

# A randomized controlled parallel study of nalbuphine and fentanyl on hemodynamic response to laryngoscopic and laparoscopic stress in patients undergoing laparoscopic appendectomy under general anaesthesia

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## Abstract

**Aims:** Hemodynamic changes caused by laryngoscopy, endotracheal intubation and creation of pneumoperitoneum in laparoscopic surgeries is deleterious to patients. This study was done to compare nalbuphine an agonist antagonist opioid with fentanyl, a gold standard opioid, when used in patients undergoing laparoscopic appendectomy under general anaesthesia.

**Materials and Methods:** This study included 60 ASA I patients who underwent elective appendectomy were randomised to receive either nalbuphine 0.1mg/kg or fentanyl 2µg/kg as analgesics 5 minutes prior to intubation. Heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure were recorded at baseline and at every 2 minutes post intubation till the end of surgery. The time of laparoscopic port insertion and creation of pneumoperitoneum was noted. Independent student 't' test and chi square test was used to analyse continuous variables and categorical variables respectively.

**Results:** The changes in heart rate were comparable between both groups at all time points of observation. Nalbuphine and fentanyl group showed an increase in heart rate of 3.81% and 6.03% respectively. Mean arterial pressure was comparable at all time points of observation except at the time of insertion of second port wherein fentanyl group showed 12.70% increase as compared to 4.54% fall from baseline in nalbuphine group. Side effects were comparable between both groups except sedation which was significantly more in nalbuphine group and pruritus more in fentanyl group.

**Conclusion:** Nalbuphine due to its availability without license is an effective alternative to fentanyl in laparoscopic surgeries.

**Keywords:** Nalbuphine, Fentanyl, Hemodynamic response, Laparoscopic surgery.

## Introduction

General anaesthesia, direct laryngoscopy, tracheal intubation and pneumoperitoneum created in laparoscopic surgery induce marked cardiovascular changes. A rise in plasma concentration of nor-adrenaline, adrenaline and dopamine is known to increase heart rate and blood pressure during endotracheal intubation. Though, the responses of blood pressure and heart rate is transient, it might have detrimental effect in patients with pre-existing cardiovascular disease.<sup>1-4</sup> In laparoscopic surgeries creation of pneumoperitoneum causes hemodynamic changes by both mechanical and neurohumoral factors.<sup>5-7</sup> Catecholamines, renin and vasopressin have been proposed for these changes.

Various drugs and induction agents like fentanyl, remifentanyl, morphine, buprinorphine, propofol, magnesium, esmolol, clonidine, lignocaine, dexmedetomidine etc have been used for attenuation of stress response. The adverse effect profile, duration of action, and availability of these drugs guides its usage in various clinical setting.<sup>8-16</sup>

Fentanyl, a potent opioid introduced in 1960 is a gold standard in intra operative analgesia replacing morphine and pethidine because of its short duration of action, cardiac stability and minimal respiratory depression.<sup>17</sup> Nalbuphine is an opioid agonist-antagonist used as analgesic. Its analgesic potency is equivalent to

that of morphine on a milligram basis.<sup>18</sup> It is agonist at kappa receptor and antagonists at mu receptors. It has fewer side effects as compared to other agonist antagonists such as pentazocine or butarphenol. Its cardiovascular stability, less nausea vomiting and longer duration of action makes it an ideal perioperative analgesic.<sup>18</sup> In this study we compared nalbuphine and fentanyl for its hemodynamic effect during laryngoscopy and creation of pneumoperitoneum in patients undergoing elective laparoscopic appendectomy.

## Materials and Methods

After obtaining Institutional ethics committee approval, 60 patients of ASA grade 1 was included in the study after obtaining informed consent. Patients aged 20-60, posted for elective laparoscopic appendectomy under general anaesthesia were included in the study. Patients refusing to participate in the study, ASA II and above, emergency surgeries, pregnant female, known allergy to study drugs and patients with difficult airway were excluded from the study.

A careful pre-anaesthetic evaluation was done prior to surgery and necessary investigation was done before enrolling into the study. Eligible patients who gave consent were kept nil orally for more than 6 hours before surgery. On the day of surgery all patients received premedication (glycopyrrolate 0.2 mg, and ondansetron 4 mg intravenous) in pre operative room. In the operative

room patients were attached with monitors (ECG, NIBP and pulse oximeter) and baseline reading was recorded. Based on randomization table generated prior, patients were divided into two groups. Group I received Nalbuphine 0.1 mg/kg and Group II received Fentanyl 2µg/kg five minutes before Induction. Both group patients were induced with propofol titrated according to loss of consciousness and paralysed with atracurium 0.5 mg/kg followed by 4 minutes of bag mask ventilation. Then the patients were intubated with appropriate endotracheal tube. Patients having unanticipated difficult airway were excluded from the study.

Heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, oxygen saturation (Spo<sub>2</sub>) and end tidal CO<sub>2</sub> was recorded at baseline, 5 minutes after study drug, 1 minute after intubation, and then at 2 minutes interval till the end of surgery. Time of first port insertion, creation of pneumoperitonium, second port insertion and third port insertion was noted. Patients were maintained on O<sub>2</sub>, N<sub>2</sub>O and sevoflurane. Sevoflurane was kept at 1.5 on dial setting till appendectomy and then reduced to 1.0 with gradual tapering at the end for extubation. Inj glycopyrrolate (0.008mg/kg) and neostigmine 0.05 mg/kg intravenously was used for reversal. Patients were monitored every 5 minutes for 30 minutes post extubation and for 6 hours in post anaesthesia care unit. Sedation in post anaesthesia care unit was assessed by Pasero Opioid – Induced sedation scale (0 – Sleep easy to arouse; 1- Awake and alert; 2 - Slight drowsy, easily aroused; 3- Frequently drowsy, arousable, drifts off to sleep during conversation; 4 - Somnolent, minimal or no response to verbal or physical stimulation). Patients whose surgery prolonged more than 90 minutes were excluded from the study.

### Statistical Analysis

The sample size 60 with 30 in each group was based on assuming a variation of 15, a clinical acceptable difference of 10 in heart rate and systolic blood pressure, with  $\alpha$  value of 0.05 and  $\beta$  value of 0.20 and power of 0.80. Independent student t test was used for intergroup comparison of continuous variables and chi square test was used for comparing nominal variables. A P value of  $\leq 0.05$  was considered significant.

### Observation and Results

Patient demographic data was comparable between groups (Table 1). There was no significant difference in heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure between both groups at baseline (Table 1). The change in Heart rate and mean arterial pressure from baseline was considered for analysis as change in systolic and diastolic pressure reflected similar changes.

There was no significant fall in heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure in both groups 5 minutes after induction. Both groups showed increase in heart rate, 3.81% in nalbuphine group and 6.03% in fentanyl group, 1 minute after intubation but were comparable and statistically not significant. Heart rate changes were comparable between both the groups at all time points of observation. Maximum increase in heart rate was observed at the time of extubation, with nalbuphine group showing increase by 27.45% and fentanyl group 18.82%. However the increase in heart rate was not statistically significant. (Table 2 and Fig. 1)

The changes in Mean arterial Pressure were comparable between both groups at all time points of observation except at the time of insertion of second port wherein Nalbuphine group showed 4.54% fall whereas fentanyl group showed 12.70% increase from baseline which was statistically significant. Both groups showed maximum rise at the time of extubation, 15.94% in nalbuphine group and 13.5% in fentanyl group, but was not statistically significant. (Table 3 and Fig. 2). Systolic and diastolic blood pressure showed similar changes (Fig. 3 & 4).

The incidence of post operative complication such as shivering, nausea and vomiting, respiratory depression, hypertension or hypotension, tachycardia or bradycardia was comparable between both groups. The incidence of pruritus was significantly more in fentanyl group as compared to nalbuphine group (Table 4). Sedation as assessed by Pasero Opioid – Induced sedation scale was significantly higher in nalbuphine group as compared to fentanyl group at 1.0, 2.0 and 6.0 hrs after extubation in post anaesthesia care unit.

**Table 1: Demographic data and base line heart rate, Systolic blood pressure (SBP), Diastolic blood pressure (DBP) and Mean Arterial Pressure (MAP)**

	Group I (n=30)	Group II (n=30)	P value
Age	26.88 ± 8.76	26.31 ± 8.23	0.88
Gender	Female – 18 Male - 12	Female – 16 Male -14	0.72
Weight	52.56 ± 6.94	52.31 ± 9.19	0.92
ASA I	30	30	-
Heart rate	80.13 ± 13.71	86.00 ± 15.64	0.26
SBP	126.13 ± 12.3	119.94 ± 16.49	0.23
DBP	80.19 ± 8.42	76.94 ± 15.98	0.47
MAP	93.5 ± 10.21	89.04 ± 15.91	0.35

**Table 2: Changes in heart rate from baseline at various time points**

	Group I (n=30)		Group II (n=30)		P value
5 min Post Induction	-3.06 ± 10.56	↓	-5.19 ± 6.66	↓	0.50
post Intubation					
1 min	9.00 ± 16.07	↑	10.06 ± 14.81	↑	0.84
2 min	6.06 ± 13.80	↑	5.44 ± 14.75	↑	0.90
4 min	3.38 ± 12.50	↑	3.13 ± 16.29	↑	0.96
6 min	2.31 ± 12.65	↑	3.56 ± 13.27	↑	0.78
8 min	5.13 ± 13.97	↑	3.56 ± 11.31	↑	0.73
10 min	6.56 ± 13.42	↑	3.38 ± 12.09	↑	0.48
12 min	5.44 ± 15.19	↑	5.25 ± 13.25	↑	0.97
14 min	5.56 ± 18.08	↑	-0.31 ± 14.23	↓	0.31
16 min	4.69 ± 18.05	↑	-0.13 ± 13.16	↓	0.39
First port	5.06 ± 14.20	↑	7.19 ± 12.57	↑	0.65
Pneumoperitoneum	5.38 ± 12.52	↑	5.31 ± 11.28	↑	0.98
Second port	5.94 ± 14.91	↑	5.13 ± 13.76	↑	0.87
Third port	6.94 ± 16.80	↑	2.75 ± 13.95	↑	0.45
Extubation	22.00 ± 17.10	↑	16.19 ± 14.30	↑	0.30
5 min post extubation	7.19 ± 19.08	↑	9.75 ± 16.22	↑	0.68

**Table 3: Changes in Mean Arterial Pressure from baseline at various time points (↓ - decrease from base line; ↑ Increase from baseline)**

	Group I (n=30)	Change	Group II (n=30)		P value
5 min Post Induction	-20.15±14.02	↓	-18.95 ± 14.20	↓	0.81
post Intubation					
1 min	2.37±18.01	↑	1.50 ± 22.04	↑	0.90
2 min	-8.00 ± 12.61	↓	-5.06 ± 20.64	↓	0.63
4 min	-16.18 ± 12.89	↓	-5.37 ± 21.45	↓	0.09
6 min	-16.87 ± 11.85	↓	-3.64 ± 22.54	↓	0.04
8 min	-7.73 ± 17.94	↓	2.14 ± 22.07	↑	0.17
10 min	-2.68 ± 15.13	↓	6.44 ± 20.14	↑	0.15
12 min	-2.81 ± 15.46	↓	7.25 ± 14.78	↑	0.07
14 min	0.43 ± 17.11	↑	3.45 ± 19.79		0.64
16 min	-0.48 ± 15.15	↓	0.92 ± 17.87	↑	0.81
First port	-7.41 ± 15.08	↓	4.14 ± 20.07	↑	0.07
Pneumoperitoneum	-3.72 ± 15.96	↓	-9.08 ± 23.72	↓	0.08
Second port	-4.25 ± 13.15	↓	11.31 ± 20.32	↑	0.01
Third port	-2.50 ± 16.40	↓	6.52 ± 18.87	↑	0.16
Extubation	14.91 ± 15.25	↑	12.08 ± 14.76	↑	0.59
5 min post extubation	5.16±13.70	↑	9.41 ± 17.29	↑	0.45

**Table 4: Side effects in Post operative period**

	Group I (n=30)	Group II (n=30)	P value
Shivering	4/30	8/30	0.36
Pruritus	0/30	14/30	0.007
Nausea/Vomiting	Nil	Nil	
Bradycardia/tachycardia	Nil	Nil	
Hypotension/hypertension	Nil	Nil	
Sedation (1 hr)	3.0 ± 0.52	2.25 ± 0.45	0.001
Sedation (2 hr)	2.06 ± 0.25	1.69 ± 0.48	0.01
Sedation (6 hr)	1.94 ± 0.25	1.0 ± 0.1	0.001

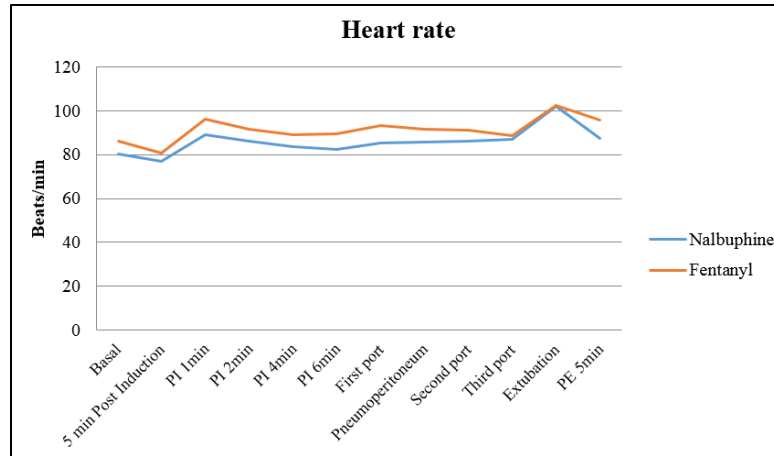


Fig. 1: Changes in heart rate at various time points (PI: Post Intubation).

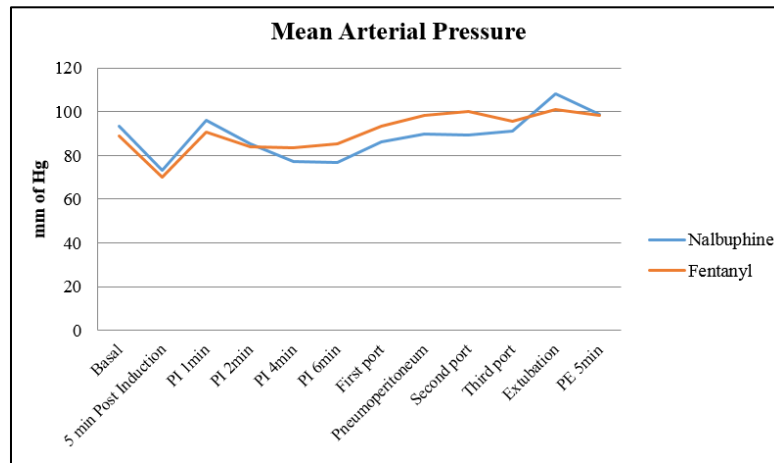


Fig. 2: Changes in mean arterial pressure at various time points (PI: Post Intubation)

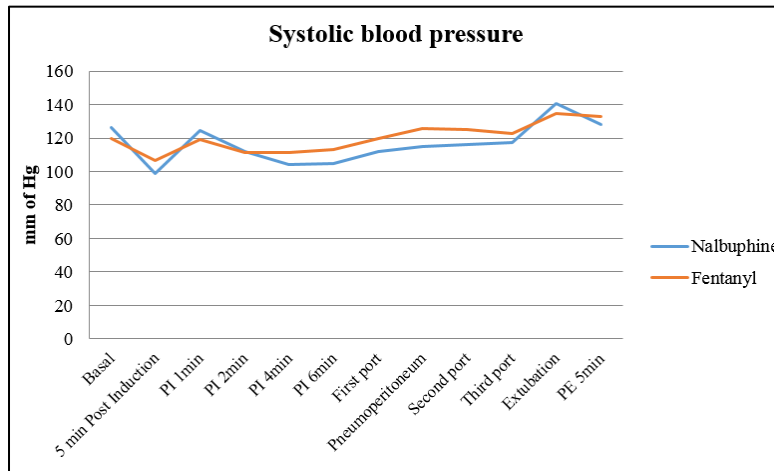
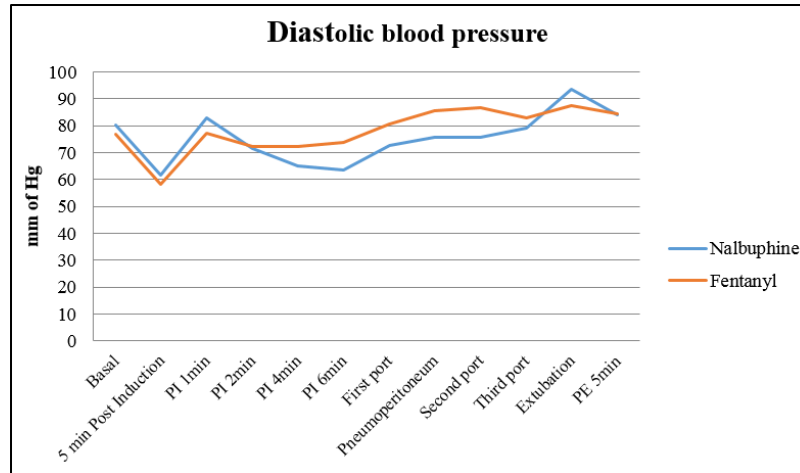


Fig. 3: Changes in systolic blood pressure at various time points (PI: Post Intubation).



**Fig. 4: Changes in diastolic blood pressure at various time points (PI: Post Intubation)**

### Discussion

The main objective of balanced anaesthesia is to provide amnesia, minimize pain and reduce the adverse effects associated with agents used for anaesthesia. The components of balanced anaesthesia include amnesia, analgesia, muscle relaxation and abolition of autonomic reflexes.<sup>19</sup> Opioids has been a mainstay analgesic in balanced anaesthesia since 1947. The advantages of opioids are less fluctuation in cardiovascular dynamics, decrease requirements of inhalation anaesthetics and increased post operative analgesia.<sup>19</sup> The use of opioids is limited by its adverse effect such as bradycardia, hypotension, respiratory depression and its availability. Because of its abuse potential opioid availability is strictly regulated by state.

Nalbuphine, is now commercially available in India and can be obtained without an opioid licence. Nalbuphine has a comparable analgesic potential to morphine as demonstrated in the study done by Joseph Yanulevich<sup>20,21</sup> Unlike morphine, nalbuphine has a plateau effect on respiratory depression and also has been used to reverse the respiratory depression due to morphine.<sup>22</sup> This study aimed at comparing effect of nalbuphine on hemodynamics with that of fentanyl, a gold standard opioid in India, in laparoscopic surgeries. Earlier studies comparing nalbuphine with fentanyl for hemodynamic response have used 0.2mg/kg–0.3 mg/kg of nalbuphine<sup>14,23-25</sup> In our study we used 0.1mg/kg of nalbuphine as nalbuphine is equipotent to morphine in milligram basis and also to minimise postoperative side effects of nalbuphine such as sedation, shivering, dizziness/vertigo and euphoria.<sup>26</sup>

In patients undergoing laparoscopic surgeries under general anaesthesia, laryngoscopy and intubation are not the only manoeuvres which cause increase in heart rate and blood pressure but also insertion of laparoscopic ports and creation of pneumoperitoneum<sup>5,7</sup> This study compared nalbuphine and fentanyl on its hemodynamic effects during these manoeuvres.

In our study, heart rate was comparable between both groups at all time points of observation. The maximum increase in heart rate post intubation was seen at 1 minute with nalbuphine showing 11.23% and fentanyl group showing 11.69%. Khan et al found a significant increase in heart rate (25%) in nalbuphine group as compared to fentanyl group (6.4%). This may be attributed to selection of patients and use of TIVA.<sup>26</sup>

At the time of intubation, mean arterial pressure showed an increase by 2.53% in nalbuphine group as compared to 1.68% in fentanyl group in our study. Tariq et al<sup>5</sup> in their study comparing nalbuphine and saline for endotracheal intubation, observed 1.40% increase in MAP at 1 min post intubation. The difference may be due to higher dose (0.2mg/kg) used in their study.

The cardiovascular response to increased abdominal pressure is phasic and transient. However, this can lead to serious complication in patients with cardiac or respiratory diseases. Hence evaluation of effect of drugs used to attenuate stress response during insertion of laparoscopic port and creation of pneumoperitoneum is essential. We found in our study that heart rate was comparable between both groups during first port insertion, creation of pneumoperitoneum, second port insertion and third port insertion. Nalbuphine group showed 6.7% increase in heart rate after pneumoperitoneum as compared to 6.17% in fentanyl group. However, mean arterial pressure showed a significant increase in fentanyl group 12.70% as compared to 4.5% fall from baseline in nalbuphine group. These changes were also reflected in both systolic and diastolic blood pressure. These finding may be due to patient group selected in our study which included patients posted for elective laparoscopic appendectomy so as to control patient and surgery related variable factor in evaluation of drug effect. Further studies are required in various other surgeries to evaluate these findings.

At the time of extubation we observed comparable increase in both heart rate and mean arterial pressure in both groups in contrast to observation by Khan et al. In

their study they observed 15% increases in heart rate in nalbuphine group as compared to 4% in fentanyl group. This may be due to additional supplementation of analgesic in fentanyl group after 1 hour of surgery in their study. In our study, fentanyl group additionally received Inj paracetamol 1gm intravenous after 45 minutes of induction. However, the average duration of surgery in both groups was less than 1 hour. Laparoscopic appendectomy was hence chosen for this study so as to control the duration of surgery.

In the post operative ward the incidence of shivering was more in nalbuphine group as compared to fentanyl group. The requirement of additional analgesic in first 6 hours of post operative observation was more in fentanyl group as compared to nalbuphine group. This might be due to longer duration of action of nalbuphine. However, further controlled studies are required to evaluate post operative analgesic effect of nalbuphine.

In our study, we included surgeries which could get over in one hour duration; further studies are required in longer duration and emergency surgeries. Recovery from anaesthesia was not objectively evaluated in our study, this may one of the limitation of our study as nalbuphine is known to cause more sedation than fentanyl.<sup>26</sup>

## Conclusion

Thus, we conclude that nalbuphine at dose of 0.1mg/kg is an effective alternative for fentanyl in laparoscopic appendectomy surgeries. Due to its availability without opioid licence makes it a better alternative for fentanyl at small hospitals.

**Conflict of Interest:** None

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