A Study to Compare Efficacy of Fentanyl Versus Nalbuphine in Attenuation of Hemodynamic Response to Laryngoscopy and Endotracheal Intubation in General Anaesthesia

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ABSTRACT

Introduction: Laryngoscopy and endotracheal intubation causes major alterations in haemodynamics such as hypertension and tachycardia, all of which have been classified as a pressor response. These responses are broadly of no serious sequel in normal blood pressure patients, but may be extravagant and henceforth more unsafe in patients with coronary artery disease, hypertension, myocardial infarction, cerebrovascular disease, thyrotoxicosis, and various other conditions as they result in heightened cardiac workload. A comparative evaluation of Fentanyl and nalbuphine to find out which drug is better in attenuating pressor response to laryngoscopy and endotracheal intubation.

Material and methods: A randomized double blinded clinical study conducted on 80 patients undergoing elective surgeries of age 20 to 50 years of ASA class I and II and divided in two groups (each 40 patients). Fentanyl (2 µg/kg) was given in group A and nalbuphine (0.2 mg/kg) in Group B, both were diluted in 10ml normal saline, which were given 5 minutes prior to intubation. Vitals (Heart rate, systolic blood pressure, mean arterial pressure, diastolic blood pressure, oxygen saturation) were monitored and documented (baseline, after induction, after intubation and 1,3,5,10 minutes after intubation.

Result: Age, gender, weight was comparable between both groups. In both groups HR was increased and nonsignificant throughout study. Difference in SBP, DBP, MAP was significant from after induction till 10 minutes, maximum increase in group A was 125.23 ± 9.12, 73.8 ± 8.86, 94.61 ± 8.85, maximum increase in group B was 136.58 ± 10.55, 80.23 ± 7.88, 99.01± 8.01. Oxygen saturation was nonsignificant in both groups.

Conclusion: After evaluating results fentanyl was found to be better in attenuating pressor response when compared with nalbuphine during laryngoscopy and endotracheal intubation.

Keywords: Fentanyl Versus, Nalbuphine in Attenuation, Hemodynamic Response, Laryngoscopy, Endotracheal Intubation, General Anaesthesia

INTRODUCTION

Laryngoscopy and endotracheal intubation (ET) is always associated with significant cardiovascular alterations such as hypertension (HTN) and tachycardia, all of which have been classified as a pressor response, which may be due to sympathetic reflex aggravated by mechanical stimulation of larynx and hence increase in plasma catecholamine concentration.[1] These responses are more unsafe in patients with coronary artery disease, HTN, myocardial infarction, cerebrovascular disease, thyrotoxicosis, and various other conditions as they result in heightened cardiac workload.[2]

In 5 seconds, adverse effects start arising due to laryngoscopy and ET intubation, at 1-2 minutes reaches at its peak. Average increase in HR has been reported to be 23 beats and increase in systolic blood pressure by 53 to 54 mmHg and decrease in the left ventricular ejection fraction by approximately 20%.[3,4]

Recent studies are using alpha 2 receptor agonist (clonidine and dexmedetomidine which are alpha 2 agonists); β-adrenergic blocking agents (esmolol); α- and β-adrenergic blockers (labetalol which is both alpha and beta antagonist); and local and regional anesthetic techniques are also used by many and found useful in attenuating haemodynamic response.[5-12]

Fentanyl from class phenylpiperidine-derivative is a synthetic µ-receptor agonist and it is more potent than morphine and has many positivity over morphine like a faster onset and shorter duration of action due to rapid redistribution.

When using Fentanyl at analgesic dose (I.V) provides safety margin, very minimum chances of respiratory depression and rapid termination of effect.[13]

Nalbuphine is an agonist-antagonist opioid that is related chemically to oxymorphone and naloxone which binds to mu, kappa, and delta receptors. Nalbuphine, being opioid has some partial reverse or blocking effect on opioid induced respiratory depression commonly done by µ-agonist analgesic.

In this study, we will compare the efficacy of two opioids, fentanyl and nalbuphine for attenuating pressor response during laryngoscopy and ET intubation. This study aims to assure the reliability and validity of the results when we will apply on different individuals and in a different setup and to strengthen the previous research by finding and correcting the limitations so that the results would be generalized.

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MATERIAL AND METHODS

After obtaining approval from institutional ethical committee, a double blinded randomized controlled study was carried out in Rohilkhand medical college and hospital, Bareilly. Informed written consent was taken from all patients prior to the procedure and patients of ASA I and II posted for elective surgeries under general anesthesia (GA) under age group 20-50 years were randomly divided into 2 groups using computer generated randomization technique.

Exclusion Criteria

- Patients not given consent
- Known allergy to the trial drugs.
- ASA III or more.
- Emergency Surgeries.
- Patients with Mallampati grading 3 and 4.
- Patients with bronchospastic disease.

Standard preanesthetic evaluation was done one day before the day of surgery by an anesthetist. Tab. alprazolam 0.25mg and tab. ranitidine 150mg was given as premedication on night prior to surgery. Patients were shifted to operating room after securing wide bore (18G) cannula and recording of baseline vitals (noninvasive blood pressure, HR and SpO2). Fentanyl (2 µg/kg) was given in group A and nalbuphine (0.2 mg/kg) in Group B, both were diluted in 10ml normal saline, which were given 5 minutes prior to intubation.

Study drug preparation will be done by anesthetist who was blinded to study protocol.

Patients were premedicated with glycopyrrolate 0.2mg intravenously 30 minutes prior to surgery, followed by study drug fentanyl 2µg/kg or nalbuphine, 0.2mg/kg intravenously, 5 minutes before induction of general anesthesia in double blind manner. After pre-oxygenation, anesthesia was induced with propofol 2.5 mg/kg, and muscle relaxant (vecuronium 0.12mg/kg) was given for smooth direct laryngoscopy and intubation. Intubation was accomplished by Macintosh curve blade laryngoscope (blade no. 3) and proper sized cuffed polyvinylchloride (PVC) ET tube (7.0 for females and 8.0 for males). Laryngoscopy and ET intubation were performed 3 mins after administration of vecuronium. Anaesthesia was maintained with oxygen plus nitrous oxide and isoflurane.

Heart rate (HR), systolic blood pressure (SBP), mean arterial pressure (MAP), diastolic blood pressure (DBP), oxygen saturation (SpO2) was measured at 1,3,5 and 10 mins after ET intubation by third person. Bolus doses of vecuronium 0.01mg/kg were used to maintain neuromuscular blockade. All patients received injection paracetamol 15mg/kg to provide intraoperative analgesia. I.V. Inj. ondansetron 0.1mg/kg was given 20 min prior completion of surgery to avoid post-operative nausea and vomiting. When surgery was about to be finished, isoflurane was halted, and neuromuscular blockade was reversed by injection neostigmine 0.05 mg/kg and injection glycopyrrolate 0.01 mg/kg intravenously. Patients then extubated and were shifted to post anesthetic care unit. HR, SBP, DBP, SpO2, MAP was recorded by an anesthetist who was blinded to study during preinduction (baseline), induction, and 1,3,5, and 10 min after intubation.

Statistics

Statistical data analysis was done using SPSS version 22.0 using independent t- test to determine mean significant difference between the two variables and $p<0.05$ is considered statistically significant. Continuous variables were expressed as mean ± standard deviation.

RESULTS

All three groups were comparable with respect to age, sex and weight. Baseline HR, SBP, DBP and MAP were comparable between all 2 groups. Increase in SBP, DBP and MAP during intubation was more in group B compare to group A, which was clinically and statistically very highly significant ($P<0.05$). Statically significant difference in SBP, DBP and MAP between 2 groups last up to 10 minutes.

Baseline mean HR (seen in table and fig 1) in both groups was comparable ($P>0.05$) to baseline. In group A and B baseline HR was 85.2 ± 9.73 and 86.85 ± 10.38. Both groups showed rise in HR after intubation shown in fig 4 and table 4. Maximum increase in HR in Group A and B was 97.5 ± 9.66 and 98.81 ± 9.38, which was just after intubation. In both groups HR come to baseline after 10 minutes of intubation. Throughout study HR was clinically insignificant. (p value >0.05)

Baseline SBP in Group A and B was 120.35 ± 8.97 and 122.5 ± 10.56. Maximum increase in SBP (seen in fig and table 2) in group A and B was 125.23 ± 9.12 and 136.58 ± 10.55.

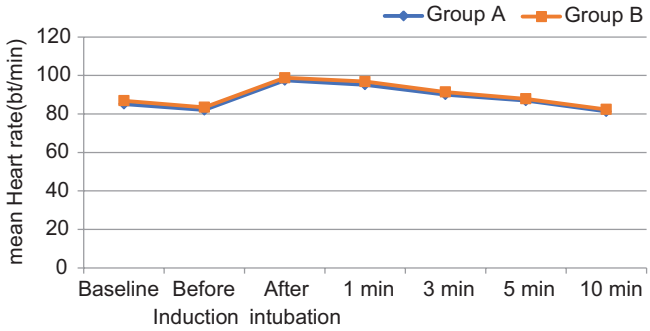

Figure-1: Comparison of mean Heart Rate at different time interval between Group A and group B

	Heart rate (bpm)		
	Group A	Group B	
Time interval	**Mean ± SD**	**Mean ± SD**	**P-Value**
Baseline	85.2±9.73	86.85±10.38	0.465#
After Induction	82.03±9.43	83.43±10.32	0.528#
After intubation	97.5±9.66	98.81±9.38	0.540#
1 min	95.2±9.73	96.82±10.36	0.473#
3 min	90.08±9.81	91.38±12.27	0.602#
5 min	86.95±9.84	87.85±12.38	0.719#
10 min	81.33±10.01	82.33±9.14	0.642#

Table-1: Comparison of Heart rate at different time interval in between Group A and Group B.

	SBP (mmHg)		
	Group A	Group B	
Time interval	**Mean ± SD**	**Mean ± SD**	**P-Value**
Baseline	120.35±8.97	122.5±10.56	0.826#
After Induction	115.5±8.81	120.5±10.56	< 0.001*
After intubation	125.23±9.12	136.58±10.55	< 0.001*
1 min	123.68±9.04	133.85±10.41	< 0.001*
3 min	120.75±9.07	132.25±10.41	< 0.001*
5 min	119.55±9.18	130.5±10.56	< 0.001*
10 min	117.83±8.91	127.5±10.56	< 0.001*

Table-2: Comparison of SBP (mmHg) at different time interval in between Group A and Group B.

	DBP (mmHg)		
	Group A	Group B	
Time interval	**Mean ± SD**	**Mean ± SD**	**P-Value**
Baseline	69.7±8.54	71.85±7.62	0.239
After Induction	67.3±8.65	70.6±7.65	< 0.001*
After intubation	73.8±8.86	80.23±7.88	< 0.001*
1 min	72.68±8.95	80.08±7.48	0.026*
3 min	70.5±8.54	79.75±7.12	< 0.001*
5 min	69.65±8.53	78.83±7.21	< 0.001*
10 min	66.7±8.54	76.95±7.61	0.0182*

Table-3: Comparison of Mean DBP (mmHg) at different time interval in between Group A and Group B.

	MAP (mmHg)		
	Group A	Group B	
Time interval	**Mean ± SD**	**Mean ± SD**	**P-Value**
Baseline	88.34±8.4	88.73±7.79	0.986
After Induction	86.24±8.36	87.23±7.70	< 0.001*
After intubation	94.61±8.85	99.01±8.01	< 0.001*
1 min	93.34±8.89	98.0±7.67	< 0.001*
3 min	92.92±8.62	97.25±7.41	< 0.001*
5 min	90.95±8.65	96.05±7.55	< 0.001*
10 min	89.41±8.57	93.8±7.78	< 0.001*

Table-4: Comparison of MAP (mmHg) at different time interval in between Group A and Group B.

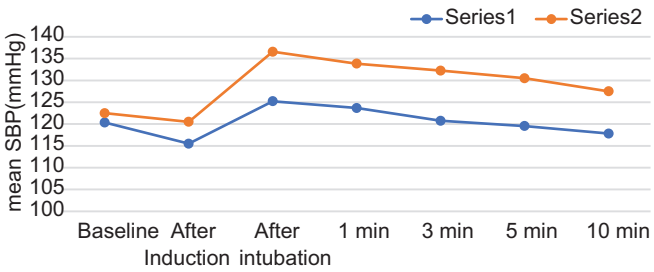

Figure-2: Comparison of mean systolic blood pressure at different time interval between group A and Group B

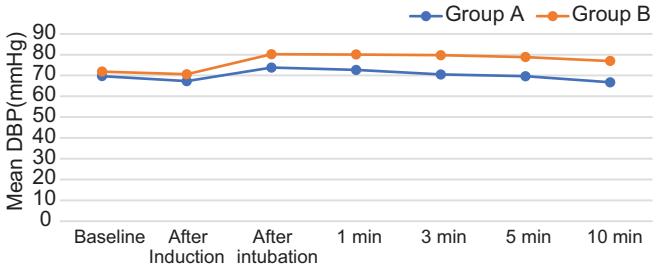

Figure-3: Comparison of mean diastolic blood pressure at different time interval between Group A and Group B

After 5 minutes of intubation SBP in group A come below baseline but in Group B it was still increased from baseline. Baseline difference was comparable between both groups but after induction, up to 10 minutes difference was statistically significant between both groups. (p value <0.001)

Baseline DBP (seen in table and fig 3) in Group A and Group B was 69.7 ± 8.54 and 71.85 ± 7.62. Group B showed significant increase in DBP after induction compared to group A (p value <0.001). Maximum increase in DBP in group A and B was 73.8 ± 8.86 and 80.23 ± 7.88. DBP in Group A come to baseline after 5 minutes of intubation but in Group B it was still higher than baseline. Difference was statistically significant from after induction up to 10 minutes after intubation.

Baseline MAP in Group A and Group B (shown in fig and table 4) was 88.34 ± 8.4 and 88.73 ± 7.79 (p value 0.986). Group B showed significant increase in MAP after induction compared to group A (p value <0.001). Maximum increase in MAP in group A and B was 94.61 ± 8.85 and 99.01 ± 8.01. Difference was statistically significant from after induction

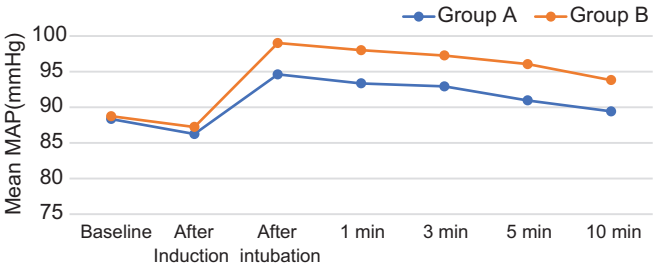

Figure-4: Comparison of mean arterial pressure at different time interval Between Group A and Group B

up to 10 minutes after intubation. (p value < 0.001)
SpO2 was comparable between both groups throughout surgery. (p value >0.05)

DISCUSSION

HTN and tachycardia which arise subsequent to ET intubation have been well documented in various studies.
Fentanyl and nalbuphine both opioids have been compared in many studies for their attenuation of haemodynamic response. Shrey et al [13] found in their study that following laryngoscopy and ET intubation there was 38.23% increase in HR from base line, SBP also increase as 40.16% from base line, and DBP increase by 22.73% from baseline.
Shoaib B K et al [14], Mohamed K A at al [15], Indira at al [16], and Naseer BK et al [17] found that fentanyl attenuates hemodynamic response better than nalbuphine due to laryngeal instrumentation.
Rajlaxmi B et al [18], Chanchal B et al [19] conducted study between nalbuphine (0.2mg/kg) and fentanyl (2mcg/kg) to find which is more efficacious in attenuating pressor response to laryngeal instrumentation, and found nalbuphine better than fentanyl.
As above studies show different results, So, we compared fentanyl (2mcg/kg) and nalbuphine (0.2mg/kg) to see which drug is better in attenuating pressor response.
Dnyaneshwar RF et al [20] conducted study between nalbuphine (0.2mg/kg) and control group receiving normal saline. He found nalbuphine is also a potent opioid in attenuating stress response to laryngeal instrumentation.
Ko et al [21], Shoaib B K et al [14], Mohamad K A et al [15], Indira et al [16], and Virsharad et al [22] found that 5minutes before study drug administration is best time to attenuate pressor response to laryngeal instrumentation, so we did laryngoscopy and ET intubation after 5 minutes of administration of study drugs.
Shoiab BK et al [14] had found in his study that fentanyl 2mcg/kg when given 5 minutes prior to intubation did not cause blunting in tachycardia, HR was on the higher side till 10 minutes after intubation. HR was comparable between fentanyl and nalbuphine same as in our study.
Chanchal B et al [19] found that both fentanyl and nalbuphine receiving patients showed an increase in HR during intubation, but came to baseline after intubation which was comparable throughout the postintubation period till 15 minutes.
Cheng YT et al [23] found best time to give fentanyl 2mcg/kg to attenuate pressor response and found 2 minutes before induction attenuates best but Ko el al [21] found fentanyl when given 5 minutes before induction attenuate the pressor response better so after evaluating results, we gave fentanyl 5 minutes before induction.
Hari P K et al [24] used fentanyl 2mcg/kg 5 minutes before induction and found increase in HR and it was comparable between fentanyl and nalbuphine same as in our study. Naseer BK et al[17] also found increase in HR in fentanyl group after intubation and remain increased till 5 minutes, and after 10 minutes of intubation HR come to baseline as in our study. Naseer BK et al [17] used 1mcg/kg fentanyl even lower than our study. To completely blunt the increase in HR higher dose of fentanyl is needed but may cause side-effects.
Kay B et al[25] used 5mcg/kg of fentanyl, he found HR increase was present but HR come to base line even before 4 minutes after intubation. Visharad T et al [22] compared 2 dose of fentanyl (2mcg/kg and 4mcg/kg) and found 4mcg/kg dose of fentanyl is better in blunting increase in HR but higher dose may cause side-effects.
Rajlaxmi B at al[18] found fentanyl better in attenuating HR when compared with nalbuphine group and result found statistically significant immediately after drug administration. The rise of HR was lesser in fentanyl group than nalbuphine group and after 1 and 3 minutes of intubation fall in HR was statistically signification.
Aqusa B et al[26] found HR increase in nalbuphine and fentanyl groups but more increase was found with fentanyl group and the difference was statistically significant. May be this difference was because we gave the study drug 5 minutes before induction and Aqusa B et al [26] gave drug 10 minutes before induction.
In our study we found that fentanyl attenuates SBP better than nalbuphine which was given 5 minutes before induction. We found mean baseline SBP was comparable in both groups with p value 0.826. We documented our result after induction, after intubation, 1, 3, 5, 10 minutes after and p value is less than 0.05 which is statistically significant. Similar results were concluded by Shoiab BK et al [14] as he found fentanyl and nalbuphine when given 5 minutes before induction showed comparable baseline SBP and after induction was statistically significant.
Mohamed KA et al [15] also found same trend in SBP as both fentanyl and nalbuphine groups increase SBP but it was more in nalbuphine group after induction and it was statistically significant.
Milon VM et al [27] conducted study to see if nalbuphine is efficacious like fentanyl in attenuating pressor response to laryngoscopy and intubation and he found fentanyl better affecting SBP but results found insignificant between both groups.
Indira et al [16] also found mean SBP at baseline was comparable between fentanyl and nalbuphine groups but 1 minute after intubation it was statistically significant as in fentanyl group there was less increase in SBP compared to nalbuphine and beyond 3 minutes till 15 minutes difference was insignificant but fentanyl group showed less increase in SBP as compared to nalbuphine group.
Bhavini S et al [28] and Visharad T et al [22] compared 2 doses of fentanyl (2mcg/kg and 4mcg/kg) to attenuate stress response during laryngeal instrumentation and found both groups were effective in blunting stress response but fentanyl 4mcg/kg was able to completely blunt rise in SBP as compared to 2mcg/kg group. Bhavini S et al [28] and Visharad T et al [22] also found study drug when given 5 minutes before induction was most effective in attenuating pressor response

so we chose this time. Abhijit M et al [29] also compared two dose of fentanyl (1mcg/kg and 2mcg/kg) and found 2mcg/kg was able to prevent pressor response and provide haemodynamically stability without any side-effects, this is also reason we selected 2mcg/kg dose to prevent side-effects like postoperative respiratory depression and more delay in recovery.

Dnyaneshwar RF et al [20] conducted study to see role of nalbuphine (0.2mg/kg) in attenuating pressor response when given 5 minutes before induction. Baseline SBP of control and nalbuphine group was 119.81±11.78 and 123.63±14.89. Up till 10 minutes after laryngoscopy, he found significant result between control and nalbuphine group, hence he concluded that nalbuphine can be used to lessen hemodynamic response.

Sadqa A et al [30] studied comparison between fentanyl/isoflurane with nalbuphine/isoflurane in those patients, who were undergoing elective CABS and he found SBP in fentanyl/isoflurane group after intubation was 126.47± 7.45 and in nalbuphine/isoflurane BP was 167.60±12.99 which was statistically significant.

Hari PK et al [24] compared fentanyl and nalbuphine to find which drug has more analgesic property and which controls hemodynamics. In his study he found SBP was more in nalbuphine group than fentanyl group. Maximum rise in SBP in nalbuphine group was 11.07% whereas in fentanyl group was 3.96%, which was statistically significant.

In our study, baseline DBP is comparable between Group A and group B. After induction, after intubation, and after 1, 3, 5, 10 minutes of intubation p value is <0.05. This shows difference is statistically significant after induction till 10 minutes and fentanyl group showed more decrease in DBP than nalbuphine group. Shoiab BK et al [14], Mohamed KA et al [15], Indira et al [16] found similar trend in DBP and found fentanyl group showed less rise in DBP than nalbuphine group throughout the study. All these studies used fentanyl 2mcg/kg and nalbuphine 0.2mg/kg dose and study drugs were given before 5 minutes before induction which is similar to our study.

Ranjithkumar RT et al [31] compared fentanyl with lignocaine for attenuation of pressor response and found fentanyl 2mcg/kg receiving patients show less rise in DBP than control and lignocaine group. So, they found 2mcg/kg dose produce 5.8 percent rise after 1 minute of intubation and DBP come below baseline after 7 minutes of intubation, in our study DBP come to baseline after 5 minutes.

Valluri AK et al [32] found in their study than fentanyl 2mcg/kg when given before induction cause less increase in DBP. Baseline DBP was 77±4.37 and after 5 minutes of intubation DBP come to baseline 77.76±4.7, which is similar to our study and Valluri AK et al [32] found fentanyl as effective drug in attenuating haemodynamics during laryngoscopy and ET intubation, which is similar to our study.

Visharad T et al [22] found both doses of fentanyl (2mcg/kg and 4mcg/kg) cause decrease in DBP when given 5 minutes before induction but more decrease was seen in patients who received 4mcg/kg but Visharad T et al [22] found that in group 2 had developed side-effects like HTN and bradycardia after IV injection of 4mcg/kg dose so it needed treatment immediately.

Hari PK et al [24] found DBP was more in nalbuphine group than fentanyl during intubation and trend was steady even after 15 minutes of study and fentanyl provided better haemodynamic stability than fentanyl.

Shoiab BK et al [14] in his study also found baseline MAP between both groups is comparable. After induction till 10 minutes, he found statistically significant result between fentanyl and nalbuphine group as fentanyl group show less rise in MAP than nalbuphine group. Indira et al [16] found MAP decrease following drug administration and after intubation was better in fentanyl group compared to nalbuphine group and result was statistically significant at 1 minute after intubation but was comparable after 1 minute but fentanyl group attenuate pressor response.

Mohamed KA et al [15] found same result as baseline MAP between both groups was comparable (p value 0.274). Just after intubation he found significant difference but after 1 minute intubation MAP was comparable.

Milon VM et al [27] found MAP was comparable between both groups but in fentanyl group maximum decrease in MAP was 22.8 percent at 4 to 5 minutes and in nalbuphine group maximum decrease was 17.4 percent and MAP doesn't rise than baseline even after intubation in fentanyl group. Anjum S et al [33] found MAP in fentanyl group was statistically significant just after doing intubation comparing to nalbuphine group patients.

CONCLUSION

Fentanyl and Nalbuphine when given in a dose of 2mcg/kg and 0.2mg/kg respectively, 5 mins before induction of anesthesia decrease pressor response of laryngeal instrumentation, however blunting of pressor response is better in fentanyl group which also decrease the risk of adverse haemodynamic outcomes like patients with CAD and other heart diseases.

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