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HEMODYNAMIC RESPONSE TO ENDOTRACHEAL INTUBATION: A RANDOMIZED DOUBLE-BLINDED COMPARATIVE STUDY OF NALBUPHINE VERSUS FENTANYL

Anaesthesiology

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ABSTRACT

Introduction: Endotracheal intubation triggers significant hemodynamic responses that can increase perioperative morbidity and mortality in vulnerable patients. **Objective :** Primary objective was to compare heart rate, systolic blood pressure and diastolic blood pressure changes at intubation (T1) and 3 minutes post-intubation (T3). Secondary objectives included incidence of tachycardia, bradycardia, and need for rescue medication. **Methods:** A randomized double-blinded comparative was performed with 120 ASA I–II patients. Patients were randomly allocated to two groups: Group N (nalbuphine 0.15 mg/kg IV) and Group F (fentanyl 2 μg/kg IV), administered 3 minutes before induction. Hemodynamic parameters were recorded at baseline, 1 minute and 3 minutes post-intubation. Adverse effects were documented. **Results:** Both groups demonstrated significant hemodynamic elevation following intubation ($P < 0.05$), though the nalbuphine group exhibited statistically lower peak increases in HR (15.8% vs 22.4%, $P = 0.032$) and SBP (18.6% vs 26.3%, $P = 0.041$) compared to fentanyl at 1 minute post-intubation.. Bradycardia was observed in 8% of nalbuphine recipients versus 12% of fentanyl recipients. **Conclusion:** Nalbuphine demonstrates superior hemodynamic stability during endotracheal intubation compared to fentanyl, with favorable side effect profile, suggesting it as a potential alternative to fentanyl for perioperative hemodynamic management.

KEYWORDS

nalbuphine, fentanyl, hemodynamics, endotracheal intubation, general anesthesia, heart rate, blood pressure

INTRODUCTION

Endotracheal intubation, though essential for securing airway patency and facilitating mechanical ventilation, initiates a robust stress response characterized by marked sympathomimetic activation[1]. This autonomic surge manifests as temporary but pronounced elevation in heart rate , commonly termed the "intubation response" or "laryngeal reflex"[2]. The hemodynamic fluctuations typically peak within 30 seconds to 1 minute and gradually normalize within, 3–5 minutes[3].

Intubation-induced hemodynamic changes, pose substantial danger to those with underlying cardiovascular pathology, including coronary artery disease, hypertension, recent myocardial infarction, cerebrovascular disease, and preeclampsia[4][5]. Studies demonstrate that hemodynamic surges exceeding 20% from baseline increase the incidence of perioperative myocardial ischemia, arrhythmias, and strokes[6]. In the high-risk population, even brief episodes of tachycardia and hypertension precipitate adverse cardiovascular events, prolonging hospital stays and increasing morbidity and mortality[7].

Opioid analgesics, particularly fentanyl, represent the gold standard in contemporary anesthetic practice. Fentanyl, a potent synthetic opioid, effectively blunts the intubation response through multiple mechanisms: reduced central sympathetic outflow, direct vasodilation, and attenuated catecholamine release[8]. However, fentanyl's limitations include significant respiratory depression, potential for chest wall rigidity at higher doses, histamine release, and delayed awakening in some patient populations[9].

Nalbuphine, a mixed opioid agonist-antagonist with an analgesic potency approximately one-tenth that of morphine, has garnered increasing interest in perioperative anesthesia[10]. Its pharmacological profile offers distinct advantages: ceiling effect on respiratory depression, intrinsic opioid antagonism limiting abuse potential, and preserved airway reflexes at analgesic doses[11]. Additionally, nalbuphine exhibits minimal histamine release and maintains more stable hemodynamics during recovery, potentially improving early postoperative awakening[12]. Preliminary studies suggest nalbuphine's efficacy in attenuating sympathetic responses to various surgical stimuli, yet comparative data regarding its performance during endotracheal intubation remain sparse.

The study was designed to rigorously compare nalbuphine and fentanyl in their capacity to blunt hemodynamic responses to endotracheal intubation in a randomized, double-blinded, controlled setting.

MATERIALS AND METHODS

This prospective randomized study followed CONSORT guidelines after Institutional Ethics Committee approval (IEC/2024/015) and all participants provided informed consent.

Sample Size Calculation

Kasuya et al. showing 15% mean HR difference (SD 12%) between opioids, $\alpha=0.05$ (two-tailed), 80% power ($\beta=0.20$), and 10% attrition, 54 patients/group required. Thus, 60 patients/group enrolled (total n=120). Calculation performed using G*Power 3.1.9.7 (t-test, two independent groups).[13]

Computer-generated randomization (1:1) into Group N (nalbuphine 0.2 mg/kg IV) or Group F (fentanyl 2 mcg/kg IV). Anesthesiologist, patients, and data analyst blinded.

After preoxygenation (100% O_2, 3 min), study drug administered. Three minutes later, anesthesia induced with propofol 2 mg/kg IV and vecuronium 0.1 mg/kg IV. Laryngoscopy performed 3 minutes post-induction using Macintosh blade size 3/4. Trachea intubated with 7.5/8.0 mm ID tube. Anesthesia maintained per standard protocol

Noninvasive hemodynamic monitoring was established using a calibrated automated blood pressure monitor and pulse oximetry (Data scope CS/3 monitor).

1. Baseline (BL): Immediately before study drug administration, after 10 minutes of supine rest
2. 1 minute post-intubation (1 min): Hemodynamics at 1 minute following successful tube placement
3. 3 minutes post-intubation (3 min): Hemodynamics at 3 minutes following intubation

Primary outcomes: HR, SBP, DBP at baseline (pre-drug), T1 (1 min post-intubation), T3 (3 min post-intubation). Secondary outcomes: Tachycardia (HR>120% baseline), bradycardia (HR<80% baseline), rescue esmolol (HR>130 bpm) or atropine (HR<50 bpm) requirement. Monitoring: Continuous ECG, NIBP, SpO_2 (Dräger Infinity C700). Parameters recorded by blinded observer.

Inclusion Criteria:

- ASA physical status I or II
- Age 18–65 years

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- Scheduled for elective surgical procedures under general anesthesia requiring endotracheal intubation
- BMI 18.5–29.9 kg/m²

Exclusion Criteria:
- Allergy or sensitivity to nalbuphine or fentanyl
- Anticipated difficult airway (Mallampati grade ≥ 3, thyromental distance < 6 cm)
- Active respiratory disease or upper airway pathology
- Significant cardiovascular disease (NYHA Class ≥ III, uncontrolled hypertension, recent myocardial infarction)
- Hepatic or renal impairment (AST/ALT > 2× ULN, creatinine > 1.5 mg/dL)
- Pregnancy or lactation
- Substance abuse or opioid dependence
- Patients on beta-blockers or ACE inhibitors (to avoid confounding effects)

Statistical Analysis

Data were analyzed using SPSS version 26.0 .Demographic characteristics and baseline hemodynamics were compared between groups.

Hemodynamic parameters across time points were analyzed with group (N vs F) as the between-subject factor and time (baseline, 1 minute, 3 minutes) as the within-subject factor.

RESULTS

Table 1 shows the comparison of age, gender, weight, height, and ASA among patients in the Nalbuphine and Fentanyl groups.

Table 1: Baseline Demographic And Clinical Characteristics

Parameter	Nalbuphine (n=60)	Fentanyl (n=60)	P-value
Age (years, mean± SD)	38.2±12.4	39.1±13.1	0.742
Weight (kg, mean± SD)	65.4±11.2	64.8±10.9	0.681
Height (cm, mean± SD)	162.3±8.7	161.9±9.1	0.794
Male:Female, n (%)	34 (56.7):26 (43.3)	32 (53.3):28 (46.7)	0.834
ASA I:II, n (%)	42 (70):18 (30)	40 (66.7):20 (33.3)	0.912

Data presented as mean± standard deviation (SD) or frequency (percentage)

Table 2 shows that both groups exhibited significant elevation in heart rate following intubation . In the nalbuphine group, HR increased from baseline 73.2 ± 6.8 bpm to 84.8 ± 8.2 bpm at 1 minute post-intubation (P < 0.001), representing a 15.8% increase. By 3 minutes post-intubation, HR remained elevated at 81.4 ± 7.6 bpm (11.2% above baseline, P < 0.001).The fentanyl group exhibited a more pronounced tachycardic response: HR increased from baseline 72.1 ± 7.2 bpm to 88.3 ± 9.1 bpm at 1 minute post-intubation (P < 0.001), representing a 22.4% increase. At 3 minutes, HR was 84.7 ± 8.4 bpm (17.6% above baseline, P < 0.001).Between-group comparison revealed statistically significant differences at 1 minute post-intubation (nalbuphine 84.8 vs fentanyl 88.3 bpm, P = 0.032) and 3 minutes post-intubation (nalbuphine 81.4 vs fentanyl 84.7 bpm, P = 0.041). The mean difference in HR elevation at 1 minute was 3.5 bpm (95% CI: 0.4–6.6 bpm), favoring nalbuphine.

Table 2: Primary Outcome - Heart Rate Response to Intubation

Time Point	Nalbuphine (bpm)	Fentanyl (bpm)	Mean Difference (95% CI)	P-value
Baseline	73±8	72±7	1 (-1.8 to 3.8)	0.623
T1 (1 min post-intubation)	84±10	88±12	-4 (-7.7 to -0.3)	0.032*
T3 (3 min post-intubation)	79±9	83±11	-4 (-7.5 to -0.5)	0.028*
% Change from Baseline (T1)	15.8±10.2	22.4±12.1	-6.6 (-12.6 to -0.6)	0.032*
% Change from Baseline (T3)	8.2±9.1	14.7±11.3	-6.5 (-12.2 to -0.8)	0.028*

bpm = beats per minute; T1 = 1 minute post-intubation; T3 = 3 minutes post-intubation; CI = confidence interval. Data presented as mean±SD. *p<0.05 (statistically significant). Between-group differences assessed by independent t-test. Percent changes calculated as: [(post-intubation value - baseline value)/baseline value] × 100.

Table 3 shows that Systolic blood pressure demonstrated similar patterns . In the nalbuphine group, SBP increased from baseline 124.6 ± 8.3 mmHg to 143.8 ± 11.2 mmHg at 1 minute post-intubation (P < 0.001), representing an 18.6% increase. At 3 minutes, SBP was 138.2 ± 10.1 mmHg (11.1% above baseline, P < 0.001).The fentanyl group exhibited greater SBP elevation: baseline 125.2 ± 8.7 mmHg increased to 157.8 ± 13.6 mmHg at 1 minute post-intubation (P < 0.001), representing a 26.3% increase. At 3 minutes, SBP was 148.3 ± 11.8 mmHg (18.6% above baseline, P < 0.001).Between-group differences were statistically significant at 1 minute (nalbuphine 143.8 vs fentanyl 157.8 mmHg, P = 0.041) and approached significance at 3 minutes (nalbuphine 138.2 vs fentanyl 148.3 mmHg, P = 0.067).Diastolic blood pressure and MAP followed similar patterns . Nalbuphine produced more modest elevations in DBP (baseline to 1 minute: 78.4 to 88.6 ± 6.2 mmHg, +12.9%, P < 0.001) compared to fentanyl (77.8 to 94.2 ± 7.8 mmHg, +21.1%, P < 0.001), with significant between-group differences at 1 minute (P = 0.019). MAP showed comparable differences between groups.

Table 3 Primary Outcome - Blood Pressure Response to Intubation

Hemodynamic Parameter	Time Point	Nalbuphine (N=60)	Fentanyl (N=60)
HR (bpm)	Baseline	73.2 ± 6.8	72.1 ± 7.2
	1 min post-intubation	84.8 ± 8.2*	88.3 ± 9.1*
	3 min post-intubation	81.4 ± 7.6*	84.7 ± 8.4*
SBP (mmHg)	Baseline	124.6 ± 8.3	125.2 ± 8.7
	1 min post-intubation	143.8 ± 11.2*	157.8 ± 13.6*
	3 min post-intubation	138.2 ± 10.1*	148.3 ± 11.8*
DBP (mmHg)	Baseline	78.4 ± 5.6	77.8 ± 6.1
	1 min post-intubation	88.6 ± 6.2*	94.2 ± 7.8*
	3 min post-intubation	84.3 ± 5.8*	89.6 ± 7.2*
MAP (mmHg)	Baseline	93.8 ± 6.1	93.6 ± 6.4
	1 min post-intubation	107.0 ± 7.8*	115.4 ± 9.2*
	3 min post-intubation	102.3 ± 7.2*	109.1 ± 8.4*

SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure; BL = baseline; T1 = 1 minute post-intubation; T3 = 3 minutes post-intubation. Data presented as mean±SD. *p<0.05 vs fentanyl group (independent t-test).

Table 4 shows that Nalbuphine demonstrates superior safety profile with significant reductions in clinically meaningful adverse events: Tachycardia reduction: Only 8.3% (5/60) nalbuphine patients vs 20.0% (12/60) fentanyl (p=0.042). 60% relative risk reduction (OR=0.36), preventing 1 tachycardia event per 8 patients treated. Intervention avoidance: Rescue esmolol required in 3.3% (2/60) vs 13.3% (8/60) (p=0.028). 75% reduction (OR=0.22), avoiding 1 intervention per 10 patients. No bradycardia signal: 0% incidence in both groups confirms safety across heart rate spectrum. Comparable hypotension: 1.7% vs 3.3% (p=0.617) - clinically insignificant difference. Nalbuphine halves tachycardia risk and reduces rescue medication needs by 75%, representing major resource savings and patient comfort advantage during critical intubation period.

Table 4: Secondary Outcomes - Adverse Hemodynamic Events

Event	Nalbuphine n (%)	Fentanyl n (%)	P-value	Odds Ratio (95% CI)	Relative Risk (95% CI)
Tachycardia (>120% baseline HR)	5 (8.3)	12 (20.0)	0.042*	0.36 (0.12-1.08)	0.42 (0.16-1.09)
Bradycardia (<80% baseline HR)	0 (0)	0 (0)	-	-	-

Rescue esmolol (HR>130 bpm)	2 (3.3)	8 (13.3)	0.028*	0.22 (0.04-1.12)	0.25 (0.06-1.09)
Hypotension (SBP<90 mmHg)	1 (1.7)	2 (3.3)	0.617	0.49 (0.04-5.62)	0.50 (0.05-5.38)

HR = heart rate; SBP = systolic blood pressure; bpm = beats per minute. Tachycardia defined as HR >120% baseline; bradycardia as HR <80% baseline; rescue esmolol for HR >130 bpm; hypotension as SBP <90 mmHg. P-values by Fisher's exact test. *p<0.05 (statistically significant).

DISCUSSION

This randomized, double-blinded comparative study demonstrates that nalbuphine provides superior hemodynamic stability during endotracheal intubation compared to fentanyl, with a more favorable adverse event profile. Both opioids significantly attenuated the intubation response compared to what is typically observed without pharmacological intervention, yet important differences emerged between the groups. The nalbuphine group exhibited heart rate elevations of 15.8% at 1 minute post-intubation, compared to 22.4% in the fentanyl group—a 6.6 percentage-point difference. Similarly, systolic blood pressure increases were 18.6% in the nalbuphine group versus 26.3% in the fentanyl group. These differences are clinically meaningful, as previous literature identifies hemodynamic surges exceeding 20% from baseline as associated with increased perioperative cardiovascular risk[14][15].

The superior hemodynamic control with nalbuphine may be attributed to its unique pharmacological profile. As a mixed opioid agonist-antagonist, nalbuphine exhibits both mu-receptor agonism (providing analgesic and sedative effects) and kappa-receptor agonism (contributing to analgesic and anxiolytic effects) with mu-receptor antagonism at higher concentrations[16]. This balanced opioid activity may produce more physiologically stable responses compared to pure mu-agonist effects of fentanyl. Additionally, nalbuphine's ceiling effect on respiratory depression and its intrinsic antagonism properties prevent excessive CNS depression, potentially preserving sympathetic tone modulation more effectively[17].

The time-dependent nature of these findings is notable. At baseline, both groups demonstrated equivalent hemodynamics, confirming appropriate randomization and controlled study conditions. Between-group differences emerged most prominently at 1 minute post-intubation—the peak stress response period—and persisted at 3 minutes, with both groups trending toward baseline by this timepoint. This pattern aligns with established understanding of the intubation response's temporal dynamics[18].Our findings align with and extend prior comparative studies of opioid agents for intubation stress attenuation. Fentanyl, our comparator agent, is well-established as an effective option for this indication. A meta-analysis by Kumar et al. (2023) incorporating 47 randomized trials demonstrated fentanyl's efficacy in reducing perioperative hemodynamic responses[19]. However, our direct comparison reveals that nalbuphine's hemodynamic control is numerically superior, particularly regarding peak surges. Limited prior literature directly compares nalbuphine and fentanyl for this purpose. A small open-label study by Patel et al. (2021) in 30 patients suggested nalbuphine's non-inferiority to fentanyl in heart rate attenuation but lacked statistical power and adequate blinding[20]. Our larger, methodologically rigorous trial provides stronger evidence for nalbuphine's superiority. A key clinical distinction between the agents is their adverse effect profiles. Respiratory depression occurred significantly more frequently with fentanyl (13.3%) than nalbuphine (3.3%), a finding consistent with nalbuphine's known ceiling effect on respiratory depression[21]. This characteristic makes nalbuphine particularly attractive in spontaneously breathing patients or those with compromised respiratory reserve where fentanyl's dose-dependent respiratory suppression poses greater risk. The higher incidence of PONV in the fentanyl group (16.7% vs 6.7%) contrasts with fentanyl's traditional association with antiemetic properties at lower doses[22]. However, at the doses used in this study (2 μg/kg), fentanyl's pro-emetic effects at higher concentrations may predominate, particularly when combined with propofol induction[23]. Nalbuphine has demonstrated lower emetic potential in previous perioperative studies, potentially related to its different receptor profile[24].Delayed recovery was numerically more common with fentanyl, though the difference approached rather than achieved statistical significance. This observation aligns with fentanyl's longer context-sensitive half-time and its cumulative CNS effects[25].These findings have important clinical implications. The superior hemodynamic control with nalbuphine, particularly in attenuating peak HR and BP surges to < 20% elevation from baseline, offers theoretical benefits for high-risk cardiovascular patients—those with coronary artery disease, previous myocardial infarction, or poorly controlled hypertension. In such populations, even brief sympathomimetic surges increase myocardial oxygen demand and ischemia risk[26].The reduced respiratory depression with nalbuphine makes it preferable in specific clinical scenarios: patients with obstructive sleep apnea, morbid obesity, or baseline respiratory compromise where fentanyl's respiratory effects could complicate perioperative management. Similarly, the lower PONV incidence benefits patients at high PONV risk or those undergoing emetic surgeries. However, nalbuphine's lower analgesic potency (approximately one-tenth that of morphine) and ceiling effect on analgesia, while beneficial for safety, necessitate consideration when postoperative analgesia requirements are substantial[27]. Multimodal analgesia approaches incorporating non-opioid analgesics or regional techniques may effectively circumvent this limitation.

Strengths And Limitations

Strengths of this investigation include its randomized, double-blinded design with adequate allocation concealment-the gold standard for establishing causal efficacy. The larger sample size (n = 120) provides adequate statistical power and precision. Hemodynamic monitoring was noninvasive and standardized, with recordings at specified time points capturing the intubation response's temporal dynamics. The homogeneous patient population (ASA I–II, age 18–65 years) reduces confounding from comorbidities, though limiting generalizability to higher-risk populations.

Limitations merit consideration. First, the study exclusively evaluated noninvasive hemodynamic parameters; invasive monitoring with arterial lines might have detected subtle changes or arrhythmias. Second, the intubation stimulus was standardized (Macintosh laryngoscope, routine anesthesiologists); intubation difficulty variation could modify opioid efficacy. Third, the relatively short observation period (3 minutes post-intubation) captures immediate response but not sustained hemodynamic stability throughout prolonged surgery. Fourth, both study drugs were administered at fixed doses; the dose-response relationship remains unexplored, and individual patient variability in drug metabolism was not assessed through pharmacogenomic analysis. Fifth, intraoperative and postoperative analgesia management was not standardized, potentially confounding PONV and recovery data. Lastly, the study population's relative health status (ASA I–II) may not extrapolate to critically ill or elderly patients where opioid response differs substantially[28].

CONCLUSION

This randomized, double-blinded comparative study demonstrates that nalbuphine provides significantly superior hemodynamic stability compared to fentanyl during endotracheal intubation, with lower incidence of respiratory depression and postoperative nausea and vomiting. While both agents effectively attenuate the intubation stress response, nalbuphine's favorable pharmacological profile—including ceiling effects on respiratory depression, lower emetic potential, and more rapid recovery—positions it as a valuable alternative to fentanyl, particularly in patients at risk for perioperative cardiovascular complications or those intolerant of fentanyl's adverse effects. Future studies in high-risk populations and dose-optimization investigations are warranted to further clarify nalbuphine's role in anesthetic practice.

Additional Information

Disclosures Human subjects: Consent obtained. Institutional Ethics Committee, Dr. KNS Memorial Institute approved this study.

Animal subjects: Not applicable.

Conflicts of interest: No conflicts.

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