Comparison of analgesic and hemodynamic effects of nalbuphine versus fentanyl: a randomized, double-blinded interventional study in patients on cardiopulmonary bypass

Anjum Saiyed[a], Saurabh Sharma[a], Arish Hussain[b]

[a]SMS Medical College & Hospital, Jaipur, Rajasthan, India, [b]RUHS Medical College & Hospital, Jaipur, Rajasthan, India

Correspondence to Anjum Saiyed, MD Anaesthesia, J-180, Rajiv Gandhi Marg, Adarsh Nagar, Jaipur, Rajasthan 302004, India.
Tel: +91 921 402 1930;
e-mail: dranjumsaiyed@gmail.com

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Background
Our study aimed to compare analgesic and hemodynamic effect of Nalbuphine vs fentanyl in patient undergoing cardiac surgery on cardiopulmonary bypass.
Study design
Prospective, double blind, randomized intervational study.
Materials and Methods
After ethical committee approval and written informed consent, 60 patients of either sex,aged between 18 to 65 yrs, ASA grade 2nd and 3rd, randomely allocated to each group. Group A received study drug Nalbuphine and group B received Fentanyl. Both the drugs were given 5 min before induction. Repeated doses of study drugs were given when BIS score >60. Haemodynamics parameters were recorded at different time intervels throughout the surgery. After extubation VAS score noted at different time interval and time of first need of analgesic (Rescue analgesia) noted when VAS >3.
Statistical analysis
All the qualitative data were analysed with chi square test and all the quantitative data were analysed with comparison of mean±SD and unpaired student t-test. The levels of significance and α - error were kept 95 % and 5 % respectively, for all statistical analyses. *P* values <0.05 were considered as Significant (S) and P value > 0.05 as statistically Non Significant (NS).
Results
The mean heart rate was statistically significantly less in group B at just after intubation and just before going on cardio pulmonary bypass (CPB) & mean arterial pressure (MAP) also was statistically significantly less at just after intubation and just after coming off CPB compare to group A. Duration of analgesia in group A (288 ±42.13 min) was significantly prolonged as compared with group B (207±50.04 min). This prolongation of duration of analgesia was statistically significant.
Conclusion
The present study demonstrate the benefit of Fentanyl over Nalbuphine for intraoperatively haemodynamic stability and Nalbuphine is better for post extubation longer duration of analgesia over fentanyl.

Keywords:
cardiopulmonary bypass, Fentanyl, Nalbuphine, VAS score

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Introduction

The inclusion of an opioid as a component of balanced anesthesia can reduce preoperative pain and anxiety, decrease somatic and autonomic responses to airway manipulations, improve hemodynamic stability, lower requirements for inhaled anesthetics, and provide immediate postoperative analgesia [1]. Fentanyl is a potent synthetic μ receptor opioid agonist. Its ability to provide cardiovascular stability and to block the stress response to surgical stimuli at high doses made it the mainstay of cardiac anesthesia [2,3]. Nalbuphine is a semisynthetic opioid. It does not increase systemic blood pressure, pulmonary artery blood pressure, heart rate (HR), or arterial filling pressure [4]. For this reason, nalbuphine may be useful to provide sedation and analgesia in patients with heart disease. So, our aim was to compare the effects of fentanyl and nalbuphine on analgesic and hemodynamic responses in cardiac surgery on cardiopulmonary bypass (CPB) to help in the selection of a better drug.

Patients and methods

This hospital-based, prospective, randomized, double-blinded, comparative interventional study was

conducted at SMS Medical College and attached group of hospitals from August 2019 to September 2019, after permission from the ethics committee. The method of randomization used was the sealed envelope method.

Patients were randomly allocated into two groups. The patients and the postgraduate students who were participating in the study were unaware about the group to which they were allocated. One medical student posted in the operation theater opened the envelope. Data were collected by the postgraduate students participating in the study and the study drug was prepared and injected by another postgraduate student who was aware about the group.

A total of 60 patients of the age group 18–65 years, American Society of Anesthesiologists (ASA) grades II and III patients of either sex, undergoing cardiac surgery with CPB were included in our study. Height of all the patients ranged from 160 to 170 cm and their weight ranged from 40 to 70 kg. Patients with a history of drug allergy, preexisting asthma, renal or hepatic dysfunction, morbidly obese patients, and pregnant/lactating patients were excluded from the study.

Primary objectives of this study were to assess and compare hemodynamic variables, HR, and mean arterial pressure (MAP) from baseline at different time intervals in both groups.

Secondary objectives were to assess and compare the time required for first rescue analgesia in both the groups in the postoperative period after extubation according to the visual analog scale (VAS) score.

To assess and compare the side effects if any.

Patients were randomly allocated into two groups (30 in each group).

Group A received an injection of nalbuphine 0.2 mg/kg intravenous slowly over 5 min before induction and thereafter repeated if the bispectral index score (BIS) is more than 60 during surgery.

Group B– received an injection of fentanyl 3 μg/kg intravenous slowly over 5 min before induction and thereafter repeated if the BIS is more than 60 during surgery.

All patients were operated using CPB after mid-sternotomy incision. Types of operations were mitral valve replacement, aortic valve replacement, and double-valve replacement.

On arrival to the operation theater, the patient was identified. Fasting status, written informed consent, and PAC were checked. Patients were explained about VAS. Routine noninvasive monitors were attached and systolic blood pressure, diastolic blood pressure, and MAP were recorded. ECG and pulse oximeter will be attached to the patient. The intravenous line was secured and intravenous fluid of Ringer's lactate was infused at a rate of 5 ml/h. Internal jugular vein and femoral arterial cannulation were done under local anesthesia.

An injection of midazolam 0.05 mg/kg was given. Baseline data were collected. The study drug was given according to the group allocated. After 5 min, induction of anesthesia was given by an injection of etomidate 0.3 mg/kg intravenous slowly and rocuronium (0.9 mg/kg). The patient was ventilated with 100% oxygen for 3 min and under direct laryngoscopy. She/he was intubated with appropriately sized ETT. Bilateral air entry was checked and the tube was secured. Hemodynamic parameters (HR, systolic blood pressure, diastolic blood pressure, and MAP) were measured just before intubation and thereafter at every 15 min interval till the patient was taken on CPB and at every 30 min interval while on CPB and again every 15 min after coming off the bypass during the intraoperative period. Surgery was allowed to start and anesthesia was maintained with 100% oxygen, with injections of 1% sevoflurane, rocuronium 0.1 mg/kg, and midazolam 0.01 mg/kg every 30 min of interval in the intraoperative period. Further incremental doses (1/3 of initial dose) of study drug were given if the BIS was more than 60 during surgery. The target BIS was in the 40–60 range. Subsequent incremental doses of the study drug were kept at one-third of the first dose keeping in mind that BIS should not exceed more than 60 as we were aware that the maximum dose of nalbuphine should not cross 160 mg in 24 h and fentanyl has a wider therapeutic range (up to 3500 μg in 24 h). As we were dealing with cardiac surgery patients, we were in the safe range.

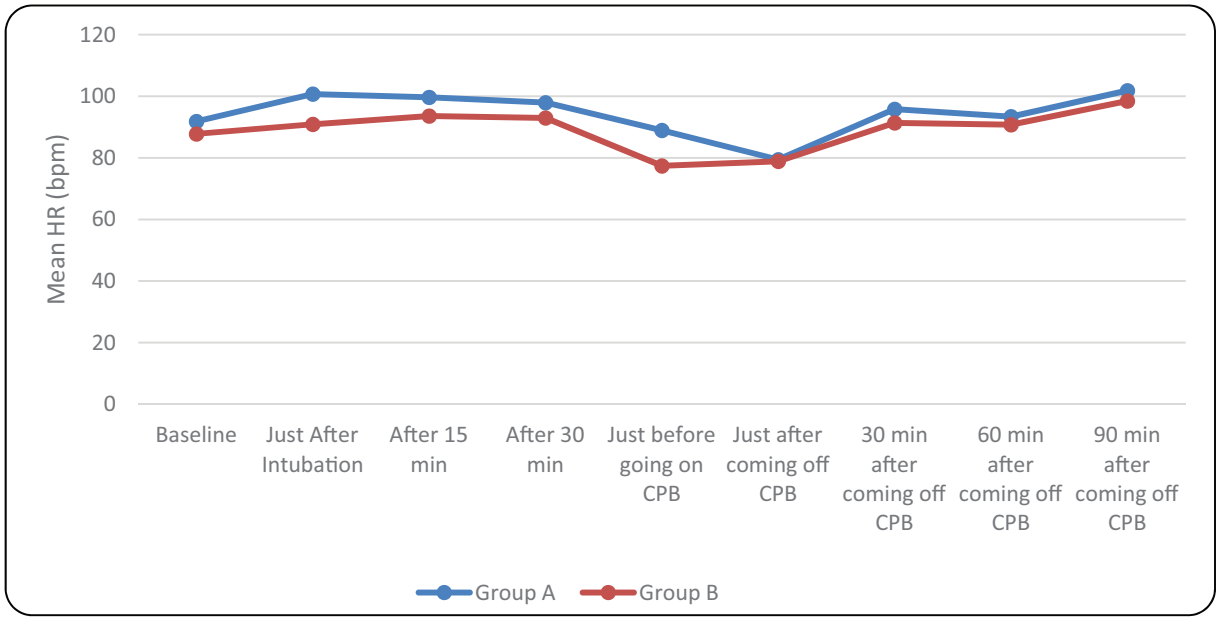
Patients were shifted to ICU with IPPV and taken on ventilator. When the patient became conscious, hemodynamically stable, and fulfilled the criteria of extubation, she/he was extubated. As per the protocol, all patients were given 1 g paracetamol intravenous every 8 h after shifting to the ICU. In the ICU, the patient was observed for any side effects.

Table 1 Demographic profile

Number of patients (60)	Group A (nalbuphine) (30 patients)		Group B (fentanyl) (30 patients)		*P* value
	Mean	SD	Mean	SD	
Sex					
M/F	19/11		15/15		0.434 (NS)
Age (years)	46.23	11.30	47.53	9.90	0.637 (NS)
ASA grade 2/3	23/7		24/6		1.000 (NS)
Weight (kg)	61.37	6.01	60.03	5.32	0.366 (NS)
Duration of surgery (min)	176.00	20.06	175.50	20.14	0.923 (NS)

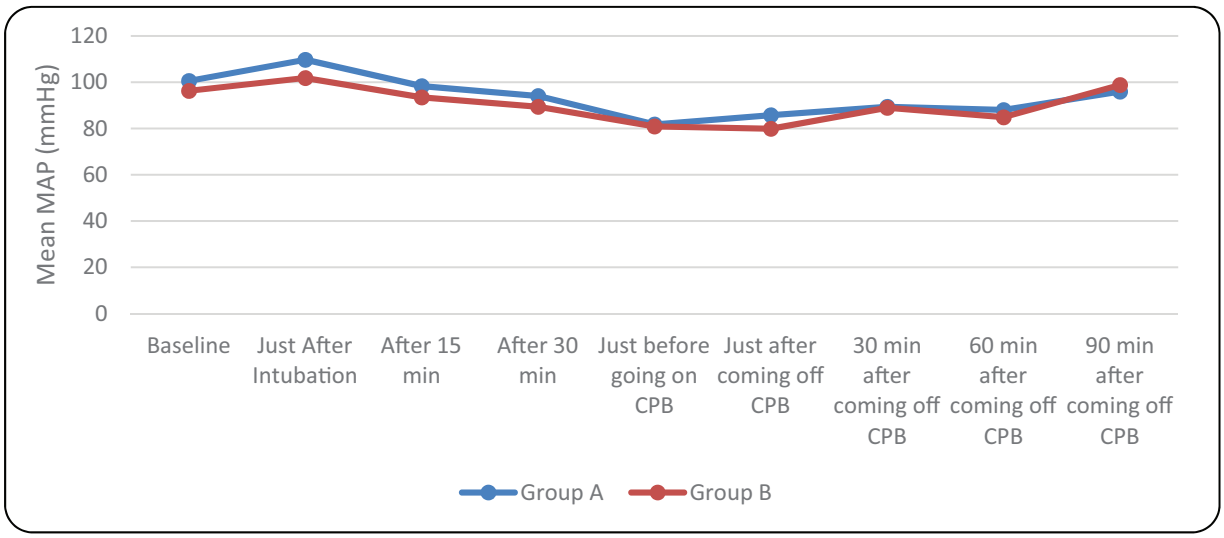
F, female; M, male.

Figure 1



Mean HR at different time intervals in both the groups. HR, heart rate.

Figure 2



MAP at different time intervals in both the groups. MAP, mean arterial pressure.

Table 2 Mean duration of surgery between the two groups

	Group A		Group B		*P* value
	Mean	SD	Mean	SD	
Mean duration of surgery	176.00	20.06	175.50	20.14	0.923 (NS)

Table 3 Time of required for first rescue analgesic drug when visual analog scale more than 3 after extubation (min)

	Group A		Group B		*P* value
	Mean	SD	Mean	SD	
First need of rescue analgesic (min)	288.00	42.13	207.00	50.04	$P<0.001$ (S)

S, significant.

After extubation, VAS score was noted at different time intervals and time required for first rescue analgesic (injection diclofenac intravenous) was noted when VAS score more than 3. Side effects (nausea, vomiting, hypotension, bradycardia, respiratory depression, and pruritus) were also noted.

Statistical analysis

Data were entered on Excel sheet MS Office Excel-2010 (Microsoft Corporation, Washington, USA) and were analyzed statistically using the SPSS Statistical software (IBM Company, Chicago) (ver.18.0.0) and XLStat (Addinsoft Company, Paris, France).

Qualitative data were analyzed with χ^2 test and the quantitative data were analyzed with comparison of mean±SD and unpaired Student's *t* test. The levels of significance and α-error were kept at 95 and 5%, respectively, for statistical analyses. *P* values less than 0.05 were considered as significant and *P* value more than 0.05 as statistically nonsignificant.

Results

Group A (nalbuphine) and group B (fentanyl) were comparable in terms of demographic variables such age, sex, weight, ASA grading, and duration of surgery (Table 1).

The baseline mean value of the HR was comparable in both the groups. The HR was significantly higher in group A than group B at the just after intubation and just before going on CPB. This difference was statistically significant (Fig. 1).

The baseline MAP value was comparable in both the groups. MAP was significantly higher in group A than group B at the just after intubation and just after coming off CPB. This difference was statistically significant (Fig. 2).

The mean duration of surgery between both the groups was comparable. No statistically significant difference was observed according to the mean duration of surgery in both the groups (Table 2).

The mean time required for first rescue analgesic drug when VAS more than 3 after extubation between both groups is comparable. This difference was statistically significant (Table 3).

Discussion

There was no change in the mean age, weight, ASA grading and sex, duration of surgery, and repetition of analgesic dose in both the groups. Both groups were comparable without any statistical significance.

The mean baseline pulse rate in group A was 91.83 ±20.99 bpm and in group B was 87.77±16.32 bpm. The difference in HR was not significant as shown by a *P* value more than 0.05. So, the baseline HR was comparable between two groups.

In our study, both the groups showed a rise in HR after intubation, but group A showed a higher rise in HR to 100.73±21.24 bpm (9.69%) from baseline but in group B it rose to 90.90±14.99 bpm (3.56%) from the basal value. There was significant difference in both groups in HR just after intubation. In our study, the mean HR at just before going on CPB was decreased in both groups, which was 88.93±16.09 bpm in group A and 77.40±9.88 bpm in group B ($P=0.001$), a higher decrease in group B compared with group A. This difference was statistically highly significant between the two groups.

Our result is strengthened by the studies by Khan [5]. In their study, HR in the nalbuphine group showed a maximum positive response (25%) compared with the fentanyl group (6.4%) after tracheal intubation. Rajlaxmi *et al.* [6] observed that just after intubation, the rise of mean HR was slower in the fentanyl group as compared with the nalbuphine group. Bhot *et al.* [7] also showed that the rise in HR in the

fentanyl group is significantly less as compared with the nalbuphine group, after intubation.

Contrary to the present study, Hari Prasad *et al*. [8] showed no significant increase in HR after intubation in both nalbuphine and fentanyl groups. Lefèvre *et al*. [9] also showed that no significant difference in HR was observed between both nalbuphine and fentanyl groups.

Our study also demonstrated that fentanyl controls HR better than nalbuphine. This effect might be due to the stimulation of the vagal center by fentanyl while nalbuphine itself causes some tachycardia.

Baseline parameter for MAP was comparable. *P* value was more than 0.05 between two groups; in group A mean of the MAP was 100.56±15.80 mmHg and in group B was 96.26±12.60 mmHg.

After endotracheal intubation, mean MAP in group A was increased to 109.70±12.48 mmHg from baseline 100.56±15.80 mmHg (9.08%) and in group B it was increased from 96.26±12.60 to 101.8±15.21 mmHg (5.75%). This was statistically significant ($P<0.05$). The same observation was also noticed just after coming off CPB. MAP in group A was 85.73±7.10 and 79.87±7.95 mmHg in group B; the difference in MAP among two groups was statistically significant ($P<0.05$).

Our results are similar to the results observed by Khan [5], who found that the mean MAP increased by 1% in the fentanyl group and 12% in the nalbuphine group. Shoiab Bashir Khanday *et al*. [6] also found that the mean MAP increased more in the nalbuphine group compared with the fentanyl just after intubation. It is also supported by Channaiah *et al*. [10], who showed a higher attenuation of diastolic blood pressure response to intubation in the fentanyl group compared with the nalbuphine group. Weiss *et al*. [11] also studied fentanyl and nalbuphine for CABG in their study; during and after intubation all patients were given nalbuphine and one patient was given fentanyl, who required nitroglycerine to control MAP. In patients receiving nalbuphine, antihypertensive drug (NTG) requirements were larger than the fentanyl group and were not influenced by the history of preoperative hypertension. This increase in MAP may be explained due to the slight but significant potential of opioid agonist–antagonist nalbuphine to provoke circulatory stimulation.

Shoiab Bashir Khanday *et al*. [6] concluded in their study that fentanyl is a pure μ agonist and is known to cause a decrease in arterial blood pressure, HR, systemic vascular resistance, and blood catecholamine level while depressing the myocardial contractility and decreasing the cardiac workload, which may be the cause of the steady fall in hemodynamic parameters in the fentanyl group just after intubation. In contrast to our study, Rajlaxmi *et al*. [6] showed that control of MAP after intubation was better in the nalbuphine group than in the fentanyl group.

Our study also demonstrated that fentanyl controls the MAP better than nalbuphine.

In our study, the time for first rescue analgesic was significantly longer in the nalbuphine group (288.00 ±42.13 min) than the fentanyl group (207.00 ±50.04 min), which was statistically significant ($P<0.05$). This was consistent with the results obtained by Hari Prasad *et al*. [8], who conducted a study to compare analgesic potential and hemodynamic response of nalbuphine and fentanyl and observed that nalbuphine provides excellent postoperative analgesia. Our results were also similar with the study of Bhot *et al*. [7] who found that nalbuphine provides longer duration of analgesia compared with fentanyl or pentazocine. Sharma *et al*. [12] also showed that postoperative pain was better managed with nalbuphine as compared with fentanyl.In a study by Khan [5], the mean time to the first analgesic dose after extubation was 37±11 and 62±35 min in fentanyl and nalbuphine groups, respectively. This difference was statistically significant. This result supports our study. The mean time required for first rescue analgesic drug when VAS more than 3 after extubation in our study was 288.00± 42.13 in group A and 207±50.04 in group B. The possible cause for the large difference in our values was the longer duration of our surgeries (176 ±20.06 min in group A, 175.50±20.14 min in group B). Due to this prolonged duration of surgery, consumption of the study drug was more, which can lead to cumulative effect and saturation of depots.

We were fortunate enough to not get any side effects in the intraoperative or postoperative period.

In contrast to this study, Canning *et al*. [13] showed that fentanyl had a longer duration of pain relief postoperatively than did nalbuphine. Thus, we concluded that nalbuphine provides better analgesic potential than fentanyl.

Conclusion

It is concluded from our study that fentanyl provides better hemodynamic stability in response to laryngoscopy and endotracheal intubation and throughout the intraoperative period as compared with nalbuphine. Nalbuphine provides better analgesia compared with fentanyl in the postoperative period.

Group A (nalbuphine) and group B (fentanyl) were comparable in terms of demographic variables such age, sex, weight, ASA grading, and duration of surgery.

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Conflicts of interest
There are no conflicts of interest.

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