



Original Research Article

Comparison of fentanyl and nalbuphine in obtunding stressor response to laryngoscopy and endotracheal intubation

Milon V Mitragotri^{1,*}, Safiya I Sheikh¹, Roopa Sachinananda¹, Vikas Joshi¹

¹Dept. of Anaesthesia, Karnataka Institute of Medical Sciences, Hubballi, Karnataka, India



ARTICLE INFO

Article history:

Received 26-08-2020

Accepted 19-11-2020

Available online 01-06-2021

Keywords:

Nalbuphine

Fentanyl

Intubation

ABSTRACT

Objective: Fentanyl has evinced its property of being a potent opioid and benumbing stress response to laryngoscopy and intubation (L&I). However respiratory depression and chest wall rigidity limits its utility at high doses. Nalbuphine, reported to have a ceiling effect for respiratory depression, can serve as an alternative. We studied and compared the efficacy of fentanyl and nalbuphine in preventing the rise in heart rate and blood pressure after L&I.

Materials and Methods: A randomized double blind study was conducted in 60 subjects divided in two groups (Group F n=30 and Group N n=30) was done. Group F received $2\mu\text{g kg}^{-1}$ fentanyl intravenously while group N received nalbuphine 0.2mg kg^{-1} intravenously. Hemodynamic variables including heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) were measured at baseline and at intervals of five minutes of administering test drug, each minute up to five minutes after intubation, 10 minutes and 30 minutes after intubation. Complications, if any, were recorded after surgery. Change in HR, SBP, DBP and MAP between the two groups was compared using independent t-test.

Results: The two drugs were equally effective in preventing HR rise at all-time points except after 30 minutes where fentanyl performed better. The change in SBP, DBP and MAP from baseline in both the groups was comparable.

Conclusions: Nalbuphine can serve as an alternative to fentanyl in obtunding stress response when given five minutes before intubation.

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1. Introduction

Hemodynamic variability and laryngoscopy and endotracheal intubation (L&I) go hand-in-hand. The increase in HR and BP though transitory, variable, unpredictable and of no consequence in healthy individuals can be hazardous in those patients with hypertension, myocardial insufficiency and other co-morbid illness.¹ This stressor response that occurs is consequent to the variable release of 'fight and flight' hormones like adrenaline, noradrenaline and dopamine into the circulation.

Several measures and pharmacological methods have been used to decrease this hemodynamic stress

response associated with L&I. With opioids being at the forefront, nitroglycerin, sodium nitroprusside, calcium channel blockers, β blockers have been tried to treat the hemodynamic fluctuations with inconsistent responses.²

Fentanyl has proved its mettle and has become the ideal choice to prevent increase HR and BP during L&I. However, it comes at the cost of respiratory depression and chest tightness at over dosage.³ Fentanyl being a narcotic is not freely available. Hence, a search of newer potent hemodynamic stabiliser is a necessity. Kay et al. state that it would be advantageous to find a narcotic with a profile of clinical actions which include little or no respiratory depression, good analgesia and the ability to prevent the cardiovascular responses to L&I.⁴

* Corresponding author.

E-mail address: milon.mitragotri4@gmail.com (M. V. Mitragotri).

We hypothesize that nalbuphine is a non-inferior alternative to fentanyl in avoiding the rise in HR and BP following L&T. Nalbuphine is a non-narcotic analgesic, agonist at kappa receptors and weak agonist-antagonist at μ opioid receptor.² It is a cardiovascular stable drug with no respiratory depression, less nausea and vomiting and even safer when given in over dosage.

The primary objective of our study is to compare the change in mean HR from baseline after L&I in both the groups with secondary objectives being to compare the change in systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP).

2. Materials and Methods

Ethical committee approval was taken from the institutional ethical committee with the approval number being KIMS/PGS/ETHICS/479/2017-18 dated 25-01-2018 and CTRI registered with registration number CTRI/2018/04/013429.

Sixty adult patients aged between 18 to 60 years of physical status American society Anaesthesiologists grade(ASA) I & II, of either sex scheduled to undergo elective surgeries under general anaesthesia with endotracheal intubation were enrolled for the study over a period of one year. Pregnant and lactating women, those with suspected difficult intubation, allergy to opioids, cardiovascular disease; hepatic or renal disease and those on antihypertensive drugs were excluded from the study. After taking written informed consent from the participants, they were randomly allocated into the two groups by a computer generated number.⁵

Group N (n=30) patients received $0.2\mu\text{g kg}^{-1}$ nalbuphine intravenous (i.v.) diluted to 5ml with normal saline.

Group F (n=30) patients received $2\mu\text{g kg}^{-1}$ fentanyl i.v. diluted to 5ml with normal saline.

Allocation concealment was done by sequentially numbered, sealed, opaque envelope technique. The study solutions were prepared by an anaesthesiologist not involved in the study. Strict adherence to dose kg^{-1} was followed while preparing the study solutions. Thus the patient, the anaesthesiologist performing laryngoscopy and endotracheal intubation and the anaesthesiologist recording the outcome data were blinded to the study solutions being administered.

A pre-anaesthetic evaluation of the patients was performed by an anaesthesiologist a day before the surgery and patients were kept nil per orally for six hours prior to surgery. In the operation theatre, a peripheral i.v. access was secured using 18 gauge canula. Standard monitors like non-invasive blood pressure, electrocardiograph, pulse oximetry and end tidal carbon dioxide were attached and baseline HR, SBP, DBP and MAP (R1) were recorded. All the patients were premedicated with glycopyrrolate $4\mu\text{g kg}^{-1}$ and midazolam 1mg i.v. 10 minute prior to induction of

anaesthesia. Group F received fentanyl and group N received nalbuphine five minutes before intubation. Preoxygenation was then done with 100% oxygen. HR, SBP, DBP and MAP (R2) were recorded five minutes after study drug was administered and just before intubation. Anaesthesia was induced with propofol 2 mg kg^{-1} i.v. and succinylcholine 1.5 mg kg^{-1} i.v. and orotracheal intubation was performed within 30 seconds by an experienced anaesthesiologist using Macintosh laryngoscope and appropriate size endotracheal tube (ETT). Time from insertion of laryngoscopic blade to inflation of ETT cuff was recorded. (T_i) Vital parameters were subsequently measured just after intubation(R3), then after every 1 minute upto five minutes (R4-R8) and after 10, 30 minutes of intubation.(R9,R10) Anaesthesia was maintained with oxygen, nitrous oxide and sevoflurane(1-1.5%) and neuromuscular blockade was achieved using vecuronium i.v. Surgeons were requested to go ahead with the surgical incision/repositioning, if any, only after 10 minutes of intubation. After the completion of surgery, neuromuscular block was reversed using neostigmine 0.05mg kg^{-1} i.v. and inj. glycopyrrolate 0.008mg kg^{-1} i.v. followed by extubation. Patients were monitored in the post-operative care unit for up to six hours.

Any untoward intraoperative events like bradycardia and hypotension were noted and treated appropriately. Postoperative complications like respiratory depression, nausea and vomiting, pruritus were recorded.

2.1. Statistical analysis

A sample of 30 subjects was selected based on previous studies to detect a minimum difference in HR of more than 10 beats/minute and standard deviation of difference of 12 with a power of 0.8 that would permit an alpha error of 0.05. (2 and 6) Data was analyzed using SPSS software (version no-17). Comparison of demographic variables between the two groups were done using Chi square test. Quantitative variables such as age of the patient, weight of the patient, HR, SBP, DBP, MAP, time taken for laryngoscopy and dosage of drugs were presented as mean and standard deviation or median with range based on distribution of the data. Gender, ASA grading and occurrence of complications were presented as percentages.

Significance testing of quantitative variables (time taken for laryngoscopy and dosage of drugs) between the two groups was done using independent t-test. Change in HR, SBP, DBP and MAP between the two groups was compared using independent t-test.

3. Results

The flow of participants enrolled in this study is shown in Figure 1. Out of the sixty patients enrolled in the study, one patient was excluded from group F as the duration of intubation was >30s and number of attempts at intubation

was more than one. The demographic data such as ASA grading and age were comparable in both the groups while the data such as gender and weight were skewed. (Table 1) The duration of intubation was 21.8 ± 6.5 in group F and 23.9 ± 5.0 in group N which was not statistically significant. ($p=0.169$)

The baseline hemodynamic variables were comparable in both the groups. The maximum increase in HR was noted just after intubation i.e. R3 in both the groups with patients in nalbuphine group having a rise 20.6 and that in group F being 14.6. Blood pressure in both the groups was labile and had a precipitous fall with a peak fall in MAP at 10 minutes in Group N and at 5 minutes in group F. (Tables 2 and 3) The maximum percentage decrease in SBP, MAP, DBP i.e. 15.9, 17.4, 18.5 was noted at 10 minutes following nalbuphine administration and the maximum percentage fall in SBP, MAP, DBP i.e. 21.1, 22.8, 20.4 were noted at 4-5 minutes following fentanyl.

The change in the HR when compared in both the groups at different time points was not significant except at R10 where group F outperformed group N. (Table 4) However the change in SBP, DBP and MAP between the two groups at different time points was not significant. (Table 5 and Figures 2, 3 and 4) There was no rise in BP at any time points in both the groups.

Two patients had postoperative hypertension ($BP > 140/90$) in group F while one patient had the same in group N. None of the patients in group N had respiratory depression (respiratory rate $< 8-10$ breaths/minute or oxygen saturation $SpO_2 < 94\%$ on room air) while two patients had respiratory depression in group F. One patient each in both the groups had hypotension 30 minutes following intubation. ($< 90/60$ mmHg) None of the patients had arrhythmias, bradycardia, nausea, vomiting, respiratory depression, sedation, muscular rigidity and pruritus.

4. Discussion

Fentanyl with its favourable pharmacodynamic profile including profound cardiovascular stability, rapid onset and recovery has surpassed all previous measures at blunting hemodynamic stress response following L&I. Since fentanyl is highly lipid-soluble, it rapidly crosses the blood-brain barrier, and concentrations in the central nervous system usually reflect those in plasma (with a time delay of ≈ 5 min). In small doses ($1-2 \mu\text{g kg}^{-1}$), its duration of action is short, since plasma and central nervous system concentrations fall below an effective level during the distribution phase.³ The complete attenuation of stress response is possible with $5 \mu\text{g kg}^{-1}$ of fentanyl.⁶ Though fentanyl is fervent with respiratory depression and pruritus, it doesn't deter anaesthesiologists worldwide from using it as a first choice at combating stressor response following L&I, acute surgical insult, hemodynamic fluctuations etc.

Nalbuphine, on the other hand, has the advantage of a respiratory depressant ceiling-effect compared to fentanyl.⁷ Nalbuphine being a non-narcotic drug recently made available, over the counter, can serve an alternate to fentanyl in scenarios where fentanyl is not available or can't be used. Nalbuphine, unlike other agonist-antagonist opioids does not increase systemic blood pressure, pulmonary artery blood pressure, heart rate or atrial filling pressure.⁸ Hence we conducted a non-inferiority trial to assess the efficacy of nalbuphine in comparison to fentanyl.

Three factors are of paramount importance while interpreting the results of our study i.e. dosage of the drugs administered, the study drug to induction/intubation time and the duration of intubation. The selection of doses were as per studies done by Neha et al.⁸ and the rationale that nalbuphine 0.2 mg kg^{-1} is almost equipotent to fentanyl $2 \mu\text{g kg}^{-1}$.⁹ Peak effect of fentanyl and nalbuphine being five minutes, hence we chose to induce patients five minutes after administration of study drug.³ Also an adequate depth of anesthesia and quick, smooth laryngoscopy is the mainstay for blunting the stressor response.¹⁰ Hence we excluded those patients where duration of intubation was more than 30 s and/or the number of attempts at intubation was more than one.

Though demographics such as gender and weight were skewed in one group even after randomization, strict adherence to dose per kg and duration of L&I in both the groups was maintained. Group F had more number of female patients compared to male and hence we presume mean weight in this group was significantly less. Block allocation of patients based on weight could have avoided this disparity.

The mean rise in HR in group F from baseline was 13.2 ± 16.3 whereas the mean rise in HR in group N from baseline was 17.8 ± 16.1 just after L&I, with the difference being statistically insignificant. ($p=0.281$) Previous studies done also found that nalbuphine 0.2 mg/kg prevented marked rise in HR and MAP following L&I.^{11,12} However, Van den Berg et al noted nalbuphine only prevents the inotropic effect of airway instrumentation.¹³ The rise in HR in both the groups after L&I were all comparable except at 30 minutes where group F (-6 ± 16.7) outperformed group N. (6.1 ± 15.9) The variability at 30 minutes in both the groups could be attributed to different factors like better cardiostability by fentanyl, surgical insult ensuing rise of HR in group N or use of sevoflurane. Khan et al. noted in their study comparing the two drugs for total intravenous anaesthesia that heart rate response after tracheal intubation was significantly higher in the nalbuphine group (25%).⁹

In our study, the mean rise in SBP, DBP and MAP immediately following intubation and at different time points following L&I were not statistically significant in both the groups suggesting nalbuphine was effective at obtunding the stressor response like fentanyl. Kay

Table 1: Demographic variables

Variable	Nalbuphine	Fentanyl	Significance
Male: Female	14:16	11:18	0.497
American society of anaesthesiologists (ASA) grade 1:2:3	20:8:2	23:5:1	0.544
Age	37.7±12.7	34.5±15.5	0.392
Weight	56.8±8.9	48.9±9.8	0.002*

*p value<0.05 significant

Table 2: Group comparison for heart rate and their percentage variation from baseline at different intervals of time points (beats/min)

Time points	Nalbuphine		Fentanyl	
	Mean ± SD	% change	Mean ± SD	% change
R1	86.4 ± 16.4	0	90.4 ± 18.4	0
R2	89.3 ± 20.3	+3.3	92.6 ± 17.6	+2.43
R3	104.2 ± 17.3	+20.6	103.6 ± 17.5	+14.60
R4	102.6 ± 18.2	+18.75	100.9 ± 15.4	+11.61
R5	101.1 ± 16.1	+17.01	101.3 ± 16.5	+12.05
R6	100.6 ± 14.7	+16.43	100 ± 16.3	+10.61
R7	99.5 ± 14.7	+15.16	101 ± 16.4	+10.49
R8	100.2 ± 16.5	+15.97	99.5 ± 16.8	+10.06
R9	94.9 ± 14.8	+9.83	93.6 ± 13.6	+3.53
R10	92.5 ± 15.6	+7.06	86.5 ± 16.5	-4.31

Table 3: Group comparison for MAP and their percentage variation from baseline at different time points (mmHg)

Time points	Nalbuphine		Fentanyl	
	Mean SD	% Change	Mean SD	% change
R1	98.5 ± 13.6	0	98.9 ± 11.2	0
R2	88.6 ± 13.6	-10.05	89.7 ± 18	-9.30
R3	96.1 ± 18.6	-2.43	91.8 ± 17.9	-7.17
R4	89.2 ± 16.6	-9.44	85.7 ± 10.8	-13.34
R5	86.9 ± 16.6	-11.77	84.6 ± 13.8	-14.45
R6	83 ± 14.4	-15.73	83.3 ± 16	-15.77
R7	82.2 ± 14	-16.54	78.1 ± 12.5	-21.03
R8	83.4 ± 14.7	-15.32	76.3 ± 13.1	-22.85
R9	81.3 ± 14.1	-17.46	79 ± 12.4	-20.12
R10	88.7 ± 13.6	-9.94	90.5 ± 18.4	-8.49

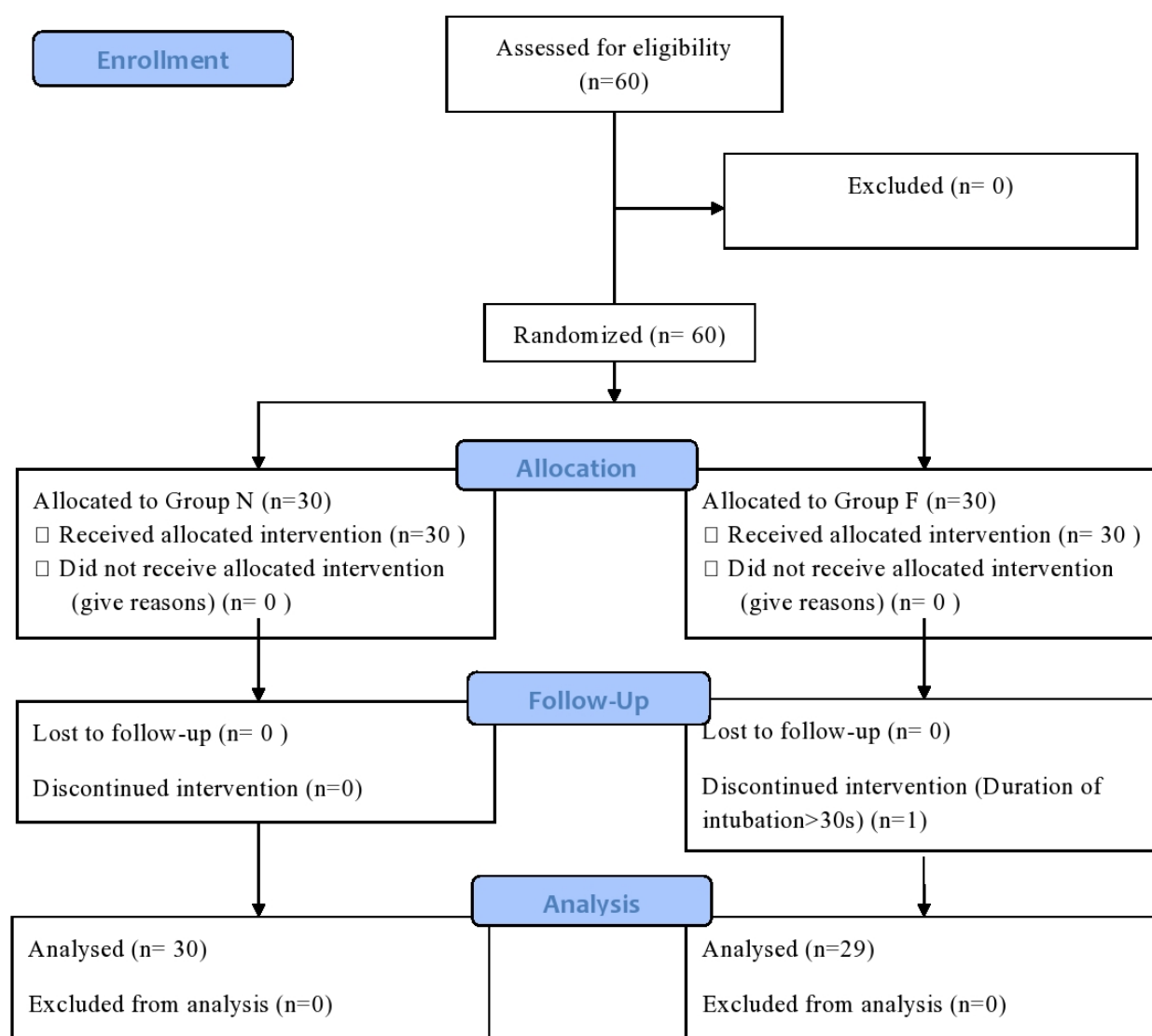
Table 4: Comparison of heart rate variation between two groups at different time points (beats/min)

	Nalbuphine	Fentanyl	P Value
	Mean ± SD	Mean ± SD	
R2-R1	2.9 ± 12.8	2.2 ± 12.2	0.823
R3-R1	17.8 ± 16.1	13.2 ± 16.3	0.281
R4-R1	16.2 ± 17.9	10.4 ± 16.3	0.202
R5-R1	14.7 ± 15.6	9.5 ± 16.4	0.223
R6-R1	14.2 ± 13.7	8.2 ± 16	0.138
R7-R1	13.1 ± 14.8	9.1 ± 15.6	0.337
R8-R1	13.8 ± 17.4	7.7 ± 14.6	0.157
R9-R1	8.5 ± 15.4	1.7 ± 15.1	0.099
R10-R1	6.1 ± 15.9	-6 ± 16.7	0.008*

*p<0.05- significant

Table 5: Comparison of MAP variation between two groups at different time points (mmHg)

	Nalbuphine Mean $\pm$ SD	Fentanyl Mean $\pm$ SD	P Value
R2-R1	-9.9 $\pm$ 15.4	-9.1 $\pm$ 16	0.847
R3-R1	-2.4 $\pm$ 20.7	-6.5 $\pm$ 17.3	0.417
R4-R1	-9.3 $\pm$ 20.9	-12.6 $\pm$ 15.4	0.489
R5-R1	-11.6 $\pm$ 20.4	-13.7 $\pm$ 18.8	0.677
R6-R1	-15.5 $\pm$ 19.1	-15 $\pm$ 17.3	0.906
R7-R1	-16.3 $\pm$ 19.3	-20.2 $\pm$ 16.7	0.423
R8-R1	-15.1 $\pm$ 20.4	-22 $\pm$ 16.4	0.161
R9-R1	-17.2 $\pm$ 19.6	-19.3 $\pm$ 15.7	0.657
R10-R1	-9.8 $\pm$ 15.3	-7 $\pm$ 21.5	0.583

**Fig. 1:** Consort flow diagram

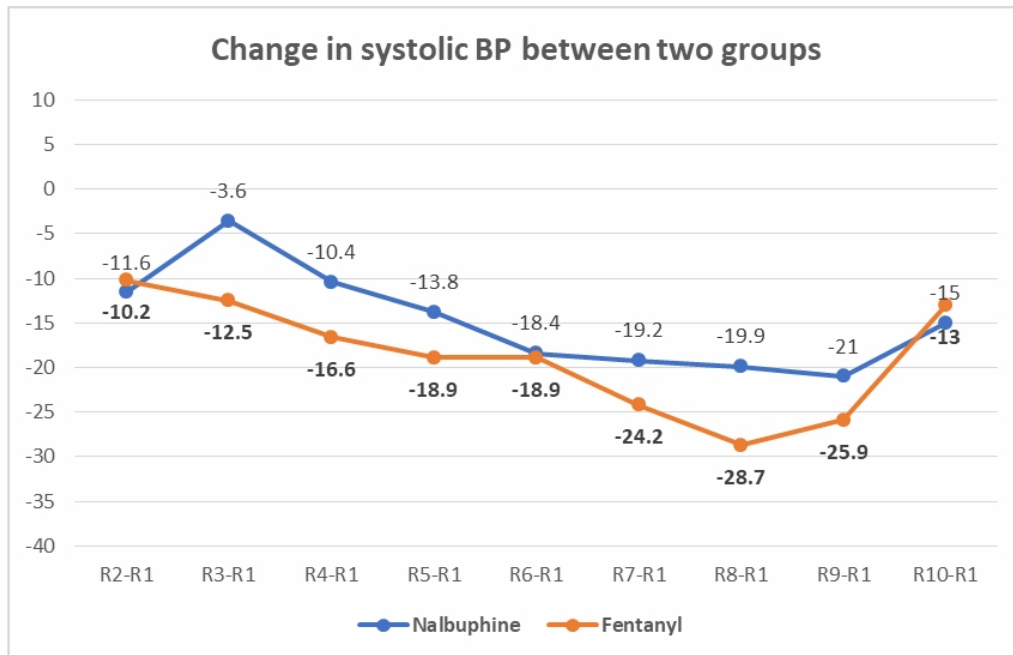


Fig. 2: Comparison of systolic BP between two groups at different time point

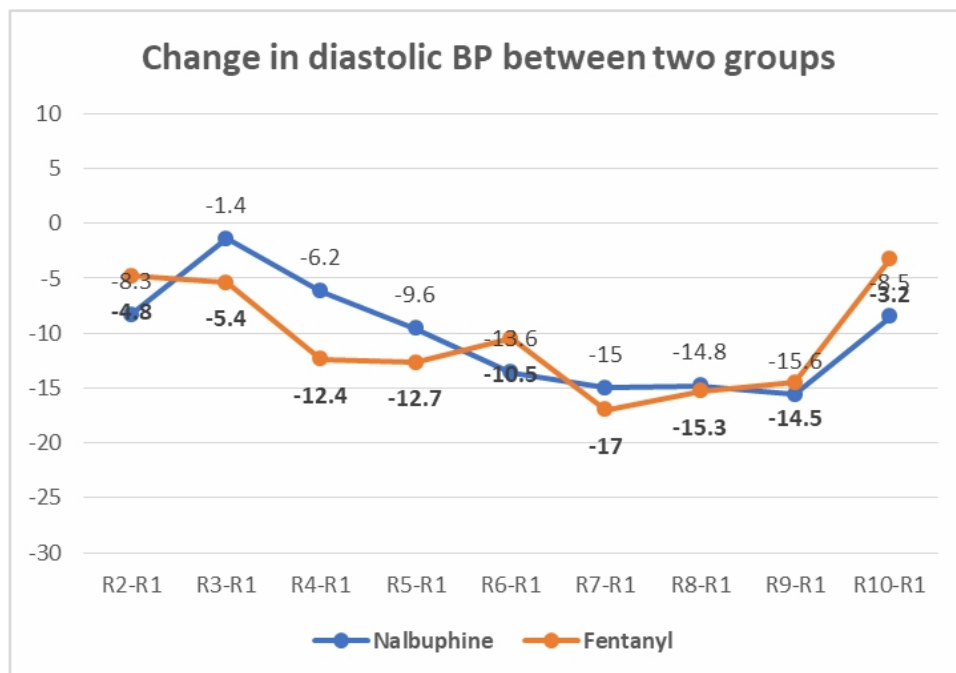


Fig. 3: Comparison of diastolic BP between two groups at different time point

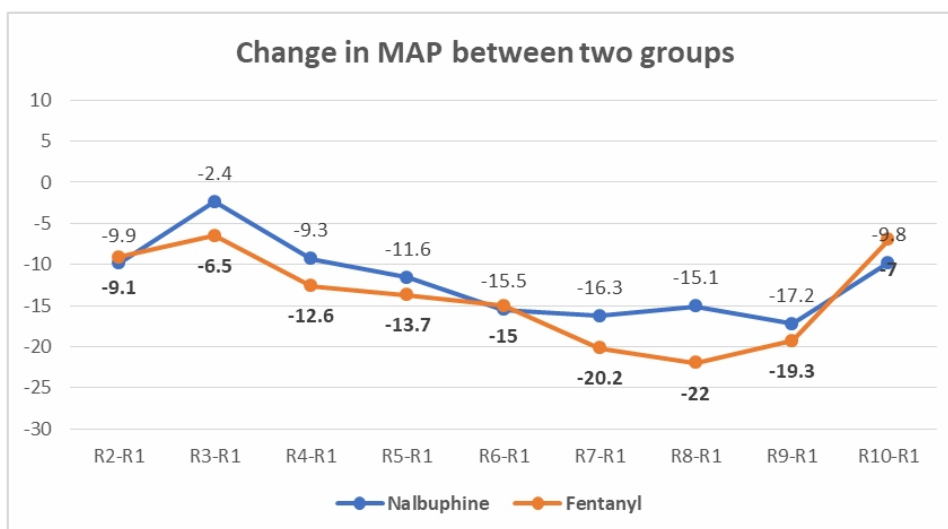


Fig. 4: Comparison of MAP between two groups at different time points

et al.⁴ suggest nalbuphine to be partially effective in decreasing the stress response; however, the duration between administration of nalbuphine and L&I was only two minutes, possibly explaining the inefficacy in their study.

A similar study done by Neha et al. noted that change in HR in both groups was insignificant, but the increase in SBP and DBP following L&I was significantly more with nalbuphine compared to fentanyl.⁸ Contrary to their study, the fall in MAP in our study following nalbuphine was lesser than that of fentanyl. The difference in the results of our study could be attributed to the difference in methodology, including the drug to induction time, use of thiopentone and excluding patients with intubation time >15s. Propofol blocks the catecholamine and haemodynamic responses to laryngeal manipulation compared to thiopentone.¹⁴ This may be one of our reasons for the contrasting results of our study as we used the commonly used propofol.

After an intravenous bolus dose of fentanyl, plasma concentrations decline rapidly (distribution half-life ≈ 13 min).³ We chose succinylcholine as the choice of muscle relaxant to avoid a delay in intubation following the administration of study drug. As it is evident by previous studies that the peak effect of the drug is after five minutes,¹⁰ it would be logical to intubate the patient after five minutes and not before 10 minutes following administration of study drug.

The changes in arterial pressure during L&I correlate with similar changes in the levels of circulating catecholamines.^{15–17} Adrenaline, noradrenaline, prolactin etc. levels can be measured prospectively following L&I and compared with baseline. Literature search for such biomarker-based studies with nalbuphine was futile. Hence further studies could be done to assess the efficacy of

nalbuphine versus fentanyl in a more objective way and reemphasize the results. However, Parida et al. state that it would be unethical to consider such studies as the catecholamine levels need to be assessed through a central venous access.¹⁸

Also, studies with different doses of nalbuphine i.e. 0.1 mg kg⁻¹, 0.2 mg kg⁻¹ and 0.3 mg kg⁻¹ could be done to pinpoint the ideal dosage to circumvent stressor response similar to research done by Kallapur et al.¹⁹ and Nath et al.²⁰ Kallapur et al.¹⁹ in their study comparing 0.1 mg kg⁻¹ and 0.2 mg kg⁻¹ nalbuphine noted better efficacy with 0.2 mg kg⁻¹ nalbuphine in preventing stress response. In contrast, Nath et al.²⁰ noted that nalbuphine in a dose of 0.1 mg/kg produced stable hemodynamics during the stressful period of laryngoscopy and intubation similar to nalbuphine in a dose of 0.2 mg/kg. Hence more clarity is needed to understand the adequate dose and the ideal dose of nalbuphine.

A recent equivalence trial by Khanday et al.²¹ in 2019, when comparing the efficacy of nalbuphine and fentanyl for stressor response, noted that fentanyl has a better control of SBP, DBP and MAP, but control of HR was equal with both groups. Our trial, being a non-inferiority trial with different methodology, gave us contrasting results. Drug to intubation versus drug to induction interval could be a decisive reason here. Though the optimal time for fentanyl is 5 min prior to intubation, it isn't optimal for nalbuphine.²² Further research to find optimal time of endotracheal intubation following nalbuphine is needed.

In conclusion, nalbuphine is an effective alternative to fentanyl in preventing hemodynamic stress response when administered in an adequate dosage and primed at an adequate interval of five minutes before L&I.

5. Source of Funding

None.

6. Conflict of Interest

The authors declare that there is no conflict of interest.

Acknowledgements

We would like to acknowledge the help of Dr. Nishant Deshpande, Dr. Priti Sherikar and Dr Minna Osheen Arackal for the logistic help during the study.

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Author biography

Milon V Mitrugotri, Assistant Professor

Safiya I Sheikh, Professor & Head

Roopa Sachinananda, Associate Professor

Vikas Joshi, Assistant Professor

Cite this article: Mitrugotri MV, Sheikh SI, Sachinananda R, Joshi V. Comparison of fentanyl and nalbuphine in obtunding stressor response to laryngoscopy and endotracheal intubation. *Indian J Clin Anaesth* 2021;8(2):294-301.