ATTENUATION OF HAEMODYNAMIC RESPONSE TO ENDOTRACHEAL INTUBATION WITH NALBUPHINE AND FENTANYL: A COMPARATIVE STUDY

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ABSTRACT: BACKGROUND: Endotracheal intubation is a most noxious stimuli in anaesthesia in form of tachycardia and hypertension. Many drugs have been tried to attenuate these adverse hemodynamic responses, but no ideal drug has been discovered. We compare the effect of fentanyl and nalbuphine on modifying the hemodynamic response to laryngoscopy and tracheal intubation.

METHODS: Two randomly assigned groups of 40 patient each, aged 20-60 years, were scheduled for elective surgery receive Group 1 inj. Fentanyl 2ug/kg or GROUP 2 inj. Nalbuphine 0.2mg/kg iv 5min before laryngoscopy and intubation. Haemodynamic parameters and post-operative complications were recorded.

RESULTS: Immediately after drug administration, the heart rate (HR) in group I decreased from basal value of 85.55±10.85bpm to 83.75±14.11bpm, in group II increased from basal value of 89.83±1.48bpm to 95.33±16.99bpm (p<0.05). The decrease in mean SBP was in both the groups, but more in group II. Immediately after drug administration decrease in DBP was in both the groups, which was more in group I than group II (p<0.05) it persisted in group II at 15 and 30 min after intubation, while group I showed an increase in DBP (p<0.05). After intubation, mean MAP increased from baseline in group I than group II observed a decrease in mean MAP from baseline (p>0.05) and it values at 5, 15, 30 min after intubation were lower in group II as compared to group I were significant (p<0.001). CONCLUSION: Nalbuphine controls the pressor response much better as compared to Fentanyl.

KEYWORDS: Endotracheal intubation, Fentanyl, Haemodynamic, Nalbuphine.

INTRODUCTION: Endotracheal intubation has been suggested as one of the most invasive stimuli in anaesthesia,1,2 producing stress response in the form of tachycardia, hypertension and increased catecholamine levels.3 This stimuli may increase morbidity and mortality in patients with recent myocardial infarction, hypertension, preeclampsia and cerebrovascular pathology such as tumors, aneurysms etc.2,4

Many agents like α agonists, vasodilators, opioids and Lidocaine have been used to attenuate the cardiovascular response to laryngoscopy and intubation,5,6,7 but are associated with adverse effects like respiratory depression, histamine release, neuroexcitatory and gastrointestinal effects.8,9

Fentanyl, a synthetic opioid acting on μ receptors, is found to be effective in blunting the pressor response to laryngoscopy and intubation due to its rapid onset, short duration of action and cardiostability.9 Nalbuphine, a new agonist-antagonist opioid acting on μ, κ and δ receptors is also effective in blunting the haemodynamic response to laryngoscopy. Its cardiovascular stability, long duration of analgesia, lack of respiratory depression, less nausea and vomiting and potential safety in
overdosage makes it an ideal anaesthetic for use in anaesthesia.

This study was done to compare the effect of Fentanyl and Nalbuphine on the haemodynamic response to laryngoscopy and intubation and complication. (If any)

METHODS: This is a randomized double blind clinical study, conducted at our Institute over a period of one year after obtaining ethical committee’s approval and written informed consent from all patients.

Two groups of 40 patients each aged 20-60 years of either sex, ASAPS 1 or II scheduled for elective surgery (determined by power analysis based on standard deviation data) receive any of the two drugs.

Group I (n=40): Inj Fentanyl citrate 2µg/kg IV 5 min before laryngoscopy and intubation

Group II (n=40): Inj Nalbuphine hydrochloride 0.2mg/kg IV 5 min before laryngoscopy and intubation.

Inclusion Criteria: Patients aged 20-60 years.
- ASA I or ASA II.
- Either sex
- Patients for elective surgery.
- Prior informed consent.

Exclusion Criteria:
1. Age <20 and >60 years.
2. ASA III and IV.
3. Refusal of consent.
4. Hypersensitivity to drug.
5. Patient with cardiac disease.
6. Patients with pulmonary diseases.

Preoperative vitals were recorded and patients were premedicated with Glycopyrrolate 0.005 mg/kg IV. The study drug Fentanyl (2µg/kg) or Nalbuphine (0.2mg/kg) was administered intravenously in double blind manner and the patient was induced with IV Propofol 2 mg/kg and IV Succinylcholine 1.5mg/kg. After 5min of administration of study drug, laryngoscopy and intubation were performed. Readings of HR, SBP, DBP and MAP were recorded – preoperatively, immediately after drug administration, immediately after intubation, at 1min, 3min, 5min, 15min and 30min after intubation.

Anaesthesia was maintained on 02: N2O (40:60), Isoflurane (0.4-1MAC) and Muscle relaxant Vecuronium Bromide. At the end of surgery the neuromuscular blockade was reversed with IV Neostigmine and IV Glycopyrrolate. The patient was extubated and shifted to the recovery room. Post-operative complications (Post-operative nausea and vomiting, bradycardia, desaturation, respiratory depression, sedation) were recorded.

Statistical Analysis: The study data was statistically analyzed using MS Excel Software and Statistical Package for Social Sciences (SPSS 11.0). Mean was calculated for all parametric quantitative data in the study. Within the groups, variances were evaluated using standard deviation. To evaluate the significance of difference in proportions between the two groups, Chi Square test was used. ‘t’ test
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for independent samples was used to compare the difference in mean values of the two groups. A ‘p’ value of <0.05 was considered as statistically significant difference as the confidence interval of the study was set at 5%.

RESULTS: The two groups were comparable in terms of baseline demographic parameters like age and sex. Majority of patients in either group were ASAPS I.

Comparison of basal hemodynamic parameters between the two groups showed that the values were statistically not significant (p>0.05), hence both the groups had comparable parameters. (Table 1)

Immediately after drug administration, the HR in group I decreased from basal value of 85.55±10.85bmp to 83.75±14.11bmp whereas in group II HR increased from basal value of 89.83±12.48bmp to 95.33±16.9bmp. This decrease and increase in mean HR in group I and II respectively was statistically significant (p>0.05). Rise of mean HR immediately after intubation was slower in group I as compared to group II. Fall of mean HR at 1min and 3min after intubation was clinically significant. At 5min, 15min and 30min after intubation, mean HR values in both the groups were lower than the baseline values. These values indicated better control of HR in group I as compared to group II. (Figure 1)

On comparison of mean SBP between both the groups, there was a decrease in mean SBP in both the groups, which was more in group II than group I (p>0.05). After intubation, an increase in mean SBP to 136.28±10.61 mm Hg was observed in group I as opposed to group II which showed a decrease in SBP to 125.73±12.56 mm Hg; which was statistically significant (p<0.001). The mean SBP at 1, 3, 5 min after intubation decreased in both groups. Till 30 min after intubation, group II showed a consistent decrease in mean SBP whereas in group I mean SBP values were increased after 5 min of intubation (p<0.001).These values indicate that immediately after intubation, control of mean SBP was better in group II as opposed to group I. (Figure 2)

On comparing mean DBP between group I and group II, the basal mean DBP was comparable in both the groups. Immediately after drug administration there was a decrease in DBP in both the groups which was statistically significant (p<0.001). Immediately after intubation, DBP in group I increased from baseline whereas in group II it decreased from baseline value (p>0.05). Decrease in DBP persisted in group II at 15 and 30 min after intubation, while group I showed an increase in DBP. The values were statistically significant (p<0.001).However towards the end of observations i.e. at 30 min after intubation, mean SBP and mean DBP value in group I returned close to baseline while in group II there was a persistent fall in mean SBP and mean DBP values. Comparison of DBP between both groups has been done in. (Figure 3)

The values of mean MAP immediately after drug administration were decreased in both groups but they were statistically not significant (p>0.05). After intubation, mean MAP was increased from baseline in group I whereas group II observed a decrease in mean MAP from baseline (p>0.05).At 1 and 3min after intubation, there was a decrease in mean MAP in both the groups, with greater fall in group II and with statistically significant difference between the two groups at 1min after intubation. The mean MAP values at 5, 15, 30min after intubation were lower in group II as compared to group I and were statistically significant (p<0.001). This showed a better control of MAP in group II compared to group I in response to intubation. (Figure 4)

In group I, 9/40 (22.5%) cases had bradycardia while in group II only 1/40 (2.5%) case reported bradycardia (p<0.01). Postoperative nausea and vomiting were found in 2/40 (5%) cases in
group I and 1/40 (2.5%) case in group II (p>0.1). Sedation was reported in 2/40 (5%) cases in group I and in 21/40 (52.5%) cases in group II. On analysis the values were of definite statistical significance (p<0.001). (Table 2)

DISCUSSION: Hypertension and tachycardia subsequent to tracheal intubation have been well documented. In susceptible patients even this short period (2-7min) of hypertension and tachycardia can result in myocardial ischemia or increased intracranial pressure. Complications resulting from these haemodynamic events after intubation include left ventricular dysfunction, hypertensive crisis, pulmonary oedema, cardiac dysrhythmias, myocardial ischemia and myocardial necrosis.

In patients with atherosclerotic heart disease, intracranial lesions and penetrating eye injuries, these responses to intubation pose a greater risk. To blunt this pressor response, various methods have been tried including adrenergic blockade, vasodilators, calcium channel blockers and alpha 2 agonists. These methods require administration of an additional costly drug, which in addition to not having any role in induction and maintenance of anaesthesia, can cause dangerous complications.

Narcotics or inhalational can also attenuate pressor response by maintaining proper depth of anaesthesia. Few studies have shown that Fentanyl or Nalbuphine are effective in blunting pressor response anaesthetic agents to laryngoscopy and endotracheal intubation.

Ko et al designed a study to examine the optimal time of injection of Fentanyl and concluded that the most effective time to administer Fentanyl to protect circulatory responses to laryngoscopy and tracheal intubation is 5min before tracheal intubation. Chawda, Pareek and Mehta studied the effect of Nalbuphine on haemodynamic response to orotracheal intubation. They observed that Nalbuphine given in the dose of 0.2mg/kg 3-5min before laryngoscopy prevented stress response to tracheal intubation.

In our study after drug administration, mean HR in Fentanyl group decreased from 85.55±10.85bpm to 83.75±14.11bpm and in Nalbuphine group it increased from 89.83±12.48bpm to 95.53±16.9bpm. This showed a decrease in mean HR after drug administration in Fentanyl group as opposed to increase in HR in Nalbuphine group. The mean HR after intubation showed significant increased value of 88±11.45bpm in Fentanyl group and 102.68±16.04bpm in Nalbuphine group. The HR gradually decreased in both the groups except at 3min in Fentanyl group which had a mean HR of 89.1±18.77bpm as compared to Nalbuphine group which had a mean HR of 92.2±15.73bpm (p>0.05)

Khan and Hameedullah conducted a similar study and observed a significant decrease in heart rate response in Fentanyl group after induction, tracheal intubation and incision. In their study the HR in the Nalbuphine group remained significantly high 5min post intubation while in our study the HR gradually settled after intubation. Rawal and Wennhager and Ahser et al also support our study.

After drug administration, there was a fall in mean SBP (121.7±12.99mmHg) from baseline value of 130.58±11.03mmHg in Fentanyl group and a fall to 125.65±9.74mmHg from baseline value of 137.33±12.97mmHg in Nalbuphine group; which was not statistically significant. Post endotracheal intubation, there was a marked significant (p<0.05) blunting of the haemodynamic response to laryngoscopy and intubation in Nalbuphine group (Mean SBP 125.73±12.56mmHg) as compared to Fentanyl group (Mean SBP 136.28±12.61mmHg). Later at 1, 3, 5min after intubation,
mean SBP decreased in both groups but on comparison it was not statistically significant (p>0.05). Till 15 and 30min after intubation, Nalbuphine group showed a consistent decrease in SBP while the Fentanyl group observed an increase in SBP; this was statistically significant (p<0.001). Contrary to the present study, Khan and Hameedullah\textsuperscript{22} observed that Nalbuphine provided lesser haemodynamic stability in comparison to Fentanyl when used as an intraoperative analgesic in TIVA with propofol. Aftabet \textsuperscript{24} compared Fentanyl/Isoflurane and Nalbuphine/Isoflurane in patients undergoing elective coronary artery bypass surgery. In contradiction to the present study, they showed that Fentanyl/Isoflurane provided better haemodynamic stability than Nalbuphine/Isoflurane (p<0.05).

After drug administration, there was a significant (p<0.05) decrease in mean DBP in the Fentanyl group (Baseline 84.33±10.92mmHg to 78.38±9.31mmHg) and in Nalbuphine group (Baseline 88.3±7.63mmHg to 85.9±8mmHg). On the other hand, after intubation the mean DBP in Fentanyl group was increased to 86.73±10.83mm Hg and in Nalbuphine group, it decreased to 86.6±8.57mm Hg and the result was found to be statistically significant (p<0.05). Control of mean DBP was comparable in both the groups immediately and till 5min after intubation but not thereafter. Channaiahet \textsuperscript{25} studied the effect of low dose Fentanyl on haemodynamic response to endotracheal intubation in normotensive patients. High attenuation of SBP and DBP pressor response to intubation in the Fentanyl group was observed at all measured times. The greatest attenuation in SBP and DBP was observed at intubation with a significant difference from the control group (p<0.001). Khan and Hameedullah\textsuperscript{22} observed in their study that DBP fell after induction but post tracheal intubation DBP significantly (p<0.05) rose to a maximum of 13% IN Nalbuphine group and 3% in Fentanyl group.30% patients in Fentanyl group compared to 50% patients in Nalbuphine group required supplemental Propofol bolus. In contrast to their study, this study showed a better and more prolonged control of DBP in Nalbuphine group. Also contrary were the results of Chung et al\textsuperscript{26} who observed that DBP increased at 10, 20min after Nalbuphine injection (p<0.05) compared to control group.

After drug administration, there was a fall in mean MAP values from baseline in Fentanyl and Nalbuphine groups which was not significant (p>0.05). After endotracheal intubation, mean MAP in Fentanyl group was 103.24±9.75mm Hg (Baseline 99.03±11.58mmHg) and in Nalbuphine group was 99.64±8.61mmHg (baseline 102.53±8.64mmHg) and this was a significant value (p<0.05). Thereafter, there was a decrease in MAP in both the groups till 5min after intubation with a significant difference between Fentanyl and Nalbuphine groups (p<0.05). Thus showing that control of MAP after laryngoscopy and intubation was better in Nalbuphine group than in Fentanyl group. Chawda, Pareek and Mehta\textsuperscript{27} showed that Nalbuphine in the dose of 0.2mg/kg 3-5min before laryngoscopy and intubation prevented its associated haemodynamic response while patients in placebo group exhibited significant increase in HR and MAP after intubation. Rise in MAP was higher in control group compared to Nalbuphine group at all times. Channaiahet al\textsuperscript{25} noted in their study that inter group MAP yielded significant attenuation in the Fentanyl group for all recorded time periods.

In the Fentanyl group,\textsuperscript{9} (22.5%) cases had bradycardia while only 1case (2.5%) in Nalbuphine group had bradycardia. Rawal and Wennhager too observed that patients in Nalbuphine group showed mild to moderate increase in pulse rate during intubation phase. There were episodes of postoperative nausea, vomiting in 2 (5%) cases in Fentanyl group and 1 case (2.5%) in Nalbuphine group; values of which were not statistically significant (p>0.1). Bone, Dawson and Smith\textsuperscript{28} compared Nalbuphine with Fentanyl for postoperative pain relief following termination of pregnancy under day
care anaesthesia. Congruous to the finding in the present study, no significant differences were found between the groups for incidence of nausea. Post-extubation, sedation was reported in 2(5%) cases in Fentanyl group and in 21 cases (52.5%) in Nalbuphine group. On analysis, the values were of definite statistical significance (p<0.001). In the study by Rawal and Wennhager23, within the first 15 min following recovery, increasing PaCO2 and EtCO2 values as well as respiratory rates below 10/min were noted in 8 patients in fentanyl group; 4 of these patients required IV Naloxone for reversal of respiratory depression. Prolonged sedation was a common factor in patients receiving Nalbuphine. In our study, there was no episode of respiratory depression in any of the two groups. Vandenberg et al29 studied the clinical comparison of intraoperative, recovery and postoperative effects of Nalbuphine, Buprenorphine, Fentanyl, Morphine and Pethidine given IV with induction of anaesthesia in ENT surgeries. Following discontinuation of the inhalational anaesthetic agents and the administration of IV Neostigmine and Atropine during reversal, the mean time to extubation was prolonged for Buprenorphine, Fentanyl, Morphine and Pethidine as compared to Nalbuphine. The mean extubation time was 3.9 min for Nalbuphine compared to 4.5, 4.9, 5.1 and 6.3 min with Morphine, Fentanyl, Pethidine and Buprenorphine respectively.

Chung et al26 observed that pure μ agonists such as Remifentanil can cause complications such as respiratory depression which can be dangerous in the recovery room. On the other hand, Nalbuphine which is an agonist-antagonist causes less respiratory depression by activating the supraspinal and spinal κ receptors. This makes nalbuphine quite useful in providing analgesia in mild to moderate postoperative pain.

CONCLUSION: It is concluded from our study that Nalbuphine controls the pressor response to laryngoscopy and intubation much better as compared to Fentanyl. However unlike Fentanyl, Nalbuphine was not found to be effective in controlling the heart rate post induction and intubation as it caused a slight increase in heart rate itself after drug administration.

Further study needs to be done in this direction to etch out a role for each of these two drugs; Nalbuphine and Fentanyl, in attenuation of the laryngoscopic response.

REFERENCES:


**Figure 3** - Changes in Mean Diastolic Blood Pressure in both groups
DBP = Diastolic Blood Pressure, Group I = Fentanyl, Group II = Nalbuphine

**Figure 4** - Changes in mean Mean Arterial Pressure (MAP) in both Groups
MAP = Mean Arterial Pressure, Group I = Fentanyl, Group II = Nalbuphine

<table>
<thead>
<tr>
<th>Basal Parameters</th>
<th>Group I (Fentanyl)</th>
<th>Group II (Nalbuphine)</th>
<th>Tests of significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Range</td>
<td>±SD</td>
</tr>
<tr>
<td>HR</td>
<td>85.6±5</td>
<td>69-108</td>
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<tr>
<td>SBP</td>
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<td>11.0</td>
</tr>
<tr>
<td>DBP</td>
<td>84.3±10</td>
<td>64-107</td>
<td>10.9</td>
</tr>
<tr>
<td>MAP</td>
<td>99.0±8</td>
<td>69-118</td>
<td>11.5</td>
</tr>
</tbody>
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**Table 1** - Comparison of basal parameters between both groups
HR – Heart rate, SBP – Systolic Blood Pressure, DBP – Diastolic Blood Pressure, MAP – Mean arterial pressure
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<table>
<thead>
<tr>
<th>Complications</th>
<th>Group I (Fentanyl) n=40</th>
<th>Group II (Nalbuphine) n=40</th>
<th>Tests of significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradycardia (HR &lt;60 bpm)</td>
<td>Present</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td></td>
<td>9 (22.5%)</td>
<td>31 (77.5%)</td>
<td>1 (2.5%)</td>
</tr>
<tr>
<td>PONV</td>
<td>2 (5%)</td>
<td>38 (95%)</td>
<td>1 (2.5%)</td>
</tr>
<tr>
<td>Sedation</td>
<td>2 (5%)</td>
<td>38 (95%)</td>
<td>21 (52.5%)</td>
</tr>
</tbody>
</table>

Table 2 - Complications in Both Groups
HR = Heart rate, PONV = Post Operative Nausea Vomiting

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