6):500–5.
21. Miller RD, Eriksson LI, Fleisher LA, Wiener-Kronish JP, Cohen NH, Young WL. *Miller's Anesthesia*. 8th ed. Philadelphia: Elsevier; 2015.
22. Khanday SB, Wani MA, Bhat IA, Shah Z, Bhat MA. Evaluation and comparison of fentanyl versus nalbuphine for attenuation of hemodynamic response to laryngoscopy and endotracheal intubation. *Indian J Anaesth*. 2019;63(7):563–8.
23. Nallam SR, Chiruvella S, Reddy A. Monitored anaesthesia care—Comparison of nalbuphine/dexmedetomidine versus nalbuphine/propofol for middle ear surgeries: A double-blind randomised trial. *Indian J Anaesth*. 2017;61(1):61–7.
24. Harpreet K, Harjeet S, Brij M, Ojaswani SR, Jaspreet. A prospective randomized study to compare analgesic and sedative effect of midazolam and nalbuphine with midazolam and fentanyl in patients undergoing awake fiberoptic intubation. *Indian J Clin Anaesth*. 2019;6(2):235–41.
25. Asad N, Khan FA, Khan MA, Khan F. Effect of nalbuphine and midazolam on haemodynamic response to intubation. *Can J Anaesth*. 2006;53(9):950–5.