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Research Article

Clinical Evaluation of Efficacy and Safety of three Different Doses of Fentanyl to Prevent Hemodynamic Stress Response During Laryngoscopy and Intubation: A Randomized Double Blind Clinical Study

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Keywords

- Fentanyl citrate
- Hemodynamic stress response
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Abstract

Background: Hemodynamic stress response to laryngoscopy and intubation produces a significant hemodynamic alteration that may adversely affect patients with cardiac and neurological diseases. Fentanyl before induction attenuates hemodynamic stress response. We compared three different doses of fentanyl so as to find the most appropriate dose which prevents the response without adverse consequences.

Methods: In this prospective double blind clinical study, 90 patients aged 18 to 40 years of American Society of Anaesthesiologist (ASA) physical status I and II, scheduled for elective surgery under general anaesthesia requiring endo tracheal intubation. Patients were randomised to three groups of 30 patients each, which received 2, 3 or 4 µg/kg of fentanyl intravenously 5 minutes before induction of anaesthesia in group I, II and III respectively. All groups were assessed for pre-operative sedation, hemodynamic changes after premedication, during laryngoscopy and intubation, after intubation at specific timing up to 20 minutes and post-operative side effects.

Results: Fentanyl in doses of 3 and 4µg/kg was effective in complete prevention of hemodynamic stress response during laryngoscopy and intubation. However, 4 µg/kg of fentanyl produced a 20-25% decrease in hemodynamic variables from baseline compared to 15-20% with 3 µg/kg of fentanyl. Sedation score at exudation was higher with higher doses of fentanyl. Three patients receiving 4µg/kg of fentanyl required O2 supplementation in immediate post operative period.

Conclusion: Fentanyl in dose of 3µg/kg, five minute before induction is the most appropriate dose in terms of efficacy and safety for preventing hemodynamic stress response during laryngoscopy and intubation.

INTRODUCTION

A powerful noxious stimulus like laryngoscopy and intubation induces hypothalamic activity and results in an increased sympathetic outflow [1]. Laryngoscopy and endotracheal intubation stimulates oropharyngeal, laryngeal and in fraglottic receptors that increases nervous system activity in the cervical sympathetic efferent fibres, which evokes an additional cardiovascular response with a further release in catecholamine level [2] Vagolytic action of drugs used during induction may also contribute significant increase in plasma concentration of adrenaline and noradrenaline in response to laryngoscopy and intubation. The predominant responses are tachycardia and hypertension.

During general anaesthesia, airway control is generally provided by endotracheal intubation. Laryngoscopy prior to intubation and intubation in itself produce a significant hemodynamic stress response in the form of tachycardia and hypertension. Though, this elevated hemodynamic response is usually transient, returns to the base line within 10-15 minutes and well tolerated by healthy individuals without cardio-respiratory compromise, can prove disastrous in the patient with cardiac and neurological diseases.

Fentanyl is a popular opioids used in anaesthesia to attenuate a pressor response to laryngoscopy and intubation. It has been used for this purpose in different doses ranging from 1.5 µg/kg to 6 µg/kg in different studies [3-7]. Most of the observers used 2 µg/kg of fentanyl for this purpose and the results show

attenuation of response with this dose but 100% prevention of response is not achieved [4,5]. It seems that a higher dose of fentanyl is required for complete elimination of hemodynamic stress response. According to one study using 3 μg/kg of fentanyl, there are unacceptable incidences of hypotension reported [3]. One study using 4 μg/kg of fentanyl [5] and another using 3μg/kg and 5 μg/kg of fentanyl [6] found complete prevention of hemodynamic stress response to intubation without any hemodynamic instability. Study using 5 μg/kg of fentanyl [7] found a significant prevention of hemodynamic stress response to laryngoscopy and intubation, but with unacceptable incidences of respiratory depression. Another study using 6 μg/Kg of fentanyl [4] found a complete prevention of hemodynamic stress response to intubation without any hemodynamic instability.

In view of conflicting results of available studies with higher doses of fentanyl, there is need for further studies comparing different doses of fentanyl for its efficacy and safety to prevent hemodynamic response to laryngoscopy and intubation. So three different doses of fentanyl (2,3 and 4 μg/kg) were used to assess maximum effectiveness and safety to prevent the stress response during laryngoscopy and intubation.

MATERIAL AND METHODS

This prospective, randomized, double blind clinical study was carried out in 90 adult patients of either gender aged 18 to 40 years of ASA physical status I or II scheduled for elective surgery under general anaesthesia requiring endotracheal intubation. After thorough pre-anaesthetic evaluation, patients with cardio respiratory diseases, diseases affecting autonomic system, taking medication affecting hemodynamic variables and sedation score, anticipated difficult intubation and intubation attempt lasting longer than 15 seconds, antenatal females and body mass index more than 25 were excluded. After ensuring 6 hours fasting period, patients were taken in the pre-anaesthetic preparation room. Monitoring for Heart rate (HR), systolic blood pressure (SBP), mean arterial pressure (MAP), diastolic blood pressure (DBP) and peripheral oxygen saturation (SpO_2) were applied and baseline vital parameters were noted. Baseline sedation was graded as per Ramsay Sedation Score. Intravenous line was secured and infusion of 5% dextrose was started (4 mL/kg/h). Premedication consisting of ondansetron 0.08 mg/kg IV and glycopyrrolate 0.004 mg/kg IM 30 minutes before and midazolam 0.04 mg/kg IV 10 minutes before induction of anaesthesia were given.

Patients were randomised into three groups of 30 patients each. Randomisation was done by using computer software generating random number sequence. Fentanyl in the doses of 2μg/kg, 3μg/kg and 4μg/kg intravenously was given 5 minutes before induction of anaesthesia in the group I, II and III respectively. All patients received a standard anaesthetic protocol. After pre-oxygenation with 100% oxygen for 3 minutes with facemask, anaesthesia was induced with 2.5% thiopentone sodium intravenously slowly till the loss of eyelash reflex. Muscle paralysis was achieved using succinyl choline 2 mg/kg intravenously. Trachea was incubated with sterile polyvinyl chloride, cuffed, a disposable endotracheal tube (sized 7.5mm for women and 8.5 mm for men) at no response of Train of Four on peripheral nerve stimulation (ulnar nerve at the wrist). The tube was attached to Bain's breathing system and after confirming successful intubation with clinical examination and end tidal CO_2 monitoring. O_2-N_2O (50-50), vecuronium bromide and sevoflurane were used for maintenance of anaesthesia. Intermittent positive pressure ventilation (IPPV) was started. Tidal volume and ventilator frequency was adjusted so as to maintain normocapnia (end tidal CO_2 40 ± 4 mmHg).

All the parameters selected (HR, SBP, DBP, MAP) were recorded at various specific timings at the baseline, 5 minutes after fentanyl administration, at the time of intubation and then at 1,3,5,10,15 and 20 minutes after intubation. More than 20% fall in systolic blood pressure from the baseline value was graded as hypotension and treated with crystalloid fluids and 6 mg of ephedrine if needed. The pulse rate of < 60 beat/ min was graded as bradycardia and treated with boluses of 0.3-0.5 mg Atropine injection. More than 30% in increase in systolic blood pressure from the baseline value was graded as hypertension and treated with the nitro-glycerine infusion.

At the end of surgery, Neostigmine 50 μg/kg and glycopyrrolate 10 μg/kg were administered intravenously to reverse the neuromuscular blockade. After satisfying the extubation criteria, extubation was performed and patients were transferred to post-anaesthesia care unit. Sedation score was recorded at base line, 5 minutes after fentanyl injection, at the time of extubation and then at 5,10,15,20,30,60,90 and 120 minutes after extubation in the postoperative period. SpO_2 less than 95% and respiratory rate less than 10 bts/minutes were considered as a sign of respiratory depression.

Sample size calculation was based on a previous study taking SBP as a primary outcome measure with 80% power of study and using 0.05 and 0.2 alpha and beta errors. Calculated sample size of 18 per study group was calculated. We recruit 30 patients per group to minimise any effect of data loss. Unpaired *t* test for intergroup and paired *t*-test for intra group comparisons were used for evaluating the hemodynamic data. Data not normally distributed was compared using a Mann Whitney U test. Categorical data was analyzed using Chi square test. *P* value less than 0.05 was considered as significant.

RESULTS

Demographic variables were comparable among three groups (Table 1). Baseline HR was comparable in all the three groups. Table (2) shows changes in HR at various specific timings in all three groups. In all three groups, there was a significant decrease in HR within 5 minutes of fentanyl premedication. The extent of decrease was 6.73% in group I, 12.19% in group II and 12.63% in group III. At the time of laryngoscopy and intubation, HR increased 3.66% from baseline in group I while it remained below baseline with 4.07% and 14.14% decrease in group II and III respectively. P<0.001 After laryngoscopy and intubation, HR started decreasing in all three groups with maximum decrease noted at 14.76%, 18.47% and 24.52% respectively, 20 minutes post intubation. None of the patients in any group developed bradycardia (Figure 1).

Baseline SBP was comparable in all the three groups. Table (3) shows changes in SBP at various specific timings in all the three groups. In all the three groups there was a significant decrease

Table 1: Demographic Profile of Patients.

Demographic Profile	Group I	Group II	Group III	Intergroup P Value		
	Mean ± SD	Mean ± SD	Mean ± SD	I & II	I & III	II & III
Age (Yrs)	28.93 ± 6.29	27.63 ± 6.27	30.26 ± 6.19	>0.05	>0.05	>0.05
Sex (M,F)	15,15	20,10	16,14	>0.05	>0.05	>0.05
Weight(Kg)	58.53 ± 7.25	57.7 ± 6.77	58.5 ± 7.38	>0.05	>0.05	>0.05
ASA (I,II)	23,7	24,6	21,9	>0.05	>0.05	>0.05
Duration of Surgery(Min)	71.66 ± 12.34	66.83 ± 10.21	72 ± 14.05	>0.05	>0.05	>0.05

Inference: Demographic profile in terms of age, sex, weight and ASA physical status were comparable in three groups. Duration of surgery was also comparable in three groups. P>0.05

Table 2: Changes in heart rate from baseline among three groups.

HR (beats/minute)		Group I		Group II		Group III		
		Mean ± SD	% change From baseline	Mean ± SD	% change From baseline	Mean ± SD	% change From baseline	P value
Baseline		90.1 ± 6.96		89.13 ± 7.31		92.83 ± 4.25		>0.05
5 Min after fentanyl (pre induction value)		84.03 ± 7.03	6.73 % ↓	78.26 ± 6.29	12.19 % ↓	81.1 ± 3.77	12.63 % ↓	<0.001
During laryngoscopy and intubation		93.4 ± 7.12	3.66 % ↑	85.5 ± 6.82	4.07 % ↓	79.7 ± 3.85	14.14% ↓	<0.001
After intubation (Min)	1	91.63 ± 7.68	1.69% ↑	83.63 ± 6.66	6.18% ↓	78.23 ± 4.05	15.73% ↓	<0.001
	3	89.93 ± 7.78	0.19% ↓	81.3 ± 6.67	8.79% ↓	76.43 ± 3.74	17.67% ↓	<0.001
	5	86.2 ± 7.72	4.32% ↓	78.8 ± 6.83	11.59% ↓	75.06 ± 3.85	19.15% ↓	<0.001
	10	82.4 ± 7.48	8.55% ↓	76.2 ± 6.81	14.51% ↓	73.16 ± 3.85	21.19% ↓	<0.001
	15	78.96 ± 7.21	14.76 % ↓	74.1 ± 6.10	16.87% ↓	71.63 ± 3.95	22.84% ↓	<0.001
	20	76.8 ± 6.82	14.76 % ↓	72.66 ± 5.88	18.47 % ↓	70.06 ± 4.20	24.52 % ↓	<0.001

Inference: 2µg/kg of fentanyl premedication could not prevent the hemodynamic stress response to intubation and HR significantly increased above baseline. 3µg/kg of fentanyl premedication could prevent the hemodynamic stress response to intubation as HR did not increase above the baseline. However, HR increased above pre- induction level. 4µg/kg of fentanyl premedication was able to prevent the hemodynamic stress response to intubation more effectively than 3µg/kg of fentanyl as HR during intubation remained below the baseline as well as below the pre-induction level.

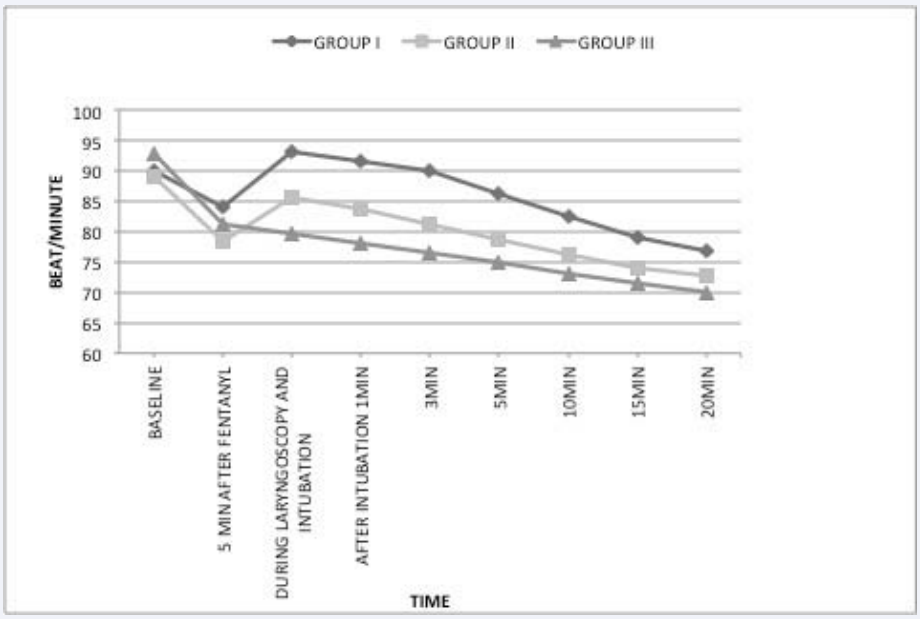

Figure 1 Graph shows comparison among 3 groups for heartrate/minute.

in SBP within 5 minutes of fentanyl premedication. The extent of decrease was 6.05% in group I, 7.35% in group II and 8.75% in group III. At the time of laryngoscopy and intubation, SBP increased 4.36% from the baseline in group I while it remained below the baseline with 2.68% and 10.35% decrease in group II and III respectively. P<0.001 After laryngoscopy and intubation, SBP started decreasing in all the three groups with maximum decrease noted was 9.69%, 13.71% and 18.56% respectively at 20 minutes post intubation.

Baseline MAP was comparable in all the three groups. Table (4) shows changes in MAP at various specific timings in three groups. In all the three groups, there was a significant decrease in MAP within 5 minutes of fentanyl premedication. The extent of decrease was 6.60% in group I, 8.33% in group II and 11.96% in group III. At the time of laryngoscopy and intubation MAP increased 5.13% from the baseline in group I while it remained below the baseline with 2.67% and 13.99% decrease in group II and III respectively. P<0.001 After laryngoscopy and intubation, MAP started decreasing in all the three groups with maximum decrease noted was 10.69%, 17.12% and 22.37% respectively at 20 minutes post intubation (Figure 2).

Sedation score averaged 2 in group II and III while it remained 1 in group I. Three patients in group III had sedation score 3 and were given oxygen supplementation in post operative period

Table 3: Changes in systolic blood pressure.

SBP (mm of Hg)		Group I		Group II		Group III		
		Mean ± SD	% change from baseline	Mean ± SD	% change from baseline	Mean ± SD	% change from baseline	P value
Baseline		124.5 ± 6.95		125.43 ± 8.05		128.4 ± 9.69		>0.05
5 Min after fentanyl (preinduction value)		116.96 ± 7.94	6.05 % ↓	116.2 ± 7.01	7.35 % ↓	117.16 ± 8.85	8.75 % ↓	<0.001
During laryngosopy and intubation		129.93 ± 7.65	4.36 % ↑	122.06 ± 7.27	2.68 % ↓	115.1 ± 8.98	10.35 % ↓	<0.001
After intubation (Min)	1	127.63 ± 7.89	2.51% ↑	120.03 ± 6.98	4.31% ↓	113.16 ± 9.75	11.87% ↓	<0.001
	3	124.9 ± 8.21	0.32% ↑	117.73 ± 7.15	6.14% ↓	110.96 ± 9.32	13.59% ↓	<0.001
	5	121.7 ± 7.80	2.25% ↓	114.5 ± 6.84	8.72% ↓	109.16 ± 9.04	14.99% ↓	<0.001
	10	117.86 ± 6.62	5.34% ↓	111.53 ± 6.57	11.09% ↓	107.1 ± 8.5	16.59% ↓	<0.001
	15	114.6 ± 5.67	7.96% ↓	110.13 ± 5.97	12.2% ↓	105.76 ± 7.99	17.64% ↓	<0.001
	20	112.43 ± 4.27	9.69 % ↓	108.23 ± 5.51	13.71 % ↓	104.56 ± 7.47	18.56% ↓	<0.001

Inference: 2µg/kg of fentanyl premedication could not prevent the hemodynamic stress response to intubation and SBP significantly increased above baseline. 3µg/kg of fentanyl premedication could prevent the hemodynamic stress response to intubation as SBP did not increase above the baseline. However, SBP increased above pre- induction level. 4µg/kg of fentanyl premedication was able to prevent the hemodynamic Stress response to intubation more effectively than 3µg/kg of fentanyl as SBP during intubation remained below the baseline as well as below the pre-induction level.

Table 4: Changes in mean arterial blood pressure (map).

MAP (mm of Hg)		Group I		Group II		Group III		
		Mean ± SD	% change from baseline	Mean ± SD	% change from baseline	Mean ± SD	% change from baseline	P value
Baseline		95.4 ± 5.87		96 ± 5.58		98.63 ± 6.7		>0.05
5 Min after fentanyl (preinduction value)		89.1 ± 5.96	6.60 % ↓	88 ± 5.40	8.33 % ↓	86.83 ± 6.06	11.96 % ↓	<0.001
During laryngoscopy and intubation		100.3 ± 5.87	5.13 % ↑	93.43 ± 5.64	2.67 % ↓	84.83 ± 6.18	13.99 % ↓	<0.001
After intubation (MIN)	1	98.26 ± 6.13	2.99% ↑	91.5 ± 5.74	4.69% ↓	82.93 ± 6.43	15.92% ↓	<0.001
	3	95.76 ± 6.40	0.37% ↑	89.16 ± 5.66	7.13% ↓	81.1 ± 6.74	17.78% ↓	<0.001
	5	92.76 ± 7.06	2.77% ↓	86.03 ± 5.87	10.39% ↓	80.13 ± 6.56	18.80% ↓	<0.001
	10	89.46 ± 5.97	6.23% ↓	83.43 ± 5.79	13.10% ↓	79.06 ± 6.40	19.85% ↓	<0.001
	15	87.03 ± 5.13	8.78% ↓	81.3 ± 5.51	15.32% ↓	77.93 ± 6.29	20.99% ↓	<0.001
	20	85.2 ± 4.64	10.69 % ↓	79.56 ± 5.41	17.12 % ↓	76.56 ± 6.22	22.37 % ↓	<0.001

Inference: 2µg/kg of fentanyl premedication could not prevent the hemodynamic stress response to intubation and MAP significantly increased above baseline. 3µg/kg of fentanyl premedication could prevent the hemodynamic stress response to intubation as MAP did not increase above the baseline. However, MAP increased above pre- induction level. 4µg/kg of fentanyl premedication was able to prevent the hemodynamic stress response to intubation more effectively than 3µg/kg of fentanyl as MAP during intubation remained below the baseline as well as below the pre-induction level.

prophylactically, though none of the patient felt in respiratory depression criteria. Within 20 minutes of extubation sedation score reached 1 in group II and III. There was no incidence of bradycardia and hypotension noted in any group.

DISCUSSION

The stimulation of laryngoscopy and tracheal intubation is considered to be stressful and cause significant hemodynamic stress response. Healthy patients without co-morbidity can tolerate the hemodynamic stress response without adverse consequences, may be hazardous especially in patients with hypertension, limited coronary and myocardial reserve or cerebrovascular diseases [8,9] Stress response to laryngoscopy and intubation may cause 20% increase in heart rate and 40-50% increase in blood pressure that may adversely affect the patients with the compromised cardiovascular and cerebro vascular system [10].

Hemodynamic stress response to laryngoscopy and intubation may be attenuated by several methods and drugs. Topical application of local anaesthetic, nerve blocks, α adrenergic blockers, vasodilators, calcium channel blockers and α 2 agonists all have been used [11-17]

These drugs can cause dangerous complications besides having no role for induction and maintenance of anaesthesia. 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, cardiostability with no histamine release and bronchospasm. These are the reasons we selected fentanyl as premedication for preventing hemodynamic stress response to intubation.

The magnitude of response is greater with increasing force and duration of laryngoscopy. The rise in blood pressure and heart rate usually occurs about 15 seconds after laryngoscopy and becomes maximal after 30-45 seconds, [18] thus limiting laryngoscopy to 15 seconds or less can minimize the stress of hemodynamic response. In the present study, laryngoscopy and intubation was accomplished within 15 seconds and it was attempted when there was no response of Train of Four on peripheral nerve stimulation (ulnar nerve at the wrist). Taking care of these two factors eliminates the preventable increase in hemodynamic stress response due to difficult intubation and intubation under suboptimal muscle relaxation. If intubation required more than 15 seconds duration, the case was excluded from the study.

Fentanyl has been used for attenuating the hemodynamic stress response effective in different doses titration ranging from 1.5 μg/kg to 6 μg/kg in different studies [1-7,20-23]. Searching the literature it was found that doses of fentanyl below 2 μg/kg is not effective in preventing the hemodynamic stress response. Most of study used 2 μg/kg [4,5,21,23-25] of fentanyl and concluded that it is capable of attenuating but not preventing the hemodynamic stress response to intubation. Fentanyl in the dose of 3 μg/kg showed conflicting results where significant attenuation of the hemodynamic stress response to intubation with stable hemodynamic was found in one study [6] in contrast to unstable hemodynamic in another. Using 4 μg/kg of fentanyl demonstrated complete prevention of the hemodynamic stress response with stable haemodynamic [5,22]. Studies using 5 μg/kg of fentanyl showed complete prevention of hemodynamic stress response to intubation with stable hemodynamic [6,19,20] and unstable hemodynamic with respiratory depression in another study [7].

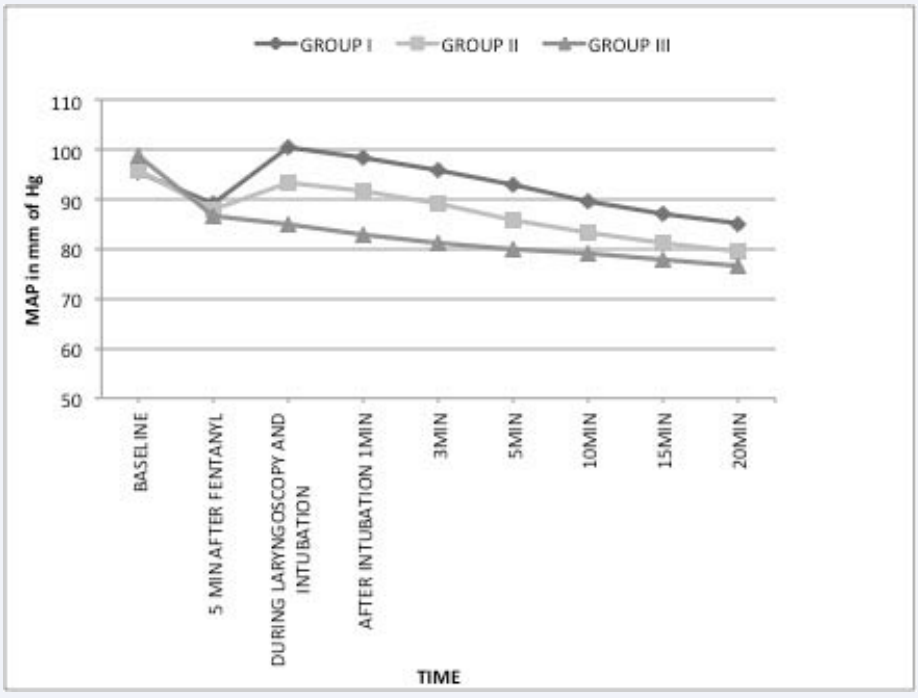

Figure 2 This graph shows comparison among 3 groups for Mean Arterial Pressure versus time duration in minutes.

Looking to the above studies it seems that dose of fentanyl below 2μg/kg is ineffective and above 5μg/kg is effective in preventing hemodynamic stress response to intubation but associated with unacceptable incidences of hemodynamic instability and respiratory depression. Because of wide variation in doses used and response achieved in various studies, we selected fentanyl in the dose of 2, 3 and 4 μg/kg for evaluating a complete prevention of hemodynamic stress response to intubation in otherwise healthy patients.

The timing of fentanyl administration before laryngoscopy and intubation is important. Onset of fentanyl action starts within minutes after intravenous injection and reaches a peak at five minutes, [26,27] which is why fentanyl was injected five minutes before starting induction so as to acquire the maximum efficacy of fentanyl at the time of laryngoscopy and intubation.

In the present study, 2 μg/kg of fentanyl could not prevent the hemodynamic stress response to laryngoscopy and intubation and the hemodynamic variable like HR, SBP, DBP and MAP increased up to 5% above the baseline. After intubation, hemodynamic variables reached comparable to the baseline within 5 minutes. Maximum fall in all the hemodynamic variables was up to 10-14%. 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 [28-30]. Although with 3 μg/kg of fentanyl, hemodynamic increased above pre-induction level, while with 4 μg/kg of fentanyl, hemodynamic were still lower than pre-induction level, showing a better efficacy of 4 μg/kg of fentanyl over 3μg/kg in preventing the hemodynamic stress response to laryngoscopy and intubation. However, a maximum decrease in hemodynamic variables with 4 μg/kg of fentanyl was 20-25% from the baseline at 20 minutes post-intubation as against 15-20% decrease with 3 μg/kg of fentanyl and three patients in group III were given oxygen supplementation as sedation score was 3 though they have not any sign of a respiratory depression [31-33].

This study was conducted on healthy, nor motensive patients with normal airways. It is therefore not known how the changes would have been in hypertensive patients. Therefore the finding of the present study may not be applicable to hypertensive patients. Although, all enrolled patients in our study were successfully incubated with the first attempt, hemodynamic parameters might be further impaired in patients with difficult intubation.

CONCLUSIONS

From the present study, it is concluded that fentanyl in the dose of 3μg/kg administered five minutes before induction is the most appropriate dose in terms of efficacy and safety for preventing hemodynamic stress response to laryngoscopy and intubation in healthy patients.

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