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A COMPARATIVE STUDY OF EFFICACY OF FENTANYL, BUTORPHANOL AND NALBUPHINE IN ATTENUATING THE INTUBATION RESPONSE

Anesthesiology

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ABSTRACT

BACKGROUND: Laryngoscopy and endotracheal intubation is associated with transitory increase in heart rate and blood pressure which can increase morbidity and mortality. We compared the efficacy of Fentanyl, Butorphanol and Nalbuphine in attenuating the intubation response.

MATERIAL AND METHODS: In this study ninety patients were randomly divided into three groups. Group N received Inj. Nalbuphine 0.2 mg/kg, Group B - Inj. Butorphanol 0.03 mg/kg and Group F- Inj. Fentanyl 2 µg/kg. The heart rate and blood pressure (Systolic, diastolic and mean) of the patient were noted before and after premedication, immediately after intubation and from there onwards every 1 minute for a period of 10 minutes. Rate pressure product was calculated from heart rate and systolic BP.

RESULTS: Values of Heart Rate, Diastolic and mean BP and rate pressure product were comparable in all the three groups at any time interval throughout the study ($p > 0.05$) however statistically significant difference was seen in Systolic BP between the three groups at 1 min post-intubation ($p = 0.009$) and at 10 min ($p = 0.012$) with group B showing higher value.

CONCLUSION: Administration of intra-venous Nalbuphine, Butorphanol and Fentanyl prior to induction of general anaesthesia is equally effective in attenuation of hemodynamic responses to laryngoscopy and endotracheal intubation.

KEYWORDS

Butorphanol, Fentanyl, Nalbuphine, Intubation, Haemodynamic response

INTRODUCTION:

Laryngoscopy and endotracheal intubation is associated with a rise in plasma concentration of catecholamines like adrenaline, noradrenaline, dopamine resulting in transitory increase in heart rate (HR) and blood pressure (BP) which can increase morbidity and mortality.[1] This pressor response may be hazardous especially in patients with hypertension, ischaemic heart disease or cerebrovascular disease predisposing them to development of pulmonary edema, myocardial infarction and cerebrovascular accidents. [2] In neurosurgical patients, it can result in sudden steep rise in intracranial pressure leading to acute cerebral edema and herniation of brain tissue. [2] Rate pressure product (RPP) is a product of systolic BP and HR and is a measure of cardiac workload. Increase in RPP increases the risk of myocardial ischemia, myocardial infarction, acute cardiac failure, pulmonary oedema and cardiac arrhythmias. [3]

Various drugs like Thiopentone, Propofol, Esmolol, Lignocaine, α_2 agonists (clonidine & dexmedetomidine) and Opioids have been tried to prevent hemodynamic response of laryngoscopy with varying success.[4] In our hospital, we routinely use Fentanyl, a potent synthetic opioid analgesic for this purpose. [5-9] For dispensing fentanyl, pharmacy needs special license and meticulous record keeping. Hence prescribing and obtaining fentanyl is a bit cumbersome process. Butorphanol is an opioid with partial agonist and antagonist activity[10-12] whereas Nalbuphine is a potent opioid analgesic, which is a kappa agonist/ antagonist at µ receptor. [1,2,4,9,13,14] Both Butorphanol and Nalbuphine, which are freely available, have been tried in preventing the intubation response. Various studies have compared effects of fentanyl with either Nalbuphine or Butorphanol. Not much work has been done comparing Nalbuphine with Butorphanol.

We conducted a study to compare the efficacy of Fentanyl, Butorphanol and Nalbuphine in attenuating the intubation response.

MATERIAL AND METHODS:

After approval from ethical committee, this prospective randomized double blind study was conducted in the department of anesthesia, MGM medical college, Aurangabad over two years. Keeping alpha error of 0.05 and beta error of 0.8, minimum sample size required was 17 in each group. Ninety patients between the age group of 18 and 65 yrs. with American Society of Anesthesiologists (ASA) physical status I and II who were to undergo elective general, urologic, orthopedic, plastic or gynecologic surgery under General Anesthesia with endotracheal intubation were included in the study. Patient on chronic opiate use, pregnant females and lactating mothers, patient with difficult intubation, BMI >30, Patient with known allergies to opioid group of drugs and patients with tachy / brady arrhythmias were excluded from the study.

Patients were kept nil per oral for 6 hours prior to surgery. Weight of the patient was recorded. Informed and written consent of the patient was taken. Patients were randomly divided into three groups using sealed envelope method.

Group-N- Inj. Nalbuphine hydrochloride 0.2 mg/kg (Inj. Nacphin by Neon pharmaceuticals)

Group B- Inj. Butorphanol Tartarate0.03 mg/kg (Inj. Butodol by Neon pharmaceuticals)

Group-F- Inj. Fentanyl citrate 2 µg/kg (Inj. Trofentyl by Troikaa)

One anesthesiologist prepared the study drugs in coded syringes while 2nd anesthesiologist administered the drugs and observed the parameters making the study double blind.

An intravenous cannula of 20G was inserted into the arm vein. Patient was pre-loaded with 5 ml/kg of Ringer lactate. All patients were monitored non-invasively for blood pressure, Heart rate (HR), oxygen saturation (SpO_2) and ECG changes. The Baseline parameters BP (systolic, diastolic, mean), HR and SpO_2 were recorded. Pre-medications in the form of Inj. Glycopyrrolate 0.004 mg/kg IV and Inj. Midazolam 0.04mg/kg IV along with one of the study drug - Nalbuphine (Group-N), Butorphanol (Group B) or Fentanyl (Group-F) were given. Haemodynamic parameters were noted 2 minutes after premedication. Pre-oxygenation with 100% O_2 was done for 3 min.and patients were induced with Inj. Propofol (2mg/kg IV) given over 30 sec. Muscle Relaxant Suxamethonium (1.5 mg/kg IV) was given to facilitate endotracheal intubation. Patients were ventilated using 100% O_2 for 1 minute and intubated using Mc-Intosh curved blade within a period of 15 seconds with appropriate sized endotracheal tube. Anaesthesia was maintained with 1% Isoflurane in oxygen + air and Inj. Vecuronium 0.1 mg/kg. Patients who required more than 15 seconds or more than one attempt for intubation were excluded from the study. The hemodynamic parameters were noted immediately after intubation and thereafter every 1 minute for a period of 10 minutes. During this period, hypertensive episodes (increase in MAP by 30% from baseline) were treated by adjusting the dial concentration of inhalational agents. Hypotensive episodes (decrease in MAP by 30% from baseline) were corrected using Inj. Mephentermine 5mg IV. To

treat tachycardia (HR >110 bpm) Inj. Esmolol 0.5mg/kg IV was given and for bradycardia (HR < 50 bpm) Inj. Atropine 0.06mg/kg IV was given.

Statistical analysis:

Statistical analysis of the data was done using SPSS software version 20. The quantitative data was represented in form of frequency and percentage. The quantitative data was represented in form of Mean, SD etc. For checking the significance difference between 3 groups, ANOVA test was applied. P value of < 0.05 was considered as statistically significant and p < 0.001 as statistically highly significant

RESULTS:

The demographic data (age, sex, weight) were comparable in both groups ($p < 0.05$)

Table 1 – Demographic data. Results are given as mean ± SD.

Parameters		Group N (n = 30)	Group B (n = 30)	Group F (n = 30)	P value
Age (in years)		36.43	38.93	35.13	P=0.487 NS
Weight (in Kilograms)		54.66	55.76	53.96	P=0.379 NS
Gender distribution (given as percentage)	Male	07 (23.3%)	08 (26.7%)	10 (33.3%)	P=0.632 NS
	Female	23 (76.7%)	22 (73.3%)	20 (67.7%)	

NS = Not significant

There was no statistically significant difference between the three groups in HR, DBP, MAP and RPP at any time interval in the study (p > 0.05) (Figures 1 – 4)

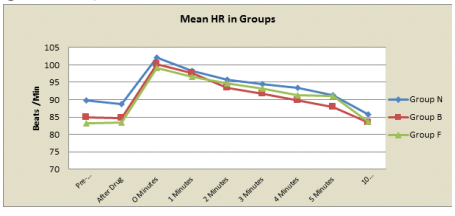


Fig. 1: Comparisons of Heart rate at different time intervals in the study Groups

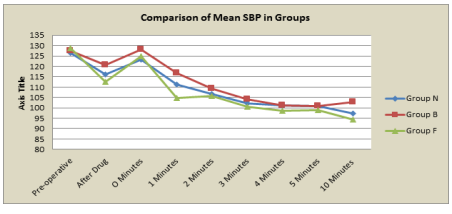


Fig. 2: Comparisons of Systolic BP at different time intervals in the study Groups

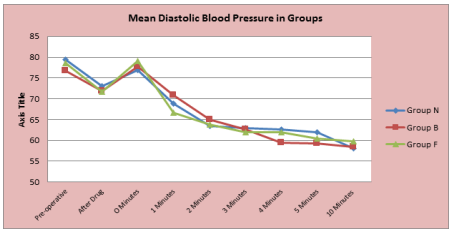


Fig. 3: Comparisons of Diastolic BP at different time intervals in the study Groups

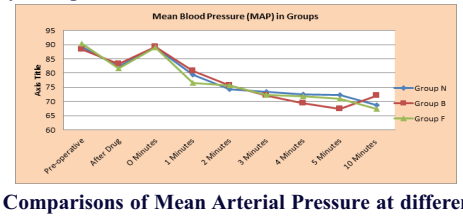


Fig. 4: Comparisons of Mean Arterial Pressure at different time intervals in the study Groups

Statistically significant difference was seen in SBP between the three groups at 1 min post-intubation (p = 0.009) and at 10 min (p = 0.012) with group B showing higher value.

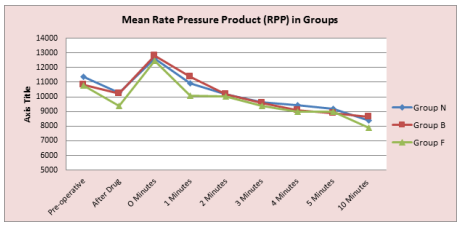


Fig. 5: Comparisons of Rate Pressure Product (RPP) at different time intervals in the study Groups

Mean percentage changes in HR, SBP DBP, MAP and RPP in all the three groups at different time intervals during the study period compared to baseline values are shown in tables 2 – 6.

Table 2 - Intra Group Comparisons (as percentage change) of Heart Rate at different time intervals compared to the baseline value

HR	Group N Percentage change	Group B Percentage change	Group F Percentage change
After Study Drug	-1.26%	-0.39%	+0.24%
Post intubation (0 Minutes)	+13.82%	+17.91%	+19.10%
1 Minute	+9.54%	+14.85%	+15.94%
2 Minutes	+6.68%	+9.88%	+13.81%
3 Minutes	+5.08%	+8.00%	+11.85%
4 Minutes	+4.04%	+5.76%	+9.57%
5 Minutes	+1.70%	+3.29%	+9.37%
10 Minutes	-4.43%	-1.92%	0.44%

Table 3 - Intra Group Comparisons (as mean percentage change) of Systolic BP in mm of Hg at different time intervals compared to the baseline value

Systolic BP	Group N Percentage change	Group B Percentage change	Group F Percentage change
After Study Drug	-8.11%	-5.37%	-12.64%
Post intubation (0 Minutes)	-2.50%	+0.49%	-3.03%
1 Minute	-12.13%	-9.50%	-18.74%
2 Minutes	-15.65%	-14.43%	-17.94%
3 Minutes	-19.17%	-18.37%	-21.93%
4 Minutes	-19.90%	-20.80%	-23.40%
5 Minutes	-20.35%	-20.83%	-23.27%
10 Minutes	-23.06%	-19.42%	-26.74%

Table 4 - Intra Group Comparisons (as mean percentage change) of diastolic BP in mm of Hg at different time intervals compared to the baseline value

Diastolic BP	Group N Percentage change	Group B Percentage change	Group F Percentage change
After Study Drug	-4.16%	-6.40%	-8.74%
Post intubation (0 Minutes)	-3.12%	+1.25%	+0.68%
1 Minute	-13.23%	-7.74%	-15.16%
2 Minutes	-20.16%	-13.7%	-14.87%
3 Minutes	-20.70%	-18.33%	-21.18%
4 Minutes	-21.04%	-22.68%	-21.02%
5 Minutes	-22.00%	-22.34%	-23.09%
10 Minutes	-26.83%	-23.93%	-24.0%

Table 5 - Intra Group Comparisons (as mean percentage change) of Mean BP (MAP) in mm of Hg at different time intervals compared to the baseline value

Mean BP (MAP)	Group N Percentage change	Group B Percentage change	Group F Percentage change
After Study Drug	-7.84%	-5.97%	-9.60%
Post intubation (0 Minutes)	-0.45%	+0.82%	-1.55%

1 Minute	-11.17%	-8.76%	-15.30%
2 Minutes	-16.76%	-14.48%	-16.66%
3 Minutes	-17.77%	-18.60%	-19.98%
4 Minutes	-18.78%	-21.60%	-20.61%
5 Minutes	-19.18%	-23.76%	-21.60%
10 Minutes	-23.10%	-18.41%	-25.67%

Table 6 - Intra Group Comparisons (as mean percentage change) of Rate pressure product (RPP) at different time intervals compared to the baseline value

Rate pressure product (RPP)	Group N Percentage change	Group B Percentage change	Group F Percentage change
After Study Drug	-9.73%	-5.46%	-12.84%
Post intubation (0 Minutes)	+10.73%	+18.78%	+15.6%
1 Minute	-4.04%	+5.47%	-6.4%
2 Minutes	-10.51%	-5.66%	-6.80%
3 Minutes	-15.51%	-11.46%	-12.91%
4 Minutes	-14.99%	-15.91%	-14.58%
5 Minutes	-19.56%	-17.7%	-14.45%
10 Minutes	-16.29%	-20.15%	-27.0%

DISCUSSION:

Manipulation of airway particularly laryngoscopy and endotracheal intubation is associated with increase in HR and BP resulting from sympathetic nervous system stimulation and catecholamine release. Effective management of stress response to endotracheal intubation is a major concern for anesthetist during surgeries under general anaesthesia (GA). Opioids have been commonly used to prevent this hemodynamic response.

Nalbuphine is a semi synthetic opioid of phenenthrene series which is structurally related to agonist oxymorphone and the antagonist naloxone. It has similar potency to that of Morphine. Butorphanol is mixed agonist-antagonist. Its interactions with opioid receptors in the central nervous system mediate its pharmacologic effects. Fentanyl is a strong μ-receptor agonist.

Dose of fentanyl commonly used for premedication is 1 – 2 mcg/kg, that of Nalbuphine is 0.2 – 0.3 mg/kg whereas dose of Butorphanol is 0.03 – 0.04 mg/kg. After thorough literature search, we decided to use Fentanyl 2 mcg/kg, Nalbuphine 0.2 mg/kg and butorphanol 0.03 mg/kg which were the most commonly used doses for attenuation of haemodynamic response to intubation in various studies.

In our study, the demographic data and pre-operative vital parameters (HR, SBP, DBP, MAP) were comparable between the three groups ($p > 0.05$).

There was no statistically significant difference between the three groups in HR at any time interval in the study ($p > 0.05$). After administration of the study drug, there was minimal decrease in mean HR in Group N and Group B whereas group F showed marginal increase. Mean HR increased in all the three groups after intubation which persisted up to 5 min. Rise was the maximum immediately after intubation though increases in HR remained within 30% of baseline in all groups at any given time. Percentage rise was more in fentanyl group at all the time intervals though the difference in HR was not statistically significant.

Chawda P *et al* [1] compared Nalbuphine (0.2mg/kg) with placebo to study hemodynamic response to orotracheal Intubation. Their study showed increase in heart rate in both the groups after giving study drug till the end of 10 minutes. The percentage rise in Group N in our study was 13.82% which is comparable to 14.2% rise in their group. Unlike our study, they did not observe decrease in HR at 10 min. This difference in findings may be because of the fact that we did not allow surgery to start till 10 min after induction in contrast to their study. Sharma N *et al* [4] *compared* fentanyl (2mcg/kg) versus nalbuphine (0.2 mg/kg) to study hemodynamic responses to intubation. They found a non-significant rise in HR after intubation in both groups (group F=12.5%, Group N=13.6%) which is comparable to our study (group F=19.10% Group N=13.82%). Kumar S *et al* [12] *in* a study comparing fentanyl (2mcg/kg) and Butorphanol 30 mcg/kg) during tracheal intubation in neurosurgical patients observed statistically comparable HR at each time interval among the two groups. There was significant rise in heart rate at 1 minute and 2 minutes post intubation in group B as compared to group F. In our study, increase in HR persisted till 5min in both group B and Group F. This difference may be because they started Propofol infusion 50-200μg/kg/min immediately after induction of anaesthesia.

We observed statistically significant difference in SBP between the three groups at 1 min post-intubation (N=111.13±13.19 mmHg, B=116.76±11.37 mmHg, F=104.67±18.86 mmHg) and at 10 min (N=97.30±11.09 mmHg, B=102.83±10.80 mmHg, F=94.36±10.80 mmHg) with group B showing higher values.There was a decrease in SBP in all groups after administration of study drugs which continued in group N and group F at all time intervals, whereas group B showed a transient marginal increase in SBP immediately after intubation (+0.49%) followed by fall till 10 min post intubation.

Sharma N et al [4] in their study observed that increase in SBP during intubation was more in group N (14.9%) compared to group F (4.8%), which was statistically very highly significant whereas we noted a fall in SBP immediately after intubation in both the groups. (Group N=2.5% and Group F=3.03%). This contrast may be due to difference in the induction agent used. Sharma N et al used Inj. Thiopentone 2.5% as induction agent and Inj. midazolam 1mg as pre-medication agent; whereas we used Inj. Propofol 2mg/kg and Inj. Midazolam 0.04 mg/kg. *Sharma K et al* [9] compared Tramadol (2mg/kg), Nalbuphine (0.3mg/kg) And Fentanyl (2mcg/kg) in attenuation of hemodynamic response to Laryngoscopy. Their study showed significant rise in SBP from baseline in Group T ($p<0.0001$). Group N and F showed some fall in SBP but the difference was not significant. All the three Groups showed rise of SBP at 1min post intubation but the rise was significant only in Tramadol group ($p<0.0001$). SBP came back to baseline in Group F (at 1 min.) and N (5 min.) early. In our study, the SBP did not rise above the baseline rather there was fall in SBP in both the groups F and N.This difference may be explained by the sedative effect of higher dose Inj. Midazolam compared to their study (0.04 mg/kg versus 0.02 mg/kg). After intubation, we started inhalational agent in concentration of 1 Mac. This also might have contributed to fall in SBP. We did not observe any statistically significant difference between the three groups in DBP at any point of time ($p > 0.05$). There was decrease in DBP in group N at all time intervals. Rise in DBP was seen immediately after intubation in group B (1.25%) and F (0.68%) followed by fall till the end of 10 min in all the 3 groups.

Sharma N et al [4] observed more rise in group N in DBP (8.8%) during intubation compared to group F (4.5%).This contrast may be due to difference in the induction agent used. Sharma N et al used Inj. Thiopentone 2.5% as induction agent and Inj. midazolam 1mg as pre-medication agent. We used Inj. Propofol 2mg/kg and Inj. Midazolam 0.04 mg/kg. *Kousar S et al* [5] compared Fentanyl (2mcg/kg) and Clonidine (2mcg/kg) for attenuation of the hemodynamic response to laryngoscopy and endotracheal intubation. In the Fentanyl group the maximum rise in DBP was 18.22% (87.98±9.48) at 5min after intubation. We found marginal rise (0.68%) in DBP immediately after intubation in Group F followed by fall till the end of 10 min in all the 3 groups. Kousar S et al used Inj. Thiopentone sodium 5mg/kg IV for induction. Use of Inj. Propofol (2 mg/kg), a potent vasodilator, as induction agent in our study might be the reason for variation in the results of both the studies.

The results we obtained show no statistically significant differences between the three groups in MAP at any point of time ($p >0.05$). There was a fall in MAP in all groups after administration of study drugs which continued in group N and group F at all time intervals, whereas in group B there was a transient marginal increase in MAP immediately after intubation (0.82%), thereafter decrease till 10 min.

Chawda P *et al* in their study of Nalbuphine (0.2mg/kg) observed that MAP increased after intubation in group N whereas, our study showed decrease in MAP after the drug administration in nalbuphine group which continued throughout the study. This contrast may be explained by higher dose of Midazolam (0.04mg/kg v/s 1mg) and difference in induction agent used (Inj. Propofol 2mg/kg v/s Inj. Thiopentone 5 mg/kg)in both the studies. *Kumar S* [9] *et al* in their study of fentanyl (2mcg/kg) and Butorphanol (30 mcg/kg), found comparable MAP in both group F and Group B immediately after intubation ($p >0.05$). There was significant rise in MAP at 1 minute post intubation in group B as compared to group F but there was no statistically significant difference in both groups at 3, 4 and 5 minutes after intubation ($p>0.05$). These results are in accordance with our study.

In our study, use of propofol, a potent vasodilator, for induction of anaesthesia followed by Isoflurane in a concentration of 1 MAC till the end of the study period (10 min.) might have contributed to the decrease in SBP, DBP as well as MAP. This decrease was < 30% in all the groups at any given time interval, hence did not warrant any intervention.

The product of HR and SBP, termed as rate-pressure product (RPP), is a very reliable indicator of myocardial oxygen demand and is widely used clinically. It has been recognized as a relevant parameter in evaluating ventricular function and high values at peak exertion reflects cardiac work. [15]

Rate pressure product is helpful in calculating the internal workload or hemodynamic response. Based on RPP, haemodynamic response can be graded as high (RPP > 30000), High Intermediate (RPP 25000 – 29999), Intermediate (RPP 20000 – 24999), Low Intermediate (RPP 15000 – 19999) and Low (RPP 10000 – 14999).

We found no statistically significant difference between the three groups in RPP at any point of time ($p > 0.05$). There was a fall in RPP in all groups after administration of study drugs. Rise in RPP was noted immediately after intubation in all groups (N= 10.73%, B=18.78%, F=15.6%) which continued till 1 min only in group B (5.47%) Thereafter a decrease in RPP was noted till the end of 10 min in all groups. The values of RPP in all the groups remained below 13000 throughout the study period suggesting low haemodynamic response to intubation.

Kothari D *et al*[13] made a comparison of nalbuphine (0.2 mg/kg) and pentazocine (0.5 mg/kg) for attenuation of hemodynamic changes during intubation and found in group N, after an initial fall in mean RPP a clinically significant rise (28.42%)which decreased to + 2.72% at the end of the study period. In our study, there was a fall in RPP in group N after administration of study drugs. Rise in RPP was noted only at 0 min after intubation in group N (10.73%) followed by fall.This difference may be contributed to the difference in induction agent used (Thiopentone sodium by *Kothari D et al* and Propofol in our study). Balasubramaniam S *et al* [10] made a comparison of fentanyl (2mcg/kg) and butorphanol (40 mcg/kg). In their study, the RPP was significantly lower in Group B when compared to Group F from the second minute after intubation. The RPP in Group B after intubation became comparable to the baseline at the fourth minute after intubation and it became significantly lower from the fifth minute after intubation. The RPP in Group F after intubation becomes comparable to the baseline at the fifth minute after intubation and it becomes significantly low at the tenth minute after intubation. In our study, increase in RPP was noted at 0 min after intubation in group B which continued till 1 min whereas Group F showed Increase in RPP only at 0 min followed by a fall in RPP till the end of 10 min. Better RPP values found by Balsubramaniyam S *et al* in Butorphanol group compared to fentanyl may be due to use of higher dose of Butorphanol (0.04 mg/kg). Observation of a lesser increase in RPP and early fall in both the groups in our study may be attributed to the use of propofol as the induction agent.

In our study, none of the patient in any of the group showed ECG changes throughout the study period underlining the stability of the cardiovascular system.

CONCLUSION:

Administration of intra venous Nalbuphine, Butorphanol and Fentanyl prior to induction of general anaesthesia is equally effective in attenuation of hemodynamic responses to laryngoscopy and endotracheal intubation; hence both Nalbuphine and Butorphanol can be used as effective alternatives to fentanyl for the same.

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