Efficacy of nalbuphine in preventing haemodynamic response to laryngoscopy and intubation in comparison to clonidine

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Abstract
To determine the efficacy of Nalbuphine in comparison to clonidine in preventing increase in heart rate and mean arterial pressure in response to laryngoscopy and tracheal intubation.

Methodology: This double blind randomized controlled trial was conducted on 60 ASA grade I–II patients scheduled for General anaesthesia. Patients were randomly allocated to receive clonidine 3µg/kg (group I, n=30) or Nalbuphine 0.2 mg/ kg (group II n=30) Each patient was given study drug 15 min before intubation. Anaesthesia was then induced with Thiopentone (6mg/ kg) and succinyl choline (2mg/kg ) IV was given for orotracheal intubation. Heart rate and mean arterial pressures were recorded before the administration of the study drug, baseline value ,3 minutes immediately after tracheal intubation and then after every 1 minute up to 5 minutes and then after 10 minutes of intubation.

Results: Clonidine significantly attenuated the sympathetic response to laryngoscopy and intubation. Nalbuphine reduced only the inotropic response to airway instrumentation so their effect was far lower than that of clonidine in attenuating the response.

Conclusion: This study showed that clonidine was far superior to nalbuphine in the attenuation of the pressor response. An intravenous bolus dose of clonidine 3µg/kg which was administered 15 min before a laryngoscopy and intubation can be recommended to attenuate the sympathetic response to the laryngoscopy and intubation, it has important role in the patients of hypertension, ischemic heart disease, thyrotoxicosis and neurosurgical patients where even minimal haemodynamic change to laryngoscopy and intubation is hazardous.

Key Words: Study drugs, Laryngoscopy, Orotracheal Intubation, Haemodynamic Response

Introduction
Laryngoscopy and tracheal intubation are commonly accompanied by increase in arterial blood pressure and heart rate.1 The magnitude of haemodynamic changes observed may depend on various factors such as depth of anaesthesia, whether any measure is taken prior to airway manipulation, the anaesthetic agent used, the duration of laryngoscopy and the intubation. Till date, the exact mechanism of haemodynamic responses to laryngoscopy and intubation has not been clarified. The principal mechanism in hypertension and tachycardia is sympathetic response 2,3 which may be the result of increase in catecholamine activity.

The increase in the pulse rate and blood pressure are usually transitory, variable and unpredictable. Transitory hypertension and tachycardia are probably of no consequences in healthy individuals. But either or both may be hazardous to those with hypertension myocardial insufficiency or cerebrovascular diseases.4 This laryngoscopic reaction in such individuals may predispose to development of pulmonary edema, myocardial insufficiency and cerebrovascular accident.5,6 Intravenous anaesthetic induction agents do not adequately or predictably suppress the circulatory responses evolved by endotracheal intubation initiating laryngoscopy, so prior to additional pharmacological measures like use of volatile anaesthetics topical and intravenous lidocaine,9,10 opioids,11,12 vasodilators,SNP,13NTG,14calcium channel blockers15,16 and b blockers,17,18 have been tried by various authors.

Besides minimising cardiovascular response, anaesthesia induction for patients at risk must also satisfy the following requirements it must be applicable regardless of patient group, prevent impairment of cerebral blood flow and avoid awareness of the patient, it should neither be time consuming nor affect the duration or modality of the ensuring anaesthesia and also should not have any effect on the recovery characteristics. Among the recommended procedures, intravenous clonidine appears to fulfil the criteria.19

Intravenous clonidine, a central a-2 agonist has become a popular agent for obtunding haemodynamic response to laryngoscopy and intubation. Further clonidine has sedative, analgesic antihypertensive action in addition to reducing the anaesthetic drugs requirement. Nalbuphine is mixed agonists antagonist opioid agonists at kappa receptors and weak agonist-antagonist at mu opioid receptor. It is cardiovascular stable, no respiratory depression, less nausea and vomiting and potential safe in over dosage so can be used in balanced anaesthesia.20

In the present study we evaluate and compare the efficacy of clonidine and nalbuphine in attenuating...
the cardiovascular effects i.e. heart rate and arterial blood pressure changes during tracheal intubation.

**Material and methods**

Sixty patients of ASA I & II aged between 16-50 years of either sex posted for elective surgical procedure were selected for study. All the patients were assessed a day before surgery and were screened for major diseases in past, any anaesthesia exposure or any drug allergy or family history of anaesthetic complications. Detailed examination was done for any cardiovascular, respiratory or endocrine diseases. Routine investigations were done. Airway assessment was done by mallampati gradation and mallampati grade I and II patients were selected for the study. Patients with hypertension, cardiac, coronary, renal, hepatic, cerebral diseases and vascular diseases, difficult airway and obese patient, endocrine diseases like hyper or hypothyroidism, diabetes mellitus, known hypersensitivity to these drugs and predicted difficult intubation, prolonged laryngoscopic time (>30 seconds) were excluded. Informed consent was obtained from all patients as per rules and regulation of our institute.

The patients were randomly allocated into two groups, with each group comprising of 30 patients. All the patients were kept “nil by mouth” for 8 hours before surgery. In the operating room multi parameter monitor was attached and preoperative PR, SBP, DBP, MAP, RR, SPO2 vital parameters are recorded. All the patients were pre medicated with Inj. Ondansetron 4 mg/kg i.v. 15 min before surgery and antisialagogue was avoided.

After recording the baseline vital parameters, in group I patients were given Inj.nalbuphine 0.2 mg/kg intravenously and in group II patients were given Inj.clonidine 3ug/kg i.v over 120 seconds, 15 minute before intubation and vital parameters of the patients were recorded after 15 minutes of test medication. The patients were pre-oxygenated with 100% oxygen by mask for 3 minutes. Induction was achieved with inj Thiopentone sodium 6mg/kg and inj succinylcholine 2mg/kg intravenously after pre-oxygenation. In both the groups intubation and laryngoscopy was performed using mackintosh curved blade within a period of 20 seconds and intubated with appropriate size of portex cuffed tube. After checking the position by bilaterally equal air entry, endotracheal tube was fixed. Anaesthesia was maintained with O2, N2O, sevoflurane and inj atracurium. At the end of surgery, patients were reversed using inj. Neostigmine 0.05 mg/kg and inj. Glycopyrrolate 0.008 mg/kg, and extubated when patients were fully conscious with normal tone and power.

The patient’s pulse rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), respiratory rate (RR), and SPO2 were recorded as pre-induction control readings (0 min), then immediately after laryngoscopy at 1,3,7,10,15 and 20 min after intubation, all the above parameters and ETCO2 were recorded.

Patients were shifted to anaesthetic recovery room and monitored for complications like nausea, vomiting, respiratory depression, hypotension, hypertension, tachycardia, bradycardia and drowsiness. Patients were followed up for 12 hours. Sedation scoring was done as per Ramsay sedation scale.

**Ramsay Sedation Scale**

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Patient is anxious and agitated or restless, or both</td>
</tr>
<tr>
<td>2</td>
<td>Patient is co-operative, oriented, and tranquil</td>
</tr>
<tr>
<td>3</td>
<td>Patient responds to commands only</td>
</tr>
<tr>
<td>4</td>
<td>Patient exhibits brisk response to light glabellar tap or loud auditory stimulus</td>
</tr>
<tr>
<td>5</td>
<td>Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus</td>
</tr>
<tr>
<td>6</td>
<td>Patient exhibits no response</td>
</tr>
</tbody>
</table>

**Observations and results**

Both groups were similar with age distribution and weight distribution and Male to female ratio in Group I was 10:20 and in Group II was 11:19.

**Fig.1: Age distribution**

Though all the general surgeries were included in this but most of the patients were of laparoscopic surgeries. I.e. appendicectomy, lap. cholecystectomy. Other surgeries were laser perforations, brachial plexus injury repair hernioplasty and pyelolithotomy.
Table 1: Comparison of mean pulse rate between two groups and its statistical evaluation

<table>
<thead>
<tr>
<th>Time</th>
<th>Group 1 (Nalbuphine)</th>
<th>Group 2 (clonidine)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-op</td>
<td>85.33 ± 5.12</td>
<td>85.33 ± 7.11</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>15 min after study</td>
<td>93.88 ± 7.5</td>
<td>80.63 ± 7.18</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>drug</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediately</td>
<td>122.5 ± 5.9</td>
<td>89.36 ± 5.98</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>after intubation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After intubation at</td>
<td>131.56 ± 5.87</td>
<td>96.2 ± 7.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>1 min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 3 min</td>
<td>118.16 ± 4.60</td>
<td>92.06 ± 7.29</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>At 5 min</td>
<td>112.2 ± 4.6</td>
<td>86.83 ± 5.61</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>At 7 min</td>
<td>100.03 ± 6.47</td>
<td>85.33 ± 7.71</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>At 10 min</td>
<td>95.4 ± 5.01</td>
<td>86.13 ± 7.39</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>At 15 min</td>
<td>97.96 ± 4.59</td>
<td>85.13 ± 7.39</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>At 20 min</td>
<td>90.76 ± 5.25</td>
<td>86.13 ± 7.39</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Mean pulse rate in Group I and Group II at pre operatively were not significant. While after 15 min of pre medications with clonidine, the decrease in pulse rate was seen more than pre operatively.
which is statistically significant. The increase in mean pulse rate in Group I was statistically highly significant compared to Group II (p<0.01) immediately after intubation and after intubation at 1, 3, 5, 7, 10, 15, and 20 minute.

There was no significant change in SBP preoperatively (p>0.05), while after 15 min of clonidine, in Group II there was significant fall in SBP, which is statistically significant (p<0.05). The increase in SBP in Group I was statistically significant compared to Group II (p<0.05) immediately after intubation and after intubation at 1, 3, 5, 7, 10, 15 minute.

Sedation scoring
In group I (Nalbuphine) Sedation score was 2.13 +/-0.48 (co-operative, oriented and tranquil) and in Group II - 2.76 +/-0.5 (responding to commands). This showed that the patients in clonidine group were more sedated than the patient in Nalbuphine group which is statistically significant (p<0.05).

There was no significant change in MAP preoperatively (p>0.05), while after 15 min of clonidine, in Group II there is significant fall in MAP statistically significant (p<0.05). The increase in MAP in Group I was statistically significant compared to Group II (p<0.05), immediately after intubation and after intubation at 1, 3, 5, 7, 10, 15 minute.

Table 5 Sedation score between group I and II.

<table>
<thead>
<tr>
<th></th>
<th>Sedation Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>2.13 +/-0.48</td>
</tr>
<tr>
<td>Group II</td>
<td>2.76 +/-0.50</td>
</tr>
</tbody>
</table>

There was no Spo2 changes observed in both the groups throughout the study period Side effects of both the drugs like nausea, vomiting, hypotension, bradycardia were not noticed in any of the group.

Fig: 2 shows statistical evaluation of change in mean MAP between two groups.

Fig: 3 shows mean pulse rate between two groups.
Fig: 4 shows mean SBP between two groups

Fig: 5: Mean DBP changes between two groups

Fig 6 : Comparison of MAP changes between two groups.

Discussion
Laryngoscopy and tracheal intubation is most critical event while giving general anaesthesia and it is associated with transient but marked increase in blood pressure and heart rate, this increase is mainly due to reflex sympathoadrenal response. These seek attention of anaesthesiologist to attenuate haemodynamic response to laryngoscopy and tracheal intubation. Various studies are carried with different techniques and drugs, but to overcome this problem most of them are only partially effective.
Nalbuphine is an opioid with agonist antagonist action, weak antagonist at mu and agonist at kappa opioid receptors. It has been used in many major surgeries intra-operatively as it is cardiovascular stable and has longer duration of action. In this study we selected a standard dose of 0.2 mg/kg which showed that this dose is adequate to control haemodynamic response to intubation with minimal side effects in our patients.
Clonidine, the alpha -2 adrenoceptor agonists, which is mainly used as an anti hypertensive agent has many properties of an ideal premedicant. Zalunardo et.al. in 1997 shown that intravenous clonidine was better than oral clonidine in attenuating the pressor response. So in this study we used intravenous clonidine. The effect of clonidine on the haemodynamic variables are dose related but increase the dose more than 4mcg/kg do not further enhance the efficacy. So, in this study, we used 3mcg/kg.

**Changes seen in heart rate 15 min after study drug.** In our study, 15 min after giving the nalbuphine in group I, there was no significant change in heart rate, increase in mean heart rate was 3.4 bpm from baseline which is statistically not significant. In Group II, 15 min after giving clonidine mean heart rate was decreased by 4.7 bpm from baseline which is statistically significant (p<0.05) and showed that significant decrease in heart rate occurred with clonidine. 

**Immediately after intubation and after intubation at 1 min** Khalid Maudoood Siddiqui et al. studied tramadol versus nalbuphine in total intravenous anaesthesia for dilatation and evacuation. There was no difference found in haemodynamic parameters. There was statistically significant difference found (p<0.05) in postoperatively, in which tramadol has more sedative effect than nalbuphine. Quality of analgesia was better in nalbuphine group but both drugs provided suitable analgesic supplementation to TIVA. And concluded that nalbuphine 0.2 mg/kg presented a marked rise in heart rate and mean arterial pressure associated with laryngoscopy and intubation.

Priti M Chawda, Mayuresh K Pareek, and Ketan D Mehta. studied efficacy of nalbuphine in preventing the increase in heart rate and mean arterial pressure in response to laryngoscopy and intubation. In their study there was significant rise in heart rate(20.4%) in control after intubation at 2 min compared to nalbuphine (16.66%). Mean arterial pressure showed rise of 12.35% in group I and 4.39% in Nalbuphine at 2 min but was not significant. Heart rate and mean arterial pressure then gradually decreased from 3-8min but remained slightly higher than group II at 8th minute. So they concluded that nalbuphine attenuated haemodynamic response to laryngoscopy and intubation.

Zalunardo MP et al. (1997) compared oral clonidine with IV clonidine 3µg /kg and observed that during endotracheal intubation, heart rate did not increase significantly in clonidine group compared with the placebo and the oral clonidine group.

Manushree Ray, Dhurjoti Prasad Bhattacharjee et al in 2010 stated in their study that immediately after laryngoscopy and intubation heart rate increased by 10 bpm in control group, where as in clonidine group, HR decreased by 10 bpm, which is statistically significant.

In our study, immediately after the laryngoscopy and intubation, the rise in the heart rate occurred in both groups. From the baseline increase in mean heart rate in Group I (nalbuphine) was 37.2 bpm and in group II (clonidine) was 4.03 bpm respectively which is statistically significant (p <0.05). but in clonidine group this rise in heart rate was less than that of the nalbuphine group and it is statistically significant again (p<0.05).

Various authors have found a similar response to I.v. Clonidine immediately after intubation.

After intubation at 1 minute, increase in heart rate was 46.23 bpm in nalbuphine group and 10.9 bpm in clonidine group.

**3rd min** mean increase in heart rate at 3rd min, in nalbuphine group was 32.83 bpm compared to basal HR, whereas the increase in the clonidine group was 6.73

**5th min, 7 min** The increase in mean heart rate in nalbuphine group sustained even at 5 min and 7 min, which was 26.9 bpm and 14.7 bpm, whereas in the clonidine group the mean heart rate increase was 1.5 bpm. At 5th min no change in mean Hr at 7th min

**10th min** Manjushree Ray M et al. studied clonidine at a dose of 3 mg/ kg and found that at 10 min following laryngoscopy and intubation HR rise by 9 bpm in the control group and decreased by 16 bpm in clonidine group.

In our study at 10 min, there was also increase in heart rate 10.1 bpm compared to basal HR in nalbuphine group, And in clonidine group it was only 0.8 bpm compared to baseline HR, so in clonidine group there wasn't significant change in HR. this change didn't match with the study by Ray M et al at 10th min following laryngoscopy and intubation.

**At 15th and 20th min** In our study increase in mean pulse rate in nalbuphine group was 12.63 bpm and 5.43bpm at 15 and 20 minutes respectively compared to basal HR. Whereas in clonidine group it was 0.2 bpm and 0.8 bpm at 15th and 20th minute respectively but at 15th min there was decrease in mean HR.

In nalbuphine group there was significant increase in heart rate immediately after intubation and at 1,3,5,7,10,15,20 min after intubation with maximum rise of 46.23 bpm (at 1 min after intubation). In clonidine group maximum increase in heart rate occurred at 1 minute after intubation of 10.97 bpm. Similar findings were also noted by Zalunardo MP et al. And this increase is significantly less as compared to nalbuphine group.

**Changes in mean arterial pressure (MAP)**

Immediately after intubation and after intubation at 1 min...
Altan A et al. studied clonidine at a dose of 3µg/kg and found that, MAP increase by 16 mm of Hg in control group, whereas in clonidine group MAP increased by 10 mm of Hg.

Ray M et al. studied clonidine at a dose of 3 mg/kg and found that MAP increased by 14 mm of Hg in control group, whereas in clonidine group MAP increased by 18 mm of Hg.

In our study, immediately after intubation there was significant increase in MAP noted in both the groups, in nalbuphine group this increase was 15.7 mm of Hg whereas in clonidine group it was 2.6 mm of Hg from the baseline but this increase in clonidine group was less than nalbuphine group. After intubation at 1 min MAP increased by 23.3 mm of Hg in nalbuphine group and 4.7 mm of Hg in clonidine group.

At 3rd, 5th and 7th min In our study the increase in MAP in nalbuphine and clonidine group at 3rd min was 15.8 mm of Hg and 1.4 mm of Hg respectively, compared to baseline.

At 5th min, increase in MAP in nalbuphine group was 9.5 mm of Hg but in clonidine group MAP decreased by 0.7 mm of Hg compared to baseline.

At 7th min, increase in MAP in nalbuphine group was 1.3 mm of Hg compared to baseline whereas in clonidine group MAP decreased by 1 mm of Hg compared to baseline.

At 10 min Manjushree Ray M et al. found that clonidine at a dose of 3mg/kg caused increase in MAP by 4 mm of Hg in control group at 10 min after intubation and decreased by 26 mm of Hg in clonidine group. In our study increase in MAP in the nalbuphine group was 1.2 mm of Hg compared to baseline at 10 min after intubation and in clonidine group MAP decreased by 2.2 mm of Hg compared to baseline comparable to our study.

At 15th and 20th min. In our study at 15th min in nalbuphine group there was no change in MAP compared to baseline, whereas in clonidine group MAP decreased by 2.5 mm of Hg compared to baseline. At 20th min in nalbuphine group there was 0.1 mm of Hg increase in MAP occurred compared to baseline and in clonidine group MAP decreased by 2.1 mm of Hg compared to baseline.

In nalbuphine group there was significant increase in MAP immediately after intubation and after intubation at 1, 3, and 5 min with maximum at 1 min of 23.3 mm of Hg. and with the maximum of 4.7 mmol/hg in clonidine group.

Changes in systolic blood pressure (SBP)

In our study, immediately after intubation there was significant increase in SBP noted in both the groups. In Nalbuphine group this increase was 15.84 mm of Hg compared to baseline which is statistically significant (p<0.05). whereas in clonidine group the increase in SBP was 1.5 mm of Hg compared to baseline.

After intubation at 1 min increase in SBP in Nalbuphine and clonidine group from the baseline was 29.24 and 4.57 mm of Hg respectively.

In nalbuphine group after intubation at 3.5, 7, 10, 15, 20 min increase in SBP compared to baseline was 20.44, 9.74, 0.9, 1.34, and 2.54 respectively. In clonidine group after intubation at 3.5, 7, 10, 15 min SBP was decreased compared to baseline which was 0.83, 1.93, 3.53, 4.43, and 3.53 out of which at 3 and 5 min.

In Nalbuphine group maximum increase in SBP of 29.24 mm of Hg noted, (after intubation at 1 min) and in clonidine group maximum increase in SBP of 4.57 mm of Hg noted (after intubation at 1 min) compared to baseline.

Sedation scoring Immediately after extubation, sedation score in group I (Nalbuphine) and in group II (clonidine) was 2.13 ± 0.48 and 2.76 ± 0.50 respectively which is statistically Significant (p<0.05). Patient in group I was cooperative, oriented and tranquil while in group II was responding to command.

Clonidine is known to produce arousable sedation by its action on locus coeruleus nucleus without producing any respiratory depression. Our study showed that clonidine was far superior to Nalbuphine in the attenuation of the pressor response. An intravenous bolus dose of clonidine 3µg/kg which is administered 15 min before a laryngoscopy and intubation can be recommended to attenuate the sympathetic response to the laryngoscopy and intubation, it has important role in the patients of hypertension, ischemic heart disease, thyrotoxicosis and neurosurgical patients where even minimal haemodynamic change to laryngoscopy and intubation is hazardous.

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