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**ORIGINAL ARTICLE**

# Comparison of Effects of Nalbuphine and Tramadol on Cardiovascular Response to Tracheal Intubation in Patients Undergoing Emergency Appendectomy

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## ABSTRACT

**Objectives:** To compare the effects of Nalbuphine with Tramadol on cardiovascular response (change in heart rate and blood pressure) to tracheal intubation in patients undergoing emergency appendectomy.

**Material and methods:** This randomized controlled trial was conducted at the Department of Anaesthesiology, CMH Mardan from January 1, 2022, to June 30, 2022. A total of 100 patients who were undergoing emergency appendectomy under general anaesthesia, with ASA grade I, aged between 30-50 years, and weighing between 50-80 kg were selected. Patients were either male or female and had normal blood pressure. They were divided into two groups: the Nalbuphine group and the Tramadol group. The study focused on analyzing the cardiovascular response (changes in heart rate and blood pressure) to tracheal intubation in both groups.

**Results:** Most of the patients in both Group A and Group B were females, with a female to male ratio of 3.54:1 and 2.57:1, respectively. The mean age of patients in Group A was 37.90±5.41, while in Group B it was 40.10±6.39. After laryngoscopy and tracheal intubation, patients in Group A had a significantly less increase in heart rate and blood pressure as compared to those in Group B.

**Conclusion:** The Nalbuphine is better than Tramadol in attenuating the cardiovascular response to laryngoscopy and tracheal intubation.

**Keywords:** Nalbuphine, Tramadol, Cardiovascular Response, Tracheal Intubation, Laryngoscopy, Heart Rate and Blood Pressure.

## INTRODUCTION

While doing laryngoscopy to be followed by endotracheal intubation may activates the sympathetic nervous system. This happens because the stimulation of certain sensory nerves in the epiglottis, hypopharynx, peritracheal area, and vocal cords causes a response in the body's fight-or-flight system.[1] The nociceptive input, or pain sensation, leads to stimulation of the cardiovascular system, causing changes in the blood flow and increased levels of certain hormones such as catecholamines specifically, noradrenaline along with significant increase in heart rate and blood pressure. Post intubation the levels of adrenaline and dopamine are not significantly increased, so altered hemodynamic response is contributed mostly by increased levels of noradrenaline.[2,3,4]

The aforementioned cardiovascular stimulation due to nociceptive input can be harmful to certain individuals who are susceptible to hypertension, raised intracranial pressure, and myocardial ischemia. This risk is even greater in patients who have pre-existing essential hypertension, whether they are receiving treatment or not, and who also have a higher likelihood of having concomitant coronary artery and cerebrovascular diseases.[5]

The morbidity and mortality can be significantly reduced by just blunting the response to laryngoscopy and orotracheal intubation by different techniques which have been tried successfully.[2]

Preparing anaesthesia with a potent volatile agents for 5-10 minutes,[6] administering a bolus of an opioid Fentanyl – alfentanil[7] – sufentanil, Nalbuphine or Tramadol,[8] administering lignocaine intravenously or intratrachealy, [9]achieving beta adrenergic blockade with esmolol[10], propranolol or labetalol, giving intravenous nitropruside and nitroglycerine, using topical airway anaesthesia or intranasaly, magnesium sulfate and calcium channel blockers,[11] and alpha adrenergic receptor agonists such as clonidine.[12]

Previous studies concluded that short acting opioid analgesics like alfentanil, remifentanil, Fentanyl and Nalbuphine have blunted the haemodynamic response to laryngoscopy and orotracheal intubation.[5,13,14] There is currently a severe shortage of certain medications in Pakistan, while drugs such as Nalbuphine and Tramadol are widely accessible throughout the country. Nalbuphine is an opioid categorized as an agonist-antagonist and is chemically similar to oxymorphone and naloxone. Studies using autoradiography have revealed that Nalbuphine binds to μ-receptors as well as k and δ-receptors, acting as an antagonist at the μ-receptor and an agonist at the k-receptor.[16] Tramadol is an phenylpipredine analogue of codeine. It possess analgesic effects by centrally acting properties with both opioid and non opioid mechanisms of action.[17]

Therefore, the rationale for this research article is to compare the effects of Nalbuphine and Tramadol on the cardiovascular response to tracheal intubation in patients undergoing emergency appendectomy. The study aims to evaluate the efficacy of these drugs in preventing the increase in heart rate and blood pressure during laryngoscopy and orotracheal intubation. This comparison can help clinicians make informed decisions about the use of these drugs in emergency surgeries and improve patient outcomes.

## MATERIAL AND METHODS

This randomized controlled trial was conducted at Department of Anaesthesiology CMH Mardan from January 1, 2022 to June 30, 2022. Total 100 patients undergoing elective surgery under general anaesthesia with ASA grade I, having age from 30-50 years, either male or female, having normal blood pressure and weight range from 50-80 kg were selected. Patients with cardiovascular diseases, diabetes, asthma, respiratory tract infection, smokers and patients having difficult intubation were excluded from the study.

Informed consent was obtained from each patient before the day of operation. An approval was taken from ethical committee of institution. Selected patients were randomly divided into two groups (Nalbuphine group and Tramadol group). Nalbuphine was

given to patients of Nalbuphine group while Tramadol was given to patients of Tramadol group.

In operating room after arrival of patient, pulse oximeter and ECG electrodes were applied and NIBP cuff was applied and BP readings were taken and intravenous infusion of Lactated Ringer's solution was started. All the patients were induced with Propofol 1,5-2.5 mg/kg 1% solution along with Atracurium 0.5mg/kg to facilitate tracheal intubation. During anaesthesia ventilation was assisted or controlled with 1.2% Isoflurane and 50% N2O in $O_2$. Either 0.2mg/kg Nalbuphine or Tramadol 3mg/kg was administered 5 minutes before the start of laryngoscopy (lasting not more than 20 seconds), which was attempted 3 minutes after the administrations of Propofol and Atracurium. Heart rate, blood pressure and mean arterial pressure recording was started 2 minutes before the administration of study drugs by using NIBP monitor. These parameters were taken immediately after the laryngoscopy and intubation at 3 and 5 minutes interval. The results were recorded on pre-designed proforma.

## RESULTS

In present study total 100 patients were selected. Mean age in Nalbuphine group was 37.90±4.51 years and in Tramadol group was 40.10±6.39 years. In Nalbuphine group, there were 36 (72%) female patients and 14 (28%) male patients. In Tramadol group, 39 (78%) patients were female and 11 (22%) patients were male. (Table 1).

The present study showed that there insignificant difference of heart rate between Nalbuphine group and Tramadol group before induction and it was taken as base line but it showed there was marked heart difference in both groups at immediately after intubation ($p < 0.01$) that is highly significant. Before induction heart rate was (85.06±10.47) and 85.18±11.90) respectively in Nalbuphine group and Tramadol group. Immediately after intubation, heart rate increased in 16.47% patients and 36% patients above base line in Nalbuphine group and Tramadol group respectively. The heart rate in both groups was 99.83±7.47 and 115.44±6.69 in Nalbuphine group and Tramadol group respectively, the difference is significant ($p < 0.01$). At three minute after intubation heart rate decreased in both groups but more in Nalbuphine group. The heart rate was (92.18±11.5) and (100.88±6.45) in Nalbuphine group and Tramadol group respectively. There is marked difference in both groups ($p < 0.01$). At five minutes after intubation heart rate becomes below base line in Nalbuphine group but remains slightly elevated in Tramadol group. There is significant difference of heart rate in both groups ($p < 0.01$) (Table 2).

There is difference of systolic and diastolic blood pressure in patients of Nalbuphine group and Tramadol group before induction. The systolic blood pressure was 121.06±6.82 and 117.48±6.04 in Nalbuphine group and Tramadol group respectively and it is taken as base line ($p < 0.05$). The diastolic blood pressure was 76.72±3.43 and 75.18±6.30 in Nalbuphine group and Tramadol group respectively ($p > 0.05$) Table 3).

The systolic blood pressure rises above base line in both groups at immediately after intubation but it was more in Tramadol group. Systolic blood pressure was (134.58±8.33) and (152.32±4.48) in Nalbuphine group and Tramadol group respectively ($p < 0.01$). The diastolic blood pressure immediately after intubation was (96.08±10.51) and (100.86±8.38) in Nalbuphine group and Tramadol group respectively ($p < 0.05$). The difference of diastolic blood pressure immediately after intubation in both groups is not significant ($p > 0.05$) The systolic blood pressure declines in both groups at three minutes after intubation but more decreases in Nalbuphine group as compared to Tramadol group. The systolic blood pressure was (119.36±8.17) and (132.48±7.43) in Nalbuphine group and Tramadol group respectively ($p < 0.01$).

The diastolic blood pressure decreases at three minutes after intubation in both groups but decreased more in Nalbuphine group as compared to Tramadol group. The diastolic blood pressure was (82.94±8.24) and (89.54±4.81) in Nalbuphine group and Tramadol group respectively at three minutes after intubation ($p < 0.01$) At five minutes after intubation systolic blood pressure decreases in both groups but becomes below base line in Nalbuphine group and remain elevated in Tramadol group ($p < 0.01$). There is a significant difference of systolic blood pressure i.e. (110.48±5.90 and 125.58±6.93) in Nalbuphine group and Tramadol group. At five minutes diastolic blood pressure decreases and comes at base line in Nalbuphine group and remains elevated in Tramadol group (74.98±7.36 and 79.98±3.48) ($p < 0.05$) (Table 4).

The mean arterial blood pressure before induction was 96.26±8.23 and 89.76±6.53 in Nalbuphine group and Tramadol group respectively. The difference is significant in two groups ($p < 0.01$). The mean arterial blood pressure rises at immediately after intubation in both groups (111.88±9.61) and (122.34±4.53) but increases more in Tramadol group B ($p < 0.01$) At three minutes after intubation mean arterial blood pressure decreases in both groups and comes at base line in group A (95.90±11.51) and remains elevated (105.40±6.67) in Tramadol group ($p < 0.01$). At five minutes after intubation mean arterial blood pressure decreases in both groups but there is significant difference between two groups (88.30±7.85) and (94.40±5.54) in Nalbuphine group and Tramadol group respectively ($p < 0.01$) (Table 5).

Table 1: Gender distribution in Nalbuphine group and Tramadol group (n=100)

| Gender | Nalbuphine | | Tramadol | |
|---|---|---|---|---|
| | N | % | N | % |
| Male | 14 | 28.0% | 11 | 22.0% |
| Female | 36 | 72.0% | 39 | 78.0% |
| Total | 50 | 100.0% | 50 | 100.0% |

Table 2: Heart Rate comparison between Nalbuphine group and Tramadol group (n=100)

| Heart Rate | Mean±SD Nalbuphine group | Mean±SD Tramadol group | P value |
|---|---|---|---|
| Heart rate before induction | 85.06±10.47 | 85.18±11.90 | t = -0.53 p = >0.05 |
| Heart rate immediate after intubation | 99.84±7.47 | 115.44±6.69 | t = -10.99 p = <0.01 |
| Heart rate after 3 minutes | 92.18±11.55 | 100.88±6.45 | t = -4.64 p = <0.01 |
| Heart rate after 5 minutes | 81.98±11.18 | 91.16±5.98 | t = -5.11 p = <0.01 |

Table 3: Systolic and Diastolic Blood Pressure before Induction in Nalbuphine group and Tramadol group

| Blood Pressure | Mean±SD Nalbuphine group | Mean±SD Tramadol group | P. value |
|---|---|---|---|
| Systolic blood pressure before induction | 121.06±6.82 | 117.48±6.04 | t = 2.77 p = <0.05 |
| Diastolic blood pressure before induction | 76.72±3.43 | 75.18±6.30 | t = 1.519 p = >0.05 |

Table 4: Blood Pressure (Systolic and Diastolic) after Intubation

| Systolic & Diastolic Blood Pressure | Mean±SD Nalbuphine group | Mean±SD Tramadol group | P value |
|---|---|---|---|
| Immediate BP (systolic) after intubation | 134.58±8.33 | 155.22±8.73 | t = -12.09 p = <0.01 |
| Immediate BP (diastolic) after intubation | 96.08±10.51 | 100.86±8.38 | t = -2.51 p = <0.05 |
| BP (Systolic) after 3 minutes after intubation | 119.36±8.17 | 132.48±7.43 | t = -8.49 p = <0.01 |
| BP (Diastolic) after 3 minutes intubation | 82.94±8.24 | 89.54±4.81 | t = -4.88 p = <0.01 |
| BP (Systolic) after 5 minutes intubation | 110.48±5.90 | 125.58±6.93 | t = -12.26 p = <0.01 |
| BP (Diastolic) after 5 minutes intubation | 74.98±7.36 | 79.98±3.48 | |

Table 5: Mean Arterial BP Comparison in Nalbuphine group and Tramadol group

| Mean Arterial Blood Pressure | Mean±SD Nalbuphine group | Mean±SD Tramadol group | P value |
|---|---|---|---|
| Mean arterial BP before induction | 96.26±8.23 | 89.76±6.53 | t = 4.37 p = <0.01 |
| Immediate mean arterial BP after intubation | 111.88±9.61 | 122.34±4.53 | t = -6.95 p = <0.01 |
| Mean arterial BP after 3 minutes | 95.90±11.51 | 104.42±4.49 | t = 0.05 p = <0.05 |
| Mean arterial BP after 5 minutes | 88.30±7.85 | 94.40±5.54 | t = -4.48 p = <0.01 |

## DISCUSSION

The objective of present study was to compare the effects of Nalbuphine with Tramadol on cardiovascular response (change in heart rate and blood pressure) to tracheal intubation. In the present study HR before induction in Nalbuphine group and Tramadol group i.e. 85.06±10.47 and 85.18±10.9 showed no statistical difference (p > 0.05) however immediately after intubation, at 3 minute and after 5 minute showed statistical significant difference in Nalbuphine group and Tramadol group respectively (99.84±7.47) (115.44±6.69) (p <0.01) at 3 minutes (92.18±11.55 (100.88±6.45) (p <0.01) after 5 minutes (81.98±11.19) (91.16±5.98) (p <0.01) at all levels Tramadol showed less attenuating response on HR. The response to BP i.e. SBP at intubation was increase which was statistically significant between Nalbuphine group and Tramadol group (134.58±8.33) (155.22±8.73) (p <0.01) systolic BP at 3 minute (119.36±8.17) (132.48±7.43) (p <0.01) and after 5 minutes was (110.48±5.90) group B (125.58±6.93) (p <0.01). There was decrease in BP in Nalbuphine group which was appreciable at 3 minute and after 5 minutes. The response to MAP and DBP followed the same pattern.

Several studies have demonstrated that Fentanyl and Nalbuphine are superior to Tramadol in depressing the unwanted reflex due to intubation. in study of Pang et al, authors compared Tramadol with Fentanyl in attenuating haemodynamic response following tracheal intubation.[8] In one study, results are not in accordance with our study in which the HR and MAP were above the base line (HR 115.44±6.69 immediately after intubation) and (SAP 155.22±8.73 immediately after intubation). In one study, it was postulated by the authors that the pre-treatment with Tramadol causes dose dependent cerebral activation on EEG.[18] So the Tramadol does not ensure the deeper level of anaesthesia and attenuate the haemodynamic response.[19] Pang et al demonstrated that at three minutes after intubation, the protection provided by Tramadol was similar to that of Fentanyl in increase of heart rate, SAP, DAP and MAP. These results differ from our study in which it was clearly demonstrated that Nalbuphine was superior to Tramadol in blocking the unwanted reflexes. This difference can be due to the timing of administration of the study drug. They administered the study drug with thiapentone sodium which did not provide adequate time for the maximum action of drug to be achieved so its effect could not be appreciated. This can be the reason that effects are appreciated by them at six and nine minutes and not on intubation an earlier period. We administered drug five minutes before intubation which provided the time for its peak effect.[8]

The study conducted by Freye et al focused on assessing the effectiveness of Nalbuphine in reducing the hemodynamic response induced by laryngoscopy and intubation. They concluded there was 16% increase in HR and 16% increase in BP as compared to baseline. Bispectral index increase 18% when compared to injection after barbiturate injection.[1] Nalbuphine is an agonist antagonist at opioid receptor. In their study they used sevoflurane for maintenance of anaesthesia. Ventilation was controlled. In the Nalbuphine group there was highly significant increase in systolic BP (p <0.001) and highly significant increase in HR (p <0.001). The increase in BP and HR can be due to stimulation of reflex mechanism of supraspinal and spinal origin. [1]

The impact of intravenous Morphine and Tramadol during laryngoscopy and endotracheal intubation was examined by Vanden et al. The study involved 80 patients divided into two groups, and the drugs were administered to the patients three minutes before the induction of anesthesia. Prior to surgery, the patients were also premedicated with oral Midazolam (7.5mg) one hour beforehand. They recorded baseline HR, BP (systolic diastolic and mean) every minute for three minutes after giving the study drug and than immediately after intubation and at one minute interval for ten minutes. In this study mean arterial BP (systolic and diastolic) remained below baseline except immediately after intubation and one to three minutes post intubation. This is not the case in present study in which these values remained above the baseline and were relatively significant up to five minutes. However in their study in Tramadol group heart rate increased significantly as it was in present study and lasted longer than five minutes. These differences of BP and HR could be attributed to the pre-medication and smaller doses of Tramadol used that is 2mg/kg respectively, this dose is less as compared to 3mg/kg used in present study and previous studies which also showed the failure of Tramadol to attenuate chronotrophic response to laryngoscopy and tracheal intubation.[20]

The efficacy of Nalbuphine in mitigating the hemodynamic response induced by laryngoscopy and orotracheal intubation was investigated by Kazmi et al. Prior to the induction of anesthesia, the patients were premedicated with 2mg of intravenous midazolam administered five minutes before the procedure. Thiopentone sodium and succinylcholine were then used to induce anesthesia. Heart rate and mean arterial blood pressure were recorded at various intervals, including before the induction of anesthesia, immediately after intubation, and at one-minute intervals up to five minutes after intubation. Measurements were taken again at the ten-minute mark after intubation. They found that heart rate increased 15.5% (p >0.05) above the baseline than heart rate gradually decreased but remained above baseline. Mean arterial blood pressure increased by 10.5% as compared to baseline and than gradually decreased but remained above baseline up to five minutes. The results of Kazmi et al study are comparable to present study. So Nalbuphine prevented marked increase in heart rate and blood pressure associated with laryngoscopy and tracheal intubation. The difference in the results of Haq study compared to present study can be attributed to pre-medication with Midazolam and Halothane 1% and nitrous oxide 50% in oxygen which were used for maintenance of anaesthesia. Thus the Halothane could also have played a role in preventing increase in heart rate and blood pressure.[2] In present study administration of the trial drug was not given with induction agent but it was given five minutes before intubation so it takes time required for its peak effect to be achieved. So the effect of Tramadol not achieved by Berg may be due to slow onset of action. The second reason can be that Tramadol is a weaker analgesic than Nalbuphine so the equipotent dose calculated from postoperative pain may be not true for Tramadol. Still it should be realized that effect of Tramadol on release and inhibition of noradrenaline re-uptake and 5 hydroxy tryptamine could have resulted in tachycardia and hypertension this may have masked a concomitant positive analgesic effect of Tramadol on stimulus of tracheal intubation. In another study of Kay et al, the effect on heart rate, SAP, MAP of Nalbuphine are also similar in which Nalbuphine attenuate the pressure but not the chronotropic response to airway instrumentation.[21]

## CONCLUSION

Our findings suggest that administering the drug with sufficient time before laryngoscopy and tracheal intubation can effectively reduce the hemodynamic response (increase in heart rate and blood pressure) associated with the procedure. Nalbuphine was found to be more effective than Tramadol in attenuating the

cardiovascular response. Additionally, Nalbuphine is readily available and has fewer opioid-related side effects such as respiratory depression. Therefore, such drug delivery should be considered in clinical practice, particularly in cases where patients have hypertension, ischemic heart disease, intracranial or intraocular hypertension, to minimize the hemodynamic response associated with instrumentation.

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