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Research Article

A controlled, double blind, study of adding Nalbuphine to Propofol for laryngeal mask insertion conditions and hemodynamics in adults

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KEYWORDS

Laryngeal mask airway (LMA);
American Society of Anesthetists (ASA);
Mean arterial pressure (MAP)

Abstract *Purpose:* The purpose of this study was to evaluate laryngeal mask airway placement conditions achieved with Nalbuphine/Propofol combination when given intravenously as well as hemodynamic changes if any.
Methods: 60 ASA grade 1 and 11 patients of age group 20–60 years, scheduled for general anesthesia with spontaneous breathing were randomly allocated to receive intravenously either Fentanyl 2 μg/kg, controlled group (Group F, $n = 30$) or Nalbuphine 0.2 mg/kg (Group N, $n = 30$), before induction of anesthesia with Propofol 2–2.5 mg/kg. Heart rate and arterial blood pressure were measured before induction of anesthesia and at 1, 3, and 5 min after LMA insertion. Assessment of LMA insertion was done using 6 variables: mouth opening, gagging, swallowing, head and limb movements, laryngospasm and resistance to insertion. Incidence and duration of apnea were recorded.
Results: The incidence of coughing/gagging was higher in the F group (50%) compared to the N group (30%), ($P = 0.019$). Swallowing was also statistically significant ($P = 0.017$), being higher in F group (50%), compared to N group (16.6%). Limb moving followed the same pattern being higher in the F group (40%) compared to (13.3%) in the N group, ($P = 0.008$). Laryngospasm was seen in neither group. There was also statistically significant difference ($P = 0.007$) in the incidence of apnea between the control group (F) 86.6% and (N) group. Heart rate variation and MAP changes were not statistically significant in either F or N groups.
Conclusion: The addition of Nalbuphine to Propofol for LMA insertion provides excellent insertion conditions with stable hemodynamics in adults.

1. Introduction

One of the most basic yet crucial skills in modern anesthetic practice is airway management and failure to secure a patent airway might end up in catastrophe [1].

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Laryngeal mask airway is one of our airway armamentaria which is non-invasive supra-glottic device with less adverse cardiovascular response than tracheal tubes simply because entry through the vocal cords into the larynx is not required [2,3]. However, deep level of anesthesia is required for safe and uneventful LMA insertion as coughing, laryngospasm, and gagging may lead to desaturation, adverse cardiovascular response and risk of regurgitation and aspiration [4–6]. Propofol has been postulated the induction agent of choice for LMA placement and this is owing to its depressant action on upper airway reflexes. Nevertheless, Propofol has its downside as it has cardiorespiratory depressant action plus purposeless patient movement [7]. So, it is not recommended as standalone drug for LMA insertion and wide range of adjuvants have been used clinically to obtain best LMA insertion criteria with negligible side effects [8,9]. The ideal adjuvant has not been reached yet [10,11]. Nevertheless, opioids have teamed up with Propofol to reach success rate up to 95% but apnea, chest tightness, and hypotension are still main unwanted side effects [12].

Nalbuphine is a potent analgesic. Receptor studies show that it binds to mu, kappa, and delta receptors, but not to sigma receptors. Nalbuphine is primarily a kappa agonist/partial mu antagonist analgesic. Its cardiovascular stability, long duration of analgesia, no respiratory depression, less nausea and vomiting and potential safety in over dosage make it an ideal analgesic to use in children [13,14]. In this research, Nalbuphine/Propofol combination was investigated for best hemodynamic and laryngeal mask airway placement conditions.

2. Patients and methods

After approval of the hospital research panel, a total of 60 American Society of Anesthetists (ASA) grade 1 and 11 patients, aged 20–60, enlisted to undergo elective day case surgery under general anesthesia with spontaneous breathing using a classic laryngeal mask airway (cLMA, the Laryngeal Mask Company, Glamorgan CF 45, UK) were assigned to the study. Hernia repair, hydroceles, varicoceles, and orthopedic elective surgeries were the most common surgeries, followed by biopsies, and postburn plastic flap. Written informed consent was obtained from each patient. Those with suspected difficult intubation, known allergy to Fentanyl, Nalbuphine or Propofol, seizures, neuromuscular disease, cardiovascular pathology, hepatic or renal disease and long surgery (more than 3 h) were excluded from the study. Patients received nothing per os 6 h before the surgery and were premedicated with oral midazolam (0.5 mg/kg) in the morning of the surgery. In the operating table, intravenous access was established and standard anesthesia monitors were connected to the patients. The monitored parameters were heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP), respiratory rate (RR), end tidal CO2 (ET CO2) and oxygen saturation (SpO2). ECG, ETCO2 and SpO2 were monitored continuously. Recording of these parameters was done at the following time intervals: baseline value, immediately before LMA insertion, one minute after LMA insertion and thereafter 3 min and 5 min. Sealed pre-coded envelopes, were used to randomly assign patients into 2 groups: group F = Fentanyl group (n = 30), and group N = Nalbuphine group (n = 30).

Fentanyl was given in a dose 2 μg/kg intravenously over 10 s to group F. Nalbuphine in a dose of 0.2 mg/kg was given as a bolus intravenous dose to group N. Pre-oxygenation was carried out with 100% oxygen for 5 min. General anesthesia was induced with Propofol in the dose of 2 mg/kg with 1/2 mL Lidocaine 2% given over 15 s [14], then, we ventilated the lungs for 60 s with 100% oxygen, immediately followed by testing loss of corneal reflexes and jaw relaxation before attempting insertion of cLMA.

LMA insertion (size selected on basis body weight) was done by anesthetist who was unaware of the research methodology [15]. In case of cLMA malposition or malfunction, it was removed, and a further dose of Propofol (1 mg/kg) was given. 60 s later reinsertion was attempted. Endotracheal intubation was carried out after 3 unsuccessful trials of cLMA insertion and lung ventilation.

Once the cLMA was successful, spontaneous breathing was allowed as the mode of ventilation. If apnea occurred (defined as absence of respiration for 30 s), ventilation was manually assisted through cLMA with 100% oxygen to maintain the arterial oxygen saturation above 95% until regular spontaneous respiration resumed. Anesthesia was maintained with 66% air in oxygen and 1–2% Sevoflurane.

Our primary outcome was successful insertion of cLMA. Secondary outcomes were, occurrence of apnea or/and drop in blood pressure (20% decrease of systolic blood pressure under baseline value).

Based on six variables on a 3 point scales cLMA insertion criteria were assessed by two blinded investigators as follows [16–19]:

1. Resistance to mouth opening: Nil/Slight/Gross
2. Resistance to insertion: Nil/Slight/Gross
3. Swallowing: Nil/Slight/Gross
4. Coughing/gagging: Nil/Slight/Gross
5. Limb/head movements: Nil/Slight/Gross
6. Laryngospasm: Nil/Slight/Gross

For our study purpose occurrence of any of the above variables that did not require cLMA reposition or reinsertion was labeled as slight, where gross was the term given to any episode that leads to cLMA reposition or reinsertion.

2.1. Statistical analysis

Fisher exact test was used to compare dichotomous parameters. Shapiro-Wilk test analyzed the normal distribution of demographic and procedural data.

A two factor ANOVA using ROC MIXED procedures was used to analyze repeated measurements of continuous variables. Data were reported as mean ± SD or median (interquartile range). A power analysis was initially done, assuming that LMA placement conditions were continuous data with normal distribution. In a previous study [16], the summed score SD of LMA placement conditions intergroup was 2.5. In order to achieve an intergroup difference of more than 2, a sample size of 30 patients in each group would be required. This would create a power of 80% and P value ($P < 0.05\%$) was accepted as statistically significant. LMA insertion conditions were compared using the Kruskal–Wallis test, and the Mann–Whitney test was used for multiple intergroup comparisons.

3. Results

Anesthesia and surgery were uneventful in all patients. Demographic characteristics including age, weight, height, male/female ratio and duration of surgery were not significantly different ($P > 0.05$) between F and N groups (Table 1).

Table 2 shows that the incidence of resistance to mouth opening between the two groups was statistically insignificant ($P = 0.322$). Resistance to cLMA placement was (10%) in the F group, higher than N group (6.7%); however, this difference was statistically insignificant ($P = 0.289$).

A statistically significant difference was detected between the two groups ($P = 0.019$) as regards coughing/gagging being higher in the F group (50%) compared to the N group (30%). The incidence of swallowing was significantly ($P = 0.017$) higher in F group (50%), compared to N group (16.6%).

In case of coughing/gagging, further dose of Propofol 1 mg/kg was given to control the incident followed by another attempt of cLMA insertion 60 s later. No further dose was needed. Total amount of Propofol was 1485 mg in Fentanyl group and 1132 mg in Nalbuphine.

Limb moving followed the same pattern being higher in the F group (40%) compared to (13.3%) the N group. This difference was statistically significant ($P = 0.008$). Laryngospasm was not seen in either group.

The total incidence of cLMA reinsertion was higher (13.3%) in the F group compared to (6.67%) the N group; however, this difference was not statistically significant ($P = 0.311$).

Table 3 shows statistically significant difference ($P = 0.008$) in the incidence of apnea between the two groups, being 86.6% in the F group higher than the N group, 53.3%. Fig. 1 shows that in F group, heart rate went higher than baseline values 1 and 3 min after cLMA placement, then, gently dropped below baseline values at minute 5. Likewise, heart rate variations in N group showed similar pattern. However, heart rate variation was not statistically significant in neither F nor N group ($P = 0.14$).

In the N group, MAP was higher than baseline values, before cLMA insertion then went up after cLMA placement, at minute 1 before reaching values lower than baseline ones at minute 3, and 5. In the F group, there was similar pattern, although there was slight decrease in MAP just before insertion of cLMA. Nevertheless, this MAP changes were not statistically significant in neither F nor N group ($p = 0.62$), Fig. 2.

4. Discussion

This study showed that the combination of Nalbuphine and Propofol improves cLMA insertion compared to Fentanyl–Propofol.

Table 1 Patient characteristics.

Patient characteristics	F group ($n = 30$)	N group ($n = 30$)	P
Age (years)	41 ± 0.44	38 ± 0.36	0.45
Weight (kg)	17.2	16.9 ± 0.36	0.36
Height (cm)	162 ± 0.36	164 ± 0.36	0.11
Gender M/F	18:12	17:13	0.21
Surgery duration (in min)	76 ± 0.36	81 ± 0.36	0.12

Data are expressed as means ± SD or number (proportion).

Table 2 Conditions during LMA placement.

LMA placement conditions	F group ($n = 30$)	N group ($n = 30$)	P value
Resistance to mouth opening Nil/Slight/Gross	28/2/0	28/3/0	0.322
Resistance to placement Nil/Slight/Gross	29/3/0	28/1/1	0.289
Coughing or Gagging Nil/Slight/Gross	15/13/2	21/8/1	0.019
Swallowing Nil/Slight/Gross	15/14/1	25/5/0	0.017
Movement Nil/Slight/Gross	18/12/0	26/4/0	0.008
Laryngospasm Nil/slight/gross	0/0/0	0/0/0	

** Values are number or median.

Table 3 Incidence of apnea.

	F group ($n = 30$)	N group ($n = 30$)	P value
Apnea	26 (86.6%)	16 (53.3%)	0.008

** Values are numbers.

The following were the cLMA insertion criteria: cough/gagging; swallowing; limb movement; laryngospasm; mouth opening and resistance to insertion.

Cough and gagging were observed more in Fentanyl group compared to the Nalbuphine group. This higher incidence could be due to Fentanyl onset of action. We gave 90 s time between intravenous Fentanyl administration and cLMA insertion which was not sufficient for full action of Fentanyl to insert cLMA in a considerable number of patients in this study. This observation was in accordance with another study which demonstrated higher dose of Fentanyl was associated with considerable high incidence of coughing and laryngospasm and attributed these episodes to Fentanyl rather than to cLMA insertion [20]. Moreover, the antitussive action of Nalbuphine might have attributed to the low incidence observed in Nalbuphine compared to Fentanyl group.

Patients in Nalbuphine group showed also less swallowing and less limb movement than those in Fentanyl group. Indeed, centrally acting drugs such as Fentanyl and Nalbuphine would be expected to affect central respiratory network and consequently may have resulted in a dose related network change of nasopharyngeal airway reflexes [21–23]. Moreover, Nalbuphine mode of action (agonist on K receptors and antagonist on μ receptors, whereas, Fentanyl exerts full agonist activity on μ and k receptors), might directly or indirectly participate in the less incidence of swallowing and limb movement in the Nalbuphine group. Furthermore, the incidence of apnea was higher in the fentanyl group and this might alter the reflex responses to Fentanyl such as decrease in ventilatory drive resulting in an increase of carbon dioxide. However, it cannot go without saying that co-administration of Fentanyl with other anesthetics or administration of higher doses of Fentanyl may result in different LMA insertion criteria outcomes.

A significant difference was also detected between the 2 groups ($P = 0.008$) as regards higher incidence of apnea in F group compared to N group. This is to be expected for two

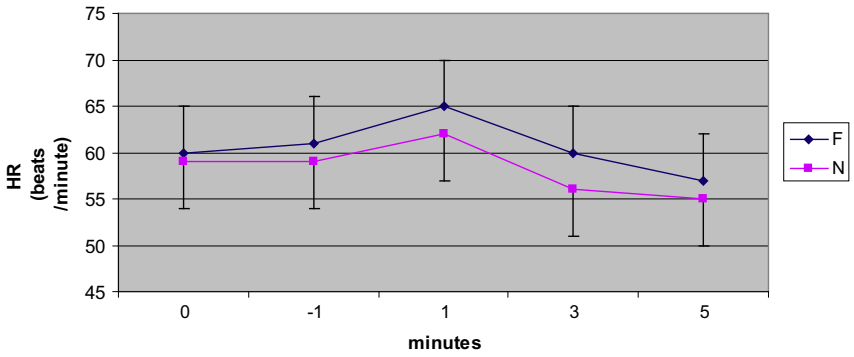

Figure 1 Changes in heart rate t_0, baseline value; t_{-1}, one minute prior to LMA placement; t_1, t_3 and t_5 are 1, 3 and 5 min after LMA placement. Values are mean ± SD or number.

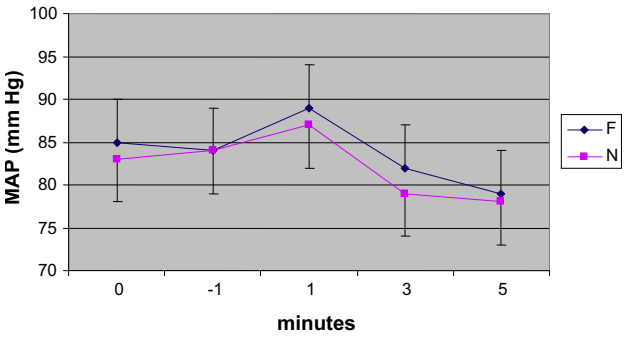

Figure 2 Changes in mean arterial blood pressure t_0, baseline value; t_{-1}, one minute prior to LMA placement; t_1, t_3 and t_5 are 1, 3 and 5 min after LMA placement. Values are mean ± SD or number.

reasons: first, intravenous Fentanyl is known to cause apnea [24]; second, Nalbuphine has limited respiratory depression action owing to its μ receptors antagonism. Our results are in accordance with other studies that investigated upper way reflexes during Fentanyl–Propofol anesthesia [25,12] and showed high incidence of apnea with Fentanyl. However, our results show higher incidence of apnea than that reported by the latter studies, which might be due to the dose of Fentanyl administered in our study (2 μg/kg) as twice as the dose used by them 1 μg/kg.

In a placebo controlled [26] study that investigated the effect of Nalbuphine on heart rate and mean arterial pressure, it showed significant response to intravenous Nalbuphine administration i.e., more than 20% rise from baseline compared to placebo group. Our study results showed increase in heart rate and mean arterial blood pressure in both F and N groups, being higher than baseline values. However, no statistical significance could be detected in neither F nor N group ($P = 0.14$).

This finding was in accordance with Khan et al. [27] who tested Nalbuphine versus Fentanyl on hemodynamics after intubation, and showed no significant alteration in MAP but HR was significantly higher in Nalbuphine group (25%). Chestnutt et al. [28] also showed smooth hemodynamic response with intravenous Nalbuphine.

Our study though has got its limitations. First, our research did not distinguish between central and peripheral apnea in Nalbuphine or Fentanyl groups. Second, we cannot exclude that pre-anesthetic medication (midazolam) might modulate respiratory reflex responses either directly or through interactions with our investigated drugs. However, our rationale behind using Midazolam is it represents a standard anesthetic practice.

To conclude, the addition of Nalbuphine to Propofol for LMA insertion provides excellent insertion conditions with stable hemodynamics in adults.

Conflict of interest

The authors declare that there is no conflict of interest.

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