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A Comparative Study of Two Different Doses of Fentanyl 2mcg/kg and 4 mcg/kg in Attenuating the Hemodynamic Stress Response During Laryngoscopy and Endotracheal Intubation

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Abstract

Introduction: Direct laryngoscopy and endotracheal intubation induces cardiovascular stress response which in turn leads to increase in plasma catecholamine concentration and rise in blood pressure and heart rate. Fentanyl is a popular opioid used to attenuate a presser response to laryngoscopy and intubation. In this study, we compared two different doses of fentanyl 2 mcg/kg and 4 mcg/kg to asses maximum effectiveness and safety to prevent stress response during laryngoscopy and intubation. *Methods:* In this prospective comparative clinical study, 30 patients aged 18 to 50 years of ASA physical status I and II, scheduled for elective surgery under general anesthesia requiring endo tracheal intubation. Patients were randomized into two groups of 15 patients each: Group A: Received 2 µg/kg of fentanyl IV 5 minutes before induction. Group B: Received 4 µg/kg of fentanyl IV 5 minutes before induction. All groups were assessed for hemodynamic changes after premedication, during laryngoscopy and intubation, after intubation at 1, 3, 5 and 10 minutes, postoperative sedation and postoperative side effects. *Results:* Fentanyl in doses of 4 mcg/kg was effective in complete prevention of hemodynamic stress response during laryngoscopy and intubation. However, 4 mcg/kg of fentanyl produced a 15–20% decrease in hemodynamic variables from baseline compared to 5–10% with 2 mcg/kg of fentanyl. *Conclusion:* Fentanyl in dose of 4 µg/kg five minutes before induction is the most appropriate dose in terms of efficacy and safety for preventing hemodynamic stress response during laryngoscopy and intubation.

Keywords: Fentanyl; Pressor response; Endotracheal; Intubation; Hemodynamic.

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Introduction

Endotracheal intubation is an integral part of anesthetic management and critical care of patient and has been practiced following its description by Rawbo them and Magil in 1921.[1] Reild and Brace first

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described hemodynamic response to laryngoscopy and tracheal intubation.[2] Direct laryngoscopy and endotracheal intubation induces cardiovascular stress response which in turn leads to increase in plasma catecholamine concentration and rise in blood pressure and heart rate. This response is usually transient, variable and unpredictable. It occurs 30 seconds after starting the laryngoscopy and intubation and lasting for less than 10 mins.[3] These changes are well tolerated by healthy individual. But in patients with hypertension, coronary artery disease or left ventricular failure, arrhythmia, myocardial infraction, it may prove fatal.[4] This result suggests predominant sympathetic response during intubation and the need of prophylaxis in patients at risk.

Recommendations for attenuating reflex tachycardia and hypertension are manifold. The technique used should minimize these responses to anesthesia for patients at risk.

Drugs like Lidocaine, Esmolol, Fentanyl, Clonidine, Nitroglycerine, Verapamil and Nicardipine have been used to prevent pressor response to laryngoscopy and tracheal intubation.[5,6] Inhalational agents also do not have satisfactory effects and may need higher concentration which may cause serious hypotension, bradycardia and delayed recovery.

Opioid receptors are found in cardiovascular regulatory center, the sympathetic nervous system, the vagal nuclei, and the adrenal medulla. These precise locations of receptors enable fentanyl to significantly blunt the hemodynamic responses to hypopharyngeal noxious stimulation. Opioids are commonly used in perioperative period for their variety of desirable use. Fentanyl in particular has advantages over old opioids having rapid onset, short duration of action, cardio stability with no histamine release and broncho spasm. These are reasons fentanyl is being used now a days.[6] Fentanyl citrate, an opioid, is phenylpiperidine of the 4-aminopiperidine series controls both heart rate and blood pressure responses. It is an agonist at specific opioid receptors at presynaptic and postsynaptic sites in central nervous system as well as in periphery. The principle effect of opioid receptor activation is decrease in neurotransmission.[7] The present study was undertaken with an objective to compare the attenuation of the hemodynamic responses during laryngoscopy and intubation. In this study, we compared two different doses of fentanyl 2 mcg/kg and 4 mcg/kg to asses maximum effectiveness and safety to prevent stress response during laryngoscopy and intubation.

Materials and Methods

After approval from the hospital ethical committee and informed written consent, this study was carried out in Department of Anesthesiology, DY Patil Hospital and Research Centre, Pune. It was conducted in 60 adult patients belonging to American association of anesthesiologists (ASA) Grade I/II in age group of 18–60 years of age and posted for elective spine surgery under General Anesthesia.

Patients who were unwilling, or with respiratory of cardiac dysfunction or with renal or liver impairement were not included in the study. Also, patients with any coagulopathy or having known drug allergy were excluded from the study.

After detailed preanesthetic evaluation, routine and specific investigation, each patient was informed regarding nature, purpose of the study. Preoperative adequate fasting hours (6–8 hrs) were confirmed. The patients were randomized into two groups using the equal group random allocation method, that is, A and B groups. Patients were prepared by securing 20 gauge intravenous (IV) cannula, applying basic monitoring like plethysmography, standard 5-lead electrocardiography (ECG), noninvasive blood pressure. Patients in the A group received After detailed preanesthetic evaluation, routine and specific investigation, each patient was informed regarding nature, purpose of the study. Preoperative adequate fasting hours (6–8 hrs) were confirmed. The patients were randomized into two groups using the equal group random allocation method, that is, A and B groups. Patients were be prepared by securing 20 gauge intravenous (IV) cannula, applying basic monitoring like plethysmography, standard 5-lead Electrocardiography (ECG), noninvasive blood pressure.

After premedication with Inj. Glycopyrrolate 0.004 mg/kg Inj Ondansetron 0.1 mg/kg IV and Inj. Midazolam 0.0.2 mg/kg IV patients in Group A received Inj. Fentanyl 2 mcg/kg intravenously 5 minutes prior to induction and patients in Group B received Inj. Fentanyl 4 mcg/kg intravenously 5 minutes prior to induction. The vital parameters were recorded as (T1). Patient were preoxy genated with100% oxygen for 3 minutes. Induction was done with Inj. Propofol (2 mg/kg). The choice of muscle relaxant was injection succinylcholine (2 mg/kg) given after administering propofol once the patient is able to ventilate. Vital parameters were recorded as (T2). Patient were intubated with cuffed endotracheal tube. Oxygen and nitrous oxide

were started along with isoflurane. Loading dose of Vecuronium 0.1 mg/kg was given. Anesthesia was maintained with 65% nitrous oxide and 35% oxygen mixture along with isoflurane 0.8% -1% with controlled ventilation with intermittent doses of vecuronium (0.08 mg/kg) as and when required by patient. Postintubation vitals were recorded at 0, 1, 3, 5, 10 minutes.

During surgery, continuous pulse rate monitoring, SBP, DBP, Mean BP, SpO_2, respiratory rate was done, Patient was also be monitored for the side effects of the drug, if any during the course of intubation and in period following intubation. At the end of surgery patients were reversed with Inj. Glycopyrrolate 0.008 mg/kg along with Inj. Neostigmine methyl sulphate 0.05 mg/kg intravenously. Patient's after extubation were then be shifted to the recovery room.

All cases were completed in stipulated time. Data was compiled and tabulated. The statistical analysis was done using parametric test and the final interpretation was done based on 'Z' test (standard normal variant) with 95% level of significance.

Results

The patient characteristics shown in the Table 1, there was no significant differences in the two groups. (p value > 0.05).

Baseline HR was comparable in both the groups. Table 2 shows, changes in HR at various specific timings in both the groups. In both the groups, there was a significant decrease in HR within 5 minutes of fentanyl premedication. The extent of decrease was 5% in Group A, 10% in Group B. At the time of laryngoscopy and intubation, HR increased 17% from baseline in Group A while it remained below baseline with 10% decrease in Group B, (Fig. 1).

Table 1: Comparison of Patient Characteristics

	Group A Mean ± SD	Group B Mean ± SD	p - value
Sex (M/F)	9/6	11/4	0.438
Age	33.20 ± 4.74	32.67 ± 5.56	0.780
Weight	58.60 ± 4.87	58.60 ± 6.54	1.000
ASA score (I/II)	11/4	12/3	0.666

Table 2: Comparison of Heart rate

Timing	Group A		Group B		p - value
	Mean ± SD	% change	Mean ± SD	% change	
Baseline	87.87 ± 3.60	NA	89.00 ± 4.71	NA	0.465
After drug	83.07 ± 3.03	-5% ↓	80.13 ± 4.66	-10% ↓	0.052
After MR	84.87 ± 3.09	-3% ↓	79.87 ± 4.81	-10% ↓	0.002*
0 min	102.40 1.84±	17% ↑	75.53 ± 4.37	-15% ↓	0.000*
1 min	97.40 1.99±	11% ↑	76.00 ± 3.64	-15% ↓	0.000*
3 min	92.80 ± 2.70	6% ↑	73.67 ± 3.35	-17% ↓	0.000*
5 min	89.20 1.52±	2% ↑	73.00 ± 3.34	-18% ↓	0.000*
10 min	83.73 1.98±	-5% ↓	71.73 ± 2.91	-19% ↓	0.000*

* Statistically significant

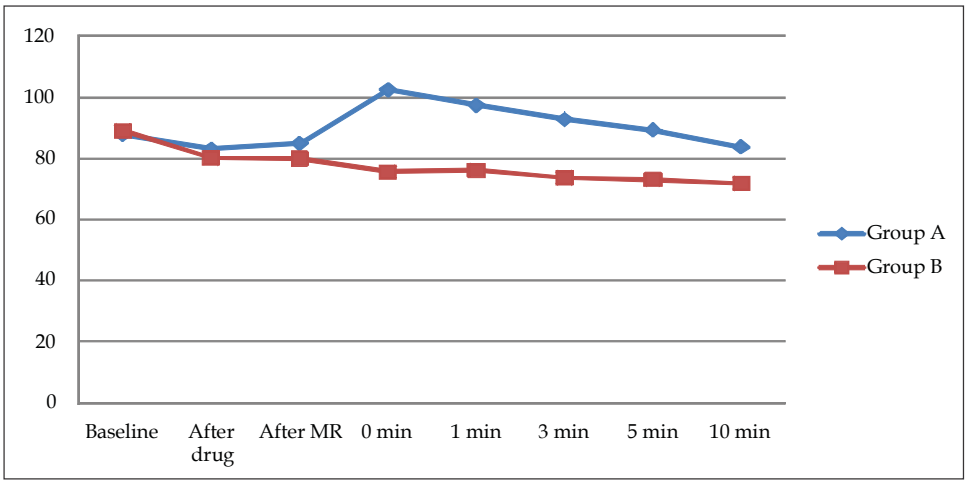

Fig. 1: Comparison of Heart rate

Table 3: Comparison of SBP

Timing	Group A		Group B		*p* - value
	Mean ± SD	% Change	Mean ± SD	% Change	
Baseline	128.20 ± 4.93	NA	121.87 ± 4.69	NA	0.001*
After drug	124.33 ± 4.51	-3% ↓	110.47 ± 4.64	-9% ↓	0.000*
After MR	126.73 ± 4.65	-1% ↓	111.67 ± 4.58	-8% ↓	0.000*
0 min	136.73 ± 3.37	7% ↑	109.00 ± 3.66	-11% ↓	0.000*
1 min	134.73 ± 3.06	5% ↑	106.93 ± 2.12	-12% ↓	0.000*
3 min	130.93±2.37	2% ↑	105.53 ± 3.78	-13% ↓	0.000*
5 min	127.20 ± 3.34	-1% ↓	104.40 ± 3.64	-14% ↓	0.000*
10 min	122.93 ± 4.03	-4% ↓	104.60 ± 3.25	-14% ↓	0.000*

* Statistically significant

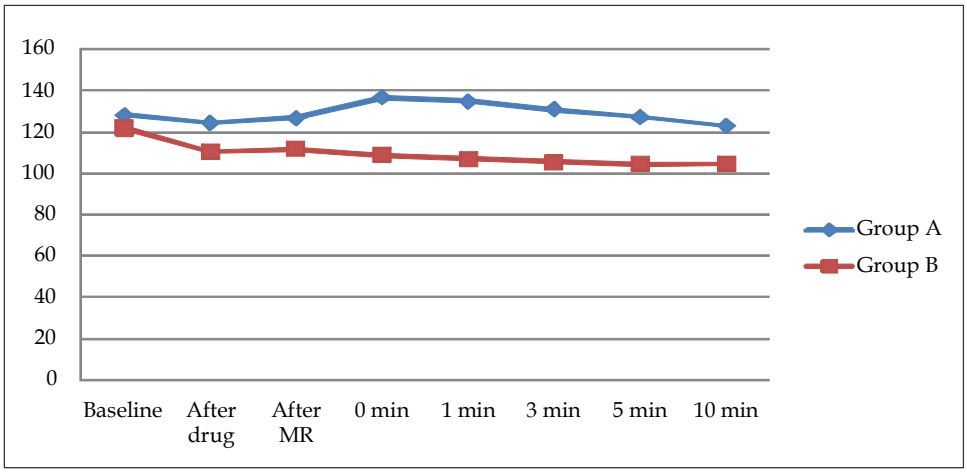

Fig. 2: Comparison of SBP

Table 4: Comparison of MAP

Timing	Group A		Group B		*p* - value
	Mean ± SD	% Change	Mean ± SD	% Change	
Baseline	97.58 ± 2.50	NA	94.31 ± 4.40	NA	0.020*
After drug	96.29 ± 2.32	-1% ↓	88.96 ± 4.60	-6% ↓	0.000*
After MR	96.73 ± 2.38	-1% ↓	88.60±3.28	-6% ↓	0.000*
0 min	101.44 ± 1.95	4% ↑	86.73 ± 2.98	-8% ↓	0.000*
1 min	99.44 ± 1.72	2% ↑	84.44 ± 1.66	-10% ↓	0.000*
3 min	98.13 ± 1.41	1% ↑	84.18 ± 1.92	-11% ↓	0.000*
5 min	96.00 ± 1.42	-2% ↓	79.60 ± 1.56	-16% ↓	0.000*
10 min	93.69 ± 1.67	-4% ↓	78.73 ± 1.35	-17% ↓	0.000*

* Statistically significant

Baseline SBP was comparable in all the three Groups. Table 3 shows, changes in SBP at various specific timings in both groups. In both groups, there was a significant decrease in SBP within 5 minutes of fentanyl premedication. The extent of decrease was 3% in Group A, and 9% in Group B. At the time of laryngoscopy and intubation, SBP increased 7% from the baseline in Group A while it remained below the baseline with 11% in Group B and III. The maximum decrease in SBP was in Group B of 14% at 10 mins after intubation as compared to baseline, (Fig. 2).

Baseline MAP was comparable in both the groups. Table 4 shows, changes in MAP at various specific timings in three groups. There was a significant decrease in MAP within 5 minutes of fentanyl premedication. The extent of decrease was 1 % in Group A and 6% in Group B. At the time of laryngoscopy and intubation MAP increased 4% from the baseline in Group A while it remained below the baseline with 8% decrease in Group B. There was maximum decrease in Group B in MAP of 17% at 10 minutes after intubation as compared to Group A which was only 4%, (Fig. 3).

Discussion

This study compared the efficacy of 2 mcg/kg fentanyl and 4 mcg/kg fentanyl to attenuate pressor response to laryngoscopy and intubation. As compared to 2 mcg/kg fentanyl, 4 mcg/kg fentanyl attenuated the increase in systolic, diastolic, and mean arterial blood pressure after intubation.

Direct layngoscopy and intubation is known to cause increase in heart rate and blood pressure. The mechanism behind this response is belived to be reflex sympathetic response due to catecholamines released when there is mechanical stimulation to upper respiratory tract i.e. larynx and trachea. There is significant elevation in serum levels of norepinephrine and epinephrine following laryngoscopy, with and without tracheal intubation.

Studies have shown that reflex changes in the cardiovascular system after laryngoscopy and intubation lead to an average increase in blood pressure by 40–50% and 20% increase in heart rate.[5]

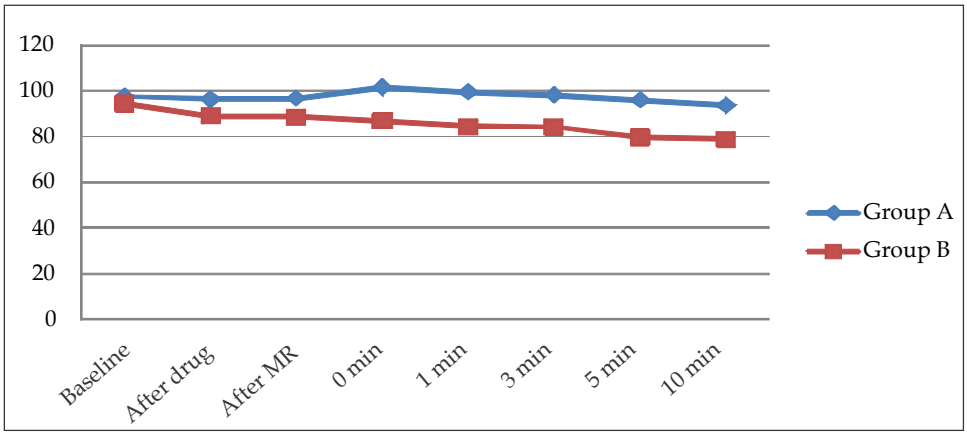

Fig. 3: Comparison of MAP

Different doses of fentanyl have been used for the same in varying range of 1.5 to 6 mcg/kg in different studies. After observing results for different doses we choose doses of 2 mcg/kg and 4 mcg/kg in our study groups.[8] In our study, we choose to administer the study drug, that is fentanyl, 5 minutes prior to induction. This was done considering the pharmacological profile of fentanyl in different studies. As the onset of action starts within minutes and peak action is at 5 minutes for fentanyl.[9] In our study, there was a significant decrease in HR within 5 minutes of fentanyl premedication in both the study groups. The extent of decrease was more when 4 mcg/kg was used. At the time of laryngoscopy and intubation, HR increased 17% from baseline in group A while it remained below baseline with 10% decrease in Group B. Thus, there was attenuation to pressor resposnse with 4 mcg/kg of Inj. Fentanyl.

In a study, done by Sellamuthu Gunalan et al. (2015) [10], they concluded that Attenuation of rise in heartrateandbloodpressurefollowinglaryngoscopy and endotracheal intubation was better with 1mcg/kg of dexmedetomidine when compared to fentanyl 2 mcg/kg. In our study too, 2 mcg/kg could not attenuate pressor response as compared to 4 mcg/kg of fentanyl.

In a study, done by Gurulingappa et al. (2012),[11] they concluded that attenuation of pressor response is seen both with lignocaine and fentanyl. Of the two drugs fentanyl 4 mg microgram IV bolus provides a consistent, reliable and effective attenuation as compared to lignocaine 1.5 mg/kg IV bolus. This result is similar to result in our study for 4 mcg/kg group.

In a study, conducted by Manoj kumar et al. (2017),[12] compared which of the three doses of fentanyl 2 mcg/kg, 3 mcg/kg and 4 mcg/kg is better to attenuate pressor response to laryngoscopy and intubation. They found that 2 µg/kg of fentanyl could not prevent the hemodynamic stress response to laryngoscopy and intubation and the hemodynamic variable like HR, SBP, DBP. Both the doses, 3 and 4 µg/kg of fentanyl were effective in complete prevention of hemodynamic stress response to intubation as patients in both the groups did not show any increase in hemodynamic parameters and were continuously below the baseline through the study period.

Although with 3 µg/kg of fentanyl, hemodynamic increased above preinduction level, while with 4 µg/kg of fentanyl, hemodynamic were still lower than preinduction level, showing a better efficacy of 4 µg/kg of fentanyl over 3 µg/kg in preventing the hemodynamic stress response to laryngoscopy and intubation.

In our study, we also found similar results on comparing between 2 mcg/kg and 4 mcg/kg for HR, SBP, MAP. In both groups, there was a significant decrease in SBP within 5 minutes of fentanyl premedication. The extent of decrease was 3% in Group A where 2 mcg/kg was given, and 9% in Group B with 4 mcg/kg fentanyl. At the time of laryngoscopy and intubation, SBP increased 7% from the baseline in Group A while it remained below the baseline with 11% in Group B and III. The maximum decrease in SBP was in patients with 4 mcg/kg of 14% at 10 mins after intubation as compared to baseline. There was a significant decrease in MAP within 5 minutes of fentanyl premedication. The extent of decrease was 1% in Group A with 2 mcg/kg of fentanyl and 6% in Group B that is with 4 mcg/kg fentanyl. At the time of laryngoscopy and intubation MAP increased 4% from the baseline in Group A while it remained below the baseline with 8% decrease in Group B. There was maximum decrease in Group B in MAP of 17% at 10 minutes after intubation as compared to Group A which was only 4%.

Conclusion

Fentanyl in dose of 4 µg/kg five minutes before induction is the most appropriate dose in terms of efficacy and safety for preventing hemodynamic stress response during laryngoscopy and intubation.

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