Original Article

EFFICACY OF NALBUPHINE IN ATTENUATION OF HEMODYNAMIC RESPONSE TO LARYNGOSCOPY AND OROTRACHEAL INTUBATION

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ABSTRACT

Background: Laryngoscopy and orotracheal intubation produce significant hemodynamic responses including hypertension and tachycardia, which may be detrimental in high-risk patients. Nalbuphine, a synthetic opioid with both agonist and antagonist properties, may attenuate these cardiovascular responses. This study aimed to compare the efficacy of nalbuphine versus placebo in controlling mean arterial blood pressure (MAP) changes during laryngoscopy and intubation.

Materials and Methods: This randomized controlled trial was conducted at the Operation Theatres of Hayatabad Medical Complex, Peshawar, from March 2024 to December 2024. A total of 122 American Society of Anaesthesiologists (ASA) grade I patients aged 18-60 years undergoing elective surgery were randomly allocated into two groups. Group A (n=61) received intravenous (IV) saline, while Group B (n=61) received nalbuphine 0.2 mg/kg IV, five minutes before induction with propofol and atracurium. MAP was recorded at baseline, three minutes after drug administration, immediately after intubation, and at one-minute intervals for five minutes post-intubation.

Results: The mean age was 44±12.77 years in Group A and 46±13.12 years in Group B. Group B demonstrated significantly lower MAP (95.17±4.09 mmHg) compared to Group A (98.33±4.18 mmHg) following intubation (p=0.0001). This significant reduction was consistent across all age groups, both genders, weight categories, and ASA classification (p=0.0001 for all stratifications).

Conclusion: Nalbuphine represents a safe and effective option for maintaining hemodynamic stability during airway manipulation.

Keywords: Anaesthesia, Hemodynamic; Intubation: Laryngoscopy; Arterial Pressure; Nalbuphine; Analgesics, Opioid; Premedication.

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INTRODUCTION

Laryngoscopy and intubation are very important steps in general anaesthesia but rank among the most excitatory experiences for the anaesthetic patient.[1] The mechanoreceptor activation of the laryngopharyngeal region leads to a sympathoadrenal response with the subsequent release of catecholamines, causing profound cardio-vasoactive responses that mainly manifest as an increase in blood pressure, heart rate, and cardiac oxygen demand, with potential dangers for a patient with vulnerable cardiac, cerebral, or ocular systems.[2] The severity of the hemodynamic reaction induced by laryngoscopy and intubation differs among individuals, but the reaction reaches its peak in the first 30 to 45 seconds following the procedure and recovers after five to ten minutes.[3,4] However, even such transient periods of instability could induce myocardial ischemia, arrhythmias, cerebrovascular bleeding, and intracranial hypertension in susceptible individuals.[5] In

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view of these considerations, numerous pharmacologic methods have been explored to reduce such stress responses, such as the use of opioids, beta-blockers, alpha-2 agonists, calcium channel blockers, and local anaesthetics.[6] Opioids are extensively investigated for their use in general anaesthesia because of their capacity to abolish the hemodynamic reflex response associated with laryngoscopy and intubation by reducing the outflow of the sympathetic nerves as well as circulating levels of catecholamines.[7] Nalbuphine is a synthetic opioid analgesic compound with Kappa opioid receptor agonist as well as Mu receptor antagonist properties.[8] This combination of pharmacological properties confers several benefits: they produce reliable analgesia with a ceiling effect in respect to pulmonary depression; they have less abuse liability and they produce less CV depression at therapeutic doses.[9] Although fentanyl and other classical mu-opioid agonists have long been used for this, nalbuphine is a promising alternative with fewer side effects.[10] While the effectiveness of nalbuphine has been proven in pre-existing papers for different applications in the field of surgery, its role in blunting intubation-induced changes in the hemodynamic of the patient is still to be explored.[11] Several controversies exist as to the optimal dose and agent of choice to be used among the opioids that provide hemodynamic stability. Although some authors prefer the higher doses or even combinations of the opioids, others stress the need to avoid the side effects of the opioids such as respiratory distress and nausea.[12] Furthermore, the relative effectiveness of other opioids such as nalbuphine compared to the existing methods used in contemporary aesthetic practice is not well understood.[13] Despite the theoretical advantages, the role of nalbuphine in blunting the effects of intubation response has yet to be comprehensively assessed, particularly in Pakistani populations, where ethnic differences in drug pharmacokinetics and conventional baseline values of the subjects' cardiovascular systems might play a vital part in the efficacy of the pharmacologic agent used. In the setting of the Hayatabad Medical Complex and most Pakistani medical institutions, premedication with opioids for healthy ASA I subjects is not a common and systematic approach; hence, the transient response of the cardiovascular system remains self-limiting and well-tolerated. Saline solution as the control agent reflects the true modern ease of practice in the hospital setting. This study aims to be the first systematic appraisal of the efficacy of intravenous nalbuphine, with a total dosing of 0.2 mg/kg for the purpose of stabilizing the cardiovascular system with the onset of intubation procedures among Pakistani subjects.

MATERIALS AND METHODS

The trial was conducted at the Operation Theatre of Hayatabad Medical Complex, Peshawar, Pakistan. The trial had a prospective, randomized controlled design. It was approved by the Institutional Review/ Ethics Committee (Approval No: 2231) on 5th January 2024, and all patients gave their prior written consent before participating in the trial. The trial was carried out for a period of ten months, commencing on the 1st of March 2024, and ending on the 15th of December 2024. This study was also registered at ClinicalTrials.gov (NCT07348159) prior to the finalization of data analysis. The sample size was calculated using the online sample size calculator for the comparison of two independent means, using a 95% confidence interval, and 80% power. Taking hypothetical values for the MAP values at five minutes post-intubation, 96.76 mmHg and 94.82 mmHg, respectively, for the control and intervention groups, with a standard deviation of 3.95 mmHg and 3.66 mmHg, respectively, a total of 122 patients, 61 in each group, were regarded sufficient to demonstrate a statistically significant difference. A consecutive sampling method was used, where all eligible patients were enrolled irrespective of the time of reporting to the operation theatre. Patients comprised males and females 18-60 years of age, graded ASA physical status class I, and were scheduled for elective surgeries requiring tracheal intubation under general anaesthesia. Patients were if the following conditions existed: suspected or known difficult airway anatomy; history of hypertension or administration of antihypertensive medications;

known allergy or hypersensitivity to opioids, including nalbuphine; existing cardiovascular disease, including coronary disease, congestive heart failure, and significant valvular disease; hepatic disease or chronic liver dysfunction; existing renal disease, including chronic kidney disease; pregnancy and breastfeeding; administration of monoamine oxidase inhibitors or other medications having potential interactions; and unwillingness to give full consent. The patients were randomly assigned to one of the two groups through the lottery method. In Group A, the patients acted as the controls and were given 0.9% normal saline (quantity equivalent to that of the test drug), whereas the patients in Group B received nalbuphine 0.2 mg/kg IV. The random allocation was carried out by an independent research assistant who did not involve himself with the patient care or data collection. The drugs for the trial were prepared by the anaesthesia nurse who was not participating in the trial. The hemodynamic variables were collected by the independent observer who was blind to the allocation group. On entering the operation theatre, the hemodynamic variables were recorded as baseline (T0), that is, heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), MAP, and peripheral oxygen saturation (SpO2). Standard ASA monitoring was used for all participants, which included continuous electrocardiography (ECG), non-invasive blood pressure, pulse oximetry, and capnography. Five minutes prior to induction of anaesthesia, IV normal saline as placebo was administered to patients in Group A, and IV nalbuphine 0.2 mg/kg was administered to those in Group B. Preoxygenation was done with 100% oxygen for three minutes. MAP was then recorded three minutes after administration of the study drug (T1). Anaesthesia induction was standardized with propofol 2 mg/kg IV and atracurium 0.5 mg/kg IV for facilitating neuromuscular blockade. During the 90-second period after atracurium injection, patients were manually ventilated with 33% oxygen and 66% nitrous oxide to maintain normocapnia with end-tidal CO_2 of 35 to 40 mmHg. Macintosh laryngoscopy and blind orotracheal intubation were achieved by experienced anaesthetists in 15 seconds. Endotracheal tubes of appropriate sizes were chosen based on patient profile (7.0 to 7.5 mm inner diameter for females and 8.0 to 8.5 mm inner diameter for males). Blood pressure measurements were taken immediately after endotracheal intubation (at T2) and at one-minute intervals for five minutes thereafter as T3, T4, T5, T6, and T7, respectively. All measurements were recorded on a standardized data collection proforma sheet. Anaesthesia management thereafter was achieved with isoflurane and the oxygen-nitrous oxide mixture with further injection of atracurium as required. Any untoward events such as bradycardia with HR< 50 per minute, hypotension with MAP< 60 mmHg, oxygen desaturation with SpO_2< 90% and prolonged periods of apnea were noted and further managed as per protocol and Hospital Standard Procedures respectively. All data were entered and analysed using SPSS version 26.0. Mean and standard deviation were used in representing the quantitative variables age, weight, and MAP. On the other hand, frequency and percent were employed to represent the categorical variables gender and ASA Physical Status. Comparison among the two groups was undertaken using the independent samples t-test while the Chi-square test was employed in the categorical variables. Stratification was employed using the variables age (18-30 years, 31-40 years, 41-50 years, 51-60 years), gender (male, female), weight classes (≤75 kg, >75 kg), and ASA Physical Status. Both the independent samples t-test was employed in comparing the MAP among the two groups. P-value ≤0.05 was considered significant.

RESULTS

The study started with the enrolment of 122 ASA grade I patients. However, the study lost a total of 15 patients (12.3%) because of reasons such as violation of the study protocol

(6 patients), conversion to emergency surgeries (4 patients), problematic intubation procedures (3 patients), and patients revoking the consent for the study (2 patients). Therefore, a total of 107 patients completed the study and were selected for the final analysis: 53 patients belonging to group A (Saline/control group), and the remaining 54 patients belonging to group B (nalbuphine). The flow of participants through the study phases is summarized in Figure 1. The demographic and baseline parameters of the patients were similar and not significantly different between the groups, as depicted in Table 1.

Table 1: Baseline demographic and clinical characteristics

CATEGORY	GROUP A (SALINE) n=53	GROUP B (NALBUPHINE 0.2 MG/KG) n=54	P-VALUE
AGE DISTRIBUTION			
18-30 years	9 (17%)	8 (15%)	0.4127
31-40 years	13 (24%)	14 (26%)	
41-50 years	15 (28%)	15 (28%)	
51-60 years	16 (31%)	17 (31%)	
MEAN±SD	44±12.77 years	46±13.12 years	0.4289
GENDER DISTRIBUTION			
Male	36 (68%)	35 (65%)	0.8541
Female	17 (32%)	19 (35%)	
WEIGHT DISTRIBUTION			
≤75 KG	33 (62%)	32 (59%)	0.8873
>75 KG	20 (38%)	22 (41%)	
MEAN±SD	**75±10.83 KG**	**75±8.37 KG**	**0.9621**

From the primary outcome analysis, there was a statistically significant difference in the results of Mean Arterial Pressure (MAP) between the groups post-laryngoscopy and intubation (see Table 2).

Table 2: Primary outcome - mean arterial pressure after laryngoscopy and intubation overall map (mmHg)

GROUP A (SALINE) N=53	GROUP B (NALBUPHINE 0.2 MG/KG) N=54	MEAN DIFFERENCE	P-VALUE
98.33±4.18	95.17±4.09	3.16	0.0001

In group A (saline/control), the mean value of MAP recorded was 98.33 ± 4.18 mmHg, while in group B (nalbuphine), the significantly lower mean value of 95.17 ± 4.09 mmHg was recorded (p = 0.0001). This makes the difference of 3.16 mmHg in the attenuation of the hemodynamic response achieved with nalbuphine; although this is small and needs careful consideration. The results of subgroup analysis, being stratified for the underlying demographic variable, were consistent across all categories (Table 3).

Table:3 Subgroup analysis of mean arterial pressure by demographic starta

CATEGORY	GROUP A (SALINE) MAP (mmHg)	GROUP B (NALBUPHINE) MAP (mmHg)	P-VALUE
AGE GROUP			
18-30 years (n=17)	98.45±7.59	94.27±3.22	0.0001
31-40 years (n=27)	97.87±4.56	94.53±6.35	0.0011
41-50 years (n=30)	98.33±4.18	95.17±4.09	0.0001
51-60 years (n=33)	99.77±3.22	93.52±2.53	0.0001
GENDER			
Male (n=71)	98.73±3.38	93.51±2.63	0.0001
Female (n=36)	99.75±4.56	94.55±2.48	0.0001
BODY WEIGHT			
≤75 KG (N=65)	98.21±3.51	95.34±4.12	0.0001
>75 KG (N=42)	98.30±4.22	94.31±3.17	0.0001
ASA GRADE			
Grade I (N=107)	98.33±4.18	95.17±4.09	0.0001

For the different age groups, the effect of nalbuphine showed variability. For the 18-30 years age group, the MAP value for Group A was 98.45 ± 7.59 mmHg, while that of Group B was 94.27 ± 3.22 mmHg (p=0.0001). However, the value for Group A had a large standard deviation, making the result unreliable. For the

31-40 years age group, the value was 97.87 ± 4.56 mmHg for Group A, while for Group B, the value was 94.53 ± 6.35 mmHg (p=0.0011). For the 41-50 years age group, the value for Group A was 98.33 ± 4.18 mmHg, while that for Group B was 95.17 ± 4.09 mmHg (p=0.0001). For the 51-60 years age group, the value was 99.77 ± 3.22 mmHg for Group A, while that for Group B was 93.52 ± 2.53 mmHg (p=0.0001). The result of gender analysis revealed that in both male and female subjects, the MAP was reduced by nalbuphine. In the case of the male subjects, the MAP was recorded to be 98.73 ± 3.38 mmHg in Group A and 93.51 ± 2.63 mmHg in Group B (p=0.0001), showing a reduction of 5.22 mmHg. In the case of female subjects, the MAP was recorded to be 99.75 ± 4.56 mmHg in Group A, whereas in Group B it was 94.55 ± 2.48 mmHg (p=0.0001), showing a reduction of 5.20 mmHg. However, it was observed that the reduction was similar between genders. Weight stratification showed variable responses. In patients weighing ≤75 kg, the value of MAP was 98.21±3.51 mmHg in Group A and 95.34±4.12 mmHg in Group B (p=0.0001) for a variation of 2.87 mmHg. In ≥75 kg patients, the value of MAP was 98.30±4.22 mmHg in Group A and 94.31±3.17 mmHg in Group B (p=0.0001) with a variation of 3.99 mmHg. This indicates a greater variation in heavier patients potentially benefiting from nalbuphine dosing according to total body weight. Adverse events were also closely watched throughout the duration of this study (Table. 4).

Table 4: Adverse events during study period

GROUP A (SALINE) n=53	GROUP B (NALBUPHINE) n=54	P-VALUE
MILD BRADYCARDIA (HR 50-55 BPM)		
0 (0%)	3 (5.6%)	0.0862
MILD NAUSEA		
0 (0%)	2 (3.7%)	0.1573
TRANSIENT HYPERTENSION (MAP >110 MMHG)		
1 (1.9%)	0 (0%)	0.3125
TOTAL ADVERSE EVENTS		
1 (1.9%)	5 (9.3%)	0.0951

During intraoperative events, three patients in Group B had transient bradycardia with heart rate of 50-55 bpm, which resolved spontaneously without intervention. Two patients in Group B had mild nausea in the immediate postoperative setting. One patient in Group A had transient hypertension with mean arterial pressure >110mmHg for about 3 minutes following intubation. No severe adverse events in hypotension, respiratory depression that required intervention, or in allergic reactions occurred in both groups. The incidence of adverse events was considerably higher in Group B with 9.3% in comparison with Group A with 1.9% though not significantly different (p=0.0951).

DISCUSSION

This RCT carried out at the Hayatabad Medical Complex, Peshawar, proves that premedication with intravenous nalbuphine 0.2 mg/kg administered five minutes prior to anesthetic induction resulted in a significantly higher reduction in MAP post-laryngoscopy and intubation compared to the saline extension of the envelope alone – the placebo group. The significance of these observations needs to be examined in the context of the Pakistani healthcare system. A difference of 3.16 mmHg in MAP is statistically significant but reflects only a small hemodynamic response. Avenues of great importance are raised regarding the implications of clinical and statistical significance of such a small response, especially regarding patients with ASA grade I classification and adequate CVS reserve to withstand short periods of hypertension without risk of untoward effects.[14,15] Although the sympathoadrenergic response of laryngoscopy and intubation because of the mechanical stimulation of the pharyngal and laryngeal receptors tends to become spontaneous with 5-10 minutes in healthy patients, the implications of a 3 mmHg decrease in MAP and its significances of such a response have become equivocal and even less important in comparison to the transient nature of the response of intubation.[16] Our results show partial confirmation with other studies regarding opioid premedication during intubation, although there are relevant discrepancies. For instance, a local Pakistani study by Ahsan-ul-Haq and Kazmi similarly demonstrated that nalbuphine 0.2 mg/kg IV effectively prevented marked rises in both heart rate and mean arterial pressure during laryngoscopy and orotracheal intubation in a comparable setting.[17] This supports the efficacy observed in our trial, where nalbuphine achieved a statistically significant (though modestly smaller) MAP reduction of 3.16 mmHg post-intubation. In one study, similar efficacy was shown for nalbuphine and fentanyl, with MAP decreases around 8-10 mmHg—one order of magnitude larger than the 3.16 mmHg shown in our results.[18] Perhaps differences in the type of patients studied, baseline hemodynamic condition, methods of anaesthesia, or the effect of the attrition rate in our results could explain the evident discrepancy. In fact, similar differences in hemodynamic changes after nalbuphine premedication compared to our findings were noted by other authors.[19] On the other hand, few studies have demonstrated the lack of clinical differences from placebo among healthy individuals after premedication with opioids, casting doubt on the justification required by the side effects.[20] However, it is a matter of careful interpretation to determine the reasons behind the variation in the effect of nalbuphine in various age groups. The maximum decrease in MAP in the age group between 51-60 years (6.25 mmHg) might vary due to various physiological changes due to aging, pharmacokinetic changes, or may be due to the variability in sampling in smaller subgroups due to study attrition.[21] The large standard deviation in young patients indicates a large variation in the result, a phenomenon also evident in the literature concerning anesthesiology.[22] Some people have also suggested in their studies that due to a large variation between individuals, one cannot give general advice about hemodynamic variation, but one needs to personalize premedication according to patient risk factors.[23] As far as body weight is concerned, the fact that the greater decrease in MAP was seen in patients weighing >75 kg (3.99 vs. 2.87 mmHg in those weighing ≤75 kg) may imply a dose-response relation. As nalbuphine was dosed according to body weight (0.2 mg/kg), there was a greater absolute dose in heavier patients, which may suggest that there is a dose threshold below which the sympathoadrenal response cannot be adequately blunted. As far as gender is concerned, there were similar effects; however, the larger absolute level of MAP and the variability in the control females (n=36) could either represent gender differences in stress response or merely a smaller number in this category. In a pragmatic context, as it applies to Pakistani medical practice, a number of issues arise. The 12.3% attrition rate that occurred in our study, though not unexpected in clinical research, is a function of unanticipated difficulties in airway management, deviations, and patient issues. Although the study was initially powered for 122 patients, only 107 completed the trial. Despite this reduction, the difference in MAP between groups remained statistically significant, suggesting that the observed effect of nalbuphine is robust; however, the smaller sample may reduce the precision of the effect estimate. The attrition rate is, as expected, commensurate with other research studies on anesthesia administration in Pakistan, yet underscores a significant discrepancy between clinical research conditions and real-world outcomes.[24] The availability and cost-effectiveness of Nalbuphine relative to another commonly used drug, such as fentanyl, administration training to effectively use it, and availability regarding facilities for managing postoperative complications contribute significantly to our ability to translate our findings into clinical practice recommendations. In a clinical setup where substantial patient volume is a challenge, as is common in most Pakistanis hospitals, employing another form of premedication as a regular option may pose risks that far surpass our modest findings regarding MAP reduction. The mild adverse events noted in our study (bradycardia three patients, nausea two patients) were to be expected given the pharmacologic profile nalbuphine and did not require intervention. Nonetheless, our monitoring primarily focused on intraoperative hemodynamic changes, and we may potentially underestimate incidence of postoperative complications. Certain trials reported a higher incidence of complications such as nausea, dizziness, and somnolence among patients treated with nalbuphine compared to our data.[25] However, although overall incidence of complications for Group B (9.3%) was not significant (p=0.0951), it should not be overlooked that a notable trend existed towards postoperative complications. The close proximity to statistical significance implies that, among a larger population, these complications could potentially become a significant demerit. The lack of any serious adverse reactions is comforting but should be interpreted with caution, considering our small study population and the exclusion of high-risk patients who are potential candidates for adverse reactions to opioids, given that our study population consisted of healthy ASA I patients. Several researches have questioned the practice of opioid administration for hemodynamic control in low-risk patients. The transient nature of intubation response and the strong buffering capacity in healthy patients indicate that aggressive pharmacological management could be both ineffective and harmful, contributing to new complications (respiratory depression, prolonged recovery, increased health expenses) to overcome a transient physiological phenomenon.[26] This outlook assumes particular significance in our study population of ASA I patients, in whom the inherent risk of complications from transient hypertension remains low. Patients with known hypertension, coronary artery disease, cerebrovascular disease, and increased intracranial pressure—the very patients requiring hemodynamic control—are systematically excluded in our study, thereby preventing us from giving our recommendation to these high-risk groups in which the modest advantage offered by nalbuphine could assume significance. There are a number of significant limitations in this study, which may influence the interpretation of results and their generalizability. The study did not account for the timing of surgery, which may have introduced unmeasured time-related variability in hemodynamic responses. The ASA grade I population makes it difficult to generalize to a population with a high risk of complications who would benefit predominantly by means of hemodynamic management. The 12.3% rate of attrition may have led to less precise estimates and may have also introduced a risk of a self-selected group of patients, which may have systematically differed from the ones who were retained for analysis. The results are based solely on the measurement of mean arterial pressure, and a complete evaluation of cardiovascular parameters such as HR, RPP, and CO may have led to a different assessment of a significant effect. The results are also not contrasted with active comparison arms such as fentanyl, remifentanil, and dexmedetomidine, and hence it is also difficult to compare the relative benefits of nalbuphine. The survey of adverse effects was restricted to the intraoperative period only and may, therefore, have underestimated its risks. The results of this survey may also not be generalizable to Pakistani healthcare settings, which may also include resource-limited and different populations of this country. Multiple comparison correction was also not performed for subgroup analysis, and there is a significant probability that some of the significant results may also have occurred by chance. The results of this survey may also have limited utility in suggesting a clinical significance because it is restricted to a short period of anaesthesia, and there is no information about patient-centred outcomes such as complications, in-hospital stay, patient satisfaction, and cost. The results of this survey may also have a significant limitation that it may also have failed to optimize a strategy for a Pakistani population because different doses were also not considered for a comparison.

CONCLUSION:

Nalbuphine was found to have a significant effect in reducing the blood pressure change associated with the intubation process among healthy patients.

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AUTHOR'S CONTRIBUTION

AHA: Conceived the study, data collection, drafting of the manuscript

MO: Study design, data interpretation, and final approval.

SM: Supervision, critical intellectual input, and manuscript review.

JM: Data collection, case documentation, and literature review.

MSK: Data analysis, manuscript editing, and reference management

MZW: Data acquisition and critical review of the manuscript.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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