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Comparative Study of Two Different Doses of Fentanyl Citrate 2 mcg/ kg and 4 mcg/kg in Attenuation of Hemodynamic Responses During Intubation

Visharad Trived[1], Sunil Ninama[2]

[1,2]Assistant Professor, Department of Cardiac Anaesthesia, U.N. Mehta Institute of Cardiology and Research Centre, Asarwa, Ahmedabad, Gujarat 380016, India.

Abstract

***Background*:** Laryngoscopy and intubation in the lightly anesthetized patient is associated with significant increase in blood pressure and heart rate. These changes occur from reflex sympathetic discharge resulting from pharyngeal and laryngotracheal stimulation with increases in plasma concentration of epinephrine and norepinephrine. This reaction is not prevented by regular premedication. This study was designed to compare the two different doses of fentanyl citrate that is 2 mcg/kg and 4 mcg/kg in attenuation of hemodynamic effects during laryngoscopy and intubation. *Methods:* 80 adult patients 40 in each group ranging from 18–60 years of age and from both sexes undergoing modified radical mastectomy and total and subtotal thyroidectomy and surgeries which include oral intubation were selected for the study. Only patients belonging to ASA 1 and 2 were selected for the study. Group 1: Receives Inj. Fentanyl Citrate 2 mcg/kg. Group 2: Receives Inj, Fentanyl Citrate 4 mc/kg. All the parameters including heart rate, systolic arterial pressure, diastolic arterial pressure, and mean arterial pressure were recorded at the time of intubation and sequencially 1 min, 3 min, 5 min, and 10 minutes after intubation. *Results:* We studied all 4 parameters in both the Groups in all the patients and found out that the heart rate slightly increased during intubation in the Group 1 patients while it was either remained stable or decreased in Group 2 patients. There is consistent decrease in SBP, DBP and MBP in both the Groups from the baseline throughout the study period, and maximum decrease in all the pressures found at 10 minutes interval in Group 2 patients. *Conclusion:* Fentanyl citrate given 5 minutes before intubation produces most attenuation of the hemodynamic effects of stress response. Pretreatment with fentanyl citrate in every normal case would cause attenuation of hemodynamic effects of laryngoscopy and intubation. It will cause minimal change in heart rate, SBP, DBP, MAP, RPP during the first 10 minutes after intubation. Fentanyl citrate in 2 mcg/kg significantly attenuate but fentanyl 4 mcg/kg completely attenuates the hemodynamic responses during laryngoscopy and intubation.

Keywords: Laryngoscopy; Intubation; Fentanyl citrate.

Introduction

Laryngoscopy and intubation in the lightly anesthetized patient is associated with significant increase in blood pressure and heart rate. These increases in the pulse rate and blood pressure are usually of short duration and well-tolerated by healthy patients. However, in patients with hypertension, myocardial infarction and cardiovascular disease, these changes may lead to complications like

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Corresponding Author: Sunil Ninama, Assistant Professor, Department of Cardiac Anaesthesia, U.N. Mehta Institute of Cardiology and Research Centre, Asarwa, Ahmedabad, Gujarat 380016, India.

E-mail: sunilnninama@gmail.com

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myocardial infarction, dysrhythmia and cardiac failure, cerebrovascular catastrophes. These changes occur from reflex sympathetic discharge resulting from pharyngeal and laryngotracheal stimulation with increases in plasma concentration of epinephrine and norepinephrine. This reaction is not prevented by regular premedication.

Many methods have been identified to attenuate these responses including intravenous inhalational agents, narcotics, vasodilators, adrenergic and calcium blockers. Fentanyl citrate has been identified as an effective agent in this regard. Fentanyl citrate is effective in blunting the pressure response to laryngoscopy and intubation with different potency with different dose titration. Off course, it would have some side effects like respiratory depression and chest wall rigidity. But with doses used in clinical setting to attenuate this pressure response, side effects are minimal.

This study was therefore designed to compare the two different doses of fentanyl citrate that is 2 mcg/kg and 4 mcg/kg in attenuation of hemodynamic effects during laryngoscopy and intubation.

Materials and Methods

Eighty adult patients ranging from 18–60 years of age and from both sexes undergoing modified radical mastectomy and total and subtotal thyroidectomy and surgeries which include oral intubation were selected for the study.

Patients were assessed preoperatively through history and clinical examination. Investigatons were carried out and analyzed. Only patients belonging to ASA 1 and 2 were selected for the study. We exclude the patients on drugs affecting autonomic nervous system, Significant medical comorbidities, Patients having known allergy to study drug, Airway abnormalities, Expected difficult intubation, Nasal intubation, Surgeries requiring head and neck manipulations and throat packing. After obtaining institutional board approval, written informed consent was obtained from 80 adult patients undergoing thyroidectomy, mastectomy and other surgeries in which oral intubation required and were placed in two different Groups (40 in each Group)

Group 1: Receives Inj. Fentanyl Citrate 2 mcg/kg;

Group 2: Receives Inj. Fentanyl Citrate 4 mc/kg.

Patients were instructed to remain NBM for at least 8 hours before surgery. Patients were premedicated with Tab. Lorazepam Hydrochloride 1 mg night before surgery and Tab. Diazepam Hydrochloride 5 mg in the early morning on the day of surgery. Anesthetic technique was identical in all the patients.

On arrival in the operation theatre patients were monitored with routine noninvasive blood pressure measurement, pulse oxymetry and ECG, HR, SBP, DBP, MAP were recorded as a baseline vale designated as A.

After securing intravenous line all the patients were given inj. Glycopyrrolate 4 mcg/kg. prior to injection of the study drug HR, SBP, MAP, DBP were recorded and designated as B- preinduction value.

Now, patients in Group 1 received study drug Fentanyl citrate in a dose of 2 mcg/kg and Group 2 received Fentanyl citrate in a dose of 4 mcg/kg (0 minute). Then patients were oxygenated with 100% O_2. At 2 minutes inj. Vecuronium was given. Within its half a minute patients were induced with Inj. Thiopentone Sodium 5 mg/kg. Patients were ventilated for 3 minutes following vecuronium bromide injection. At 5 minutes patients were intubated with cuffed endotracheal tube of appropriate size. Tube was fixed and secured tightly. Anesthesia was maintained with O_2 (50%) + N_2O (50%) + Isoflurane (1%–3%) and intermittent dose of inj. Vecuronium bromide 0.1 mg/kg. Ventilation was controlled mechanically and adjusted to maintain an end tidal CO_2 concentration between 30–40 mm of Hg. All the parameters including heart rate, systolic arterial pressure, diastolic arterial pressure, and mean arterial pressure were recorded at the following intervals:

- Immediately after intubation : E
- 1minute after intubation : E + 1
- 3 minute after intubation : E + 3
- 5 minute after intubation : E + 5
- 10 minute after intubation : E + 10

We had defined following parameters for study:

(1) Hypotension was defined as SBP < 25% of baseline value or 90 mm of Hg, whichever was lower;

(2) Hypertension was defined as SBP >25 % of baseline value or 150 mm of Hg, whichever was greater;

(3) Tachycardia was defined as HR > 25 % of baseline value;

(4) Bradycardia was defined as HR < 60 beats per minute;

(5) An arrhythmia was defined as any ventricular or supraventricular premature beat or any rhythm other then sinus.

Incidences of all these parameters were recorded in all the Groups.

If there was hypotension as per definition then fluid challenge was given. If there was hypertension as per definition isoflurane was started. If there was tachycardia associated with hypotension, fluid challenge was given or if associated with hypertension, then isoflurane was started. If there was bradycardia as per definition, that was treated with injection Atropine sulfate. After 15 minutes, if there was hypotension, isoflurane was shut off; if it remained persistent intravenous fluid challenge was given. If there was hypertension, isoflurane was started or increased in incremental doses, still if persisted, bolus dose of injection Esmolol hydrochloride 0.5–2 mg/kg was given.

Results

The present study, includes 80 adult patients belonging to ASA Group 1 and 2 undergoing thyroidectomy and modified radical mastectomy and surgeries involving oral intubation. They were randomly assigned into Two Groups of 40 each. All the patients were given the drug according to methodology of our study and induced accordingly.

Group 1: Receives Inj. Fentanyl Citrate 2 mcg/kg;

Group 2: Receives Inj. Fentanyl Citrate 4 mc/kg.

There was no significant difference in the parameters mentioned above in both the Groups (Table 1).

Table1: Demographic data: Age, Sex and Weight distribution

Parameters	Group 1 (n = 40)	Group 2 (n = 40)	p - value
Age	44.20 ± 11.84	50.87 ± 11.57	0.0128
Male	14	15	1.0000
Female	26	25	1.0000
Weight	50.45 ± 6.16	52.65 ± 7.93	0.1698
Surgery duration	2.04 ± 0.26	1.94 ± 0.36	0.1584

Table 2 shows, the changes in heart rate in each of the Two Groups during the study. It shows that the heart rate slightly increased during intubation in the Group 1 patients while it was either remained stable or decreased in group 2 patients. However in both the groups stress response found to be attenuated significantly throughout the first ten minutes of intubation. These data indicates that in both the Groups heart rates decreased from the baseline value during the study period. Heart rate found significantly decreased in the Group 2 consistently (Fig. 1).

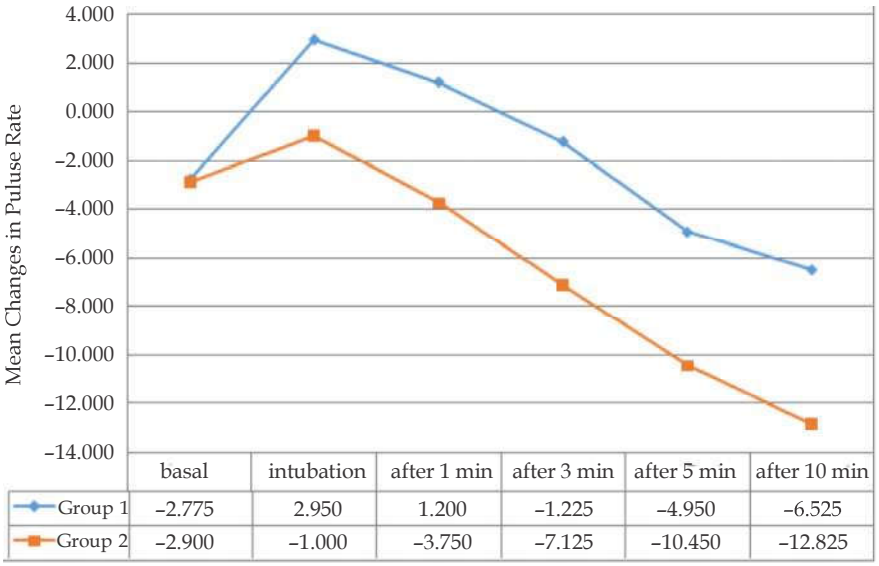


Fig. 1: Changes in Pulse Rate.

Table 2: Mean Heart rate in Two Groups

Time Interval	Group 1 (n = 40)	Group 2 (n = 40)	p - value
Basal(A)	90.42 ± 11.43	87 ± 12.21	0.1992
Preinduction(B)	87.65 ± 13.06	84.05 ± 11.41	0.1932
E	93.37 ± 10.77	86 ± 10.52	0.0027
E + 1	91.62 ± 10.84	83.25 ± 12.86	0.0027
E + 3	89.2 ± 11.38	79.87 ± 13.34	0.0012
E + 5	85.47 ± 10.67	76.55 ± 12.64	0.0010
E + 10	83.9 ± 11.89	74.17 ± 11.64	0.0004

Table 3 shows, the changes in systolic blood pressure during the study period. Looking from the data in the table we can see that there is consistent decrease in SBP in both the Groups from the baseline throughout the study period. Following chart shows SBP in both the groups were decreased below base line and the maximum decrease noted was in Group 2 patients at 10 minutes interval and that is of approximately 29.5 mm of Hg (Fig. 2).

Table 3: Mean SBP in both Groups

Time Interval	Group 1 (n = 40)	Group 2 (n = 40)	p - value
A	131.42 ± 16.03	132.7 ± 12.33	0.6912
B	125.22 ± 16.64	127.42 ± 12.24	0.5025
E	130.87 ± 20.84	122.32 ± 14.39	0.0359
E+1	123.85 ± 16.285	117.3 ± 13.42	0.0532
E+3	118.32 ± 14.24	112.22 ± 14.43	0.0607
E+5	110.47 ± 12.37	105.87 ± 14.54	0.1316
E+10	110.65 ± 14.90	103.2 ± 12.56	0.0180

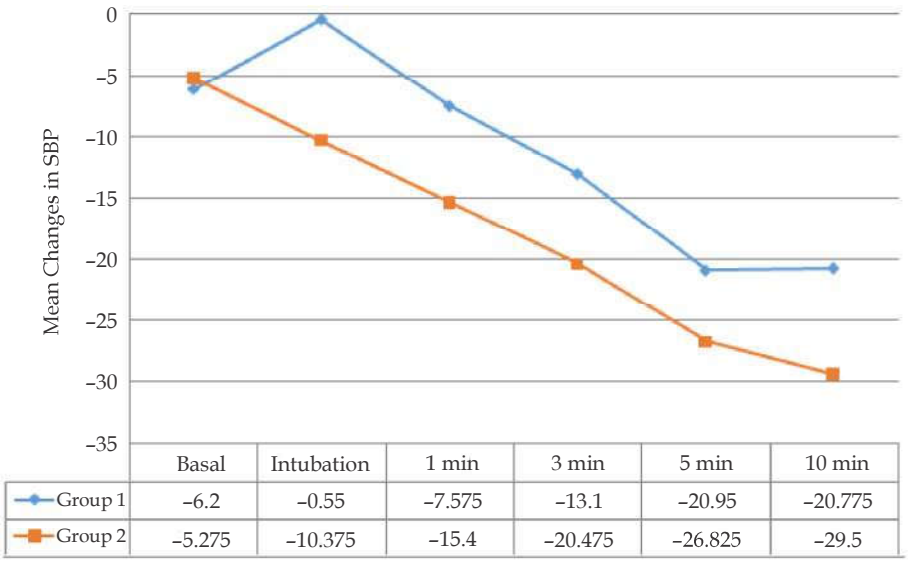


Fig. 2: Changes in SBP.

Table 4 shows, the changes in mean arterial blood pressure during the study period. Looking from the data in the table we can see that there is consistent decrease in MAP in both the Groups from the baseline throughout the study period.

Fig. 3 shows, MAP in both the Groups were decreased below base line and the maximum decrease noted was in Group 2 patients at 10 minutes interval and that is of approximately 20.75 mm of Hg. However, it was transiently increased during the time of intubation in thefirstgroup.

Table 4: Mean MAP in both Groups

Time Interval	Group 1 (n = 40)	Group 2 (n = 40)	p - value
A	96.11 ± 10.57	97.17 ± 8.22	0.6209
B	91.61 ± 10.84	92.97 ± 7.19	0.5123
E	97.64 ± 16.58	91.2 ± 11.41	0.0474
E + 1	93.10 ± 14.19	87.7 ± 10.41	0.0569
E + 3	89 ± 11.76	83.1 ± 10.79	0.0228
E + 5	84.76 ± 10.63	78.8 ± 11.43	0.0187
E + 10	83.51 ± 12.70	76.42 ± 10.42	0.0082

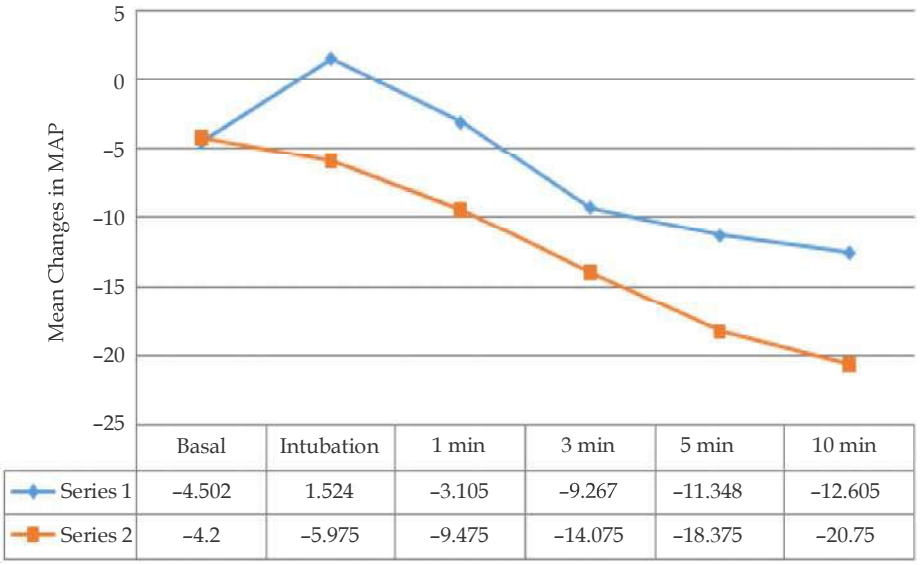


Fig. 3: Changes in MAP.

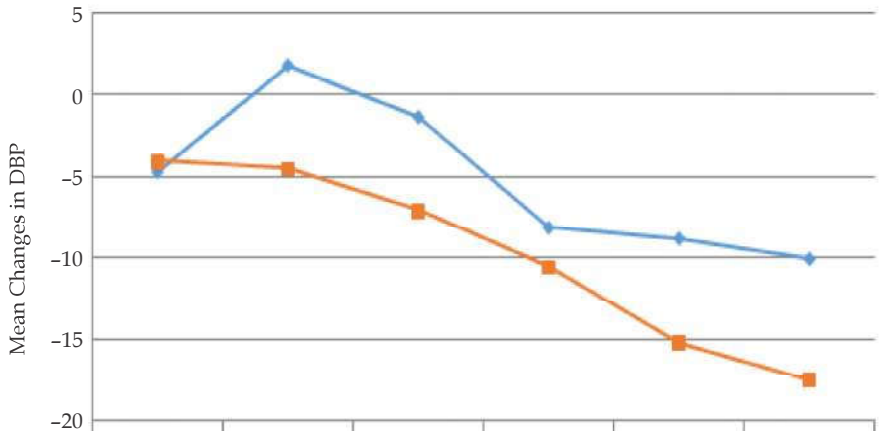
Table 5 shows, the changes in diastolic blood pressure during the study period. Looking from the data in the table we can see that there is consistent decrease in SBP in both the groups from the baseline throughout the study period.

Fig. 4 shows, DBP in both the Groups were decreased below base line and the maximum decrease noted was in Group 2 patients at 10 minutes interval and that is of approximately 17.5 mm of Hg. It was transiently increased during the time of intubation in the first group however.

There are very few adverse drug reactions noted in our patients like only two of our patients in Group 2 had developed hypotension and bradycardia following administration of 4 mcg/kg dose and was treated by infusing crystalloids and inj. Atropine Sulfate for bradycardia 0.6mg. No other side effects have reported in any other patients in both the Groups namely, hypertension or arrhythmias

Table 5: Mean DBP in both Groups

Time Interval	Group 1 (n = 40)	Group 2 (n = 40)	p - value
A	81.9 ± 10.06	82.65 ± 6.90	0.6986
B	77.17 ± 11.76	78.57 ± 6.32	0.5094
E	83.7 ± 14.86	78.12 ± 11.24	0.0622
E + 1	80.52 ± 13.88	75.52 ± 10.32	0.0715
E + 3	73.75 ± 16.06	72.1 ± 9.28	0.5754
E + 5	73.07 ± 9.74	67.45 ± 10.21	0.0137
E + 10	71.82 ± 11.61	65.15 ± 9.71	0.0066



	Basal	Intubation	1 min	3 min	5 min	10 min
Group 1	−4.725	1.8	−1.375	−8.15	−8.825	−10.075
Group 2	−4.075	−4.525	−7.125	−10.55	−15.2	−17.5

Fig. 4: Changes in DBP.

Discussion

The body reacts to external stimuli, ranging from minor to massive insult both locally and generally. The general response is in the form of wide spread endocrinal, metabolic and biochemical reactions throughout the body. The magnitude of response is highly dependent on the severity, intensity and duration of stimulus. For triggering such reflex response and presenting a complex interplay of substances between the hypothalamo and pituitary axis, the classical neuroendocrinal hormone system and autonomic nervous system is brought to action and is called "Stress Response" or "Alarm Reaction".[1]

The stress response leads to secretion of many anabolic and catabolic hormones resulting in hyper metabolism with the acceleration of most of the biochemical reactions. The response plays as a compensatory mechanism and provides maximum chances of survival because of increased cardiovascular functions, fluid preservation and supply of the increased demands for energy generating substances. If the stress response is prolonged, the continuous hyper metabolic state may result in exhaustion of essential components of the body like fat, glucose protein minerals and increase morbidity and mortality sometimes.[1]

Laryngoscopy and intubation result in increased in all the hemodynamic parameters like heart rate, systolic, diastolic and mean blood pressure. To attenuate this response various kind of drugs are in use like beta blockers, calcium channel blockers as well as nitro glycerine, propofol and central sympatholytic drugs such as clonidine, opioids like morphine, fentanyl etc.,[2] Narcotics may block afferent nerve impulses resulting from stimulation of pharynx and larynx during intubation.

It was shown that adequate depth of anesthesia and quick, smooth laryngoscopy is the mainstay for blunting this response. Narcotics have advantage of having perioperative role in anesthesia. They can be used as sole or supplementary agent for induction of anesthesia. Narcotics are very commonly used for intraoperative analgesia; therefore, there is no additional cost involved. Various narcotic drugs like morphine, fentanyl, alfentanil, sufentanil and ramifentanil have been tried for attenuation of pressure response associated with laryngoscopy and ETI.[3–8]

So, we selected the drug fentanyl citrate to attenuate the stress response associated with laryngoscopy and intubation because of its proved analgesic activity. Its duration of action as well as onset of action after intravenous administration are short with respect to other narcotics and so postoperative side effects will be less. Fentanyl citrate is available in our country since 1998 and has various advantages like no histamine release or bronchospasm, cardio stability, rapid onset and short duration of action. So, our study was designed to find out its efficacy for attenuation of pressure response in the dose of 2 mcg/kg and 4 mcg/kg.

In this clinical study, both the Groups were similar with regard to demographic datas, operative procedures & duration. Patients with significant

comorbidities, having known allergy to study drug, Airway abnormalities, expected difficult intubation, Nasal intubation, Surgeries requiring head and neck manipulations and throat packing were excluded because of having greater impact on stress response. There are various studies carried out previously to find out the optimum dose of fentanyl citrate to attenuate the stress response.

Kautto[3] found that supplementation of fentanyl 2 μg/kg significantly attenuated and 6 μg/kg completely abolished the arterial pressure and heart rate increases during laryngoscopy and intubation. In addition, decreased the amount of fentanyl needed during the operation. Respiratory depression was not observed during recovery.

Chung[4] showed that when given two minutes before laryngoscopy, fentanyl 2 μg/kg & 5 μg/kg resulted in 24% and 6% rise in maximum SBP during rapid-sequence induction in healthy patients. Black[5] and Kay[6] found complete attenuation of hemodynamic response with 5 μg/kg fentanyl. Cork[8] found that fentanyl 5 μg/kg reduced norepinephrine rise during rapid-sequence induction of anesthesia. Fentany l 6 μg/kg was found to have a useful place in attenuating the cardiovascular effects of fibre optic intubation under general anesthesia.[9] Martin[10] used thiopental, 3 mg/kg, along with fentanyl, 8 μg/kg, for induction of anesthesia. MAP rise was attenuated compared to plain thiopentone sodium 6 mg/kg Group.

Donald E Martin and Henry Rosenberg[10] found that fentanyl 8 mcg/kg used as an adjuct to thiopental for induction of anesthesia to blunt the circulatory response to tracheal intubation caused fall in SAP, DAP, PCWP. Doses of fentanyl that are low enough to cause little postoperativerespiratory depression significantly blunt postintubation hypertension when used as an adjunct to thiopental. Iyer and Russell[11] studied, 80 patients undergoing coronary artery surgery. Patients received, either 0, 2, 5, 10 or 15 μg/kg of fentanyl. Mean MAP fell at all dose levels after induction, the mean fall being about 30 mm Hg at 5 μg/kg and greater. Mean MAP exceeded preinduction values after intubation with 0 and 2 μg/kg, and progressive attenuation of the MAP rise was found as the dose of fentanyl increased. They concluded that, if a minimal fall in mean MAP after induction with no rise above preinduction MAP is the sole criterion, a fentanyl dose of about 3 μg/kg is recommended. So, in our study, we have taken the dosage of fentanyl citrate in as little to attenuate the stress response at the same time it will not produce any side effects postoperatively. So, we try to compare the efficacy of two different doses of fentanyl citrate that is 2 mcg/kg and 4 mcg/kg and we have found the decrease in all the hemodynamic parameters like HR, SBP, MAP, DBP consistently in all the patients. However, in some patients there was a transient rise in parameters during intubation in Group 1 patients while in Group 2 not a single patient found to have increase in parameters.

Ko[12] designed a study to examine the optimal time of injection of fentanyl. Patients received fentanyl (2 μg/kg) 1, 3, 5, or 10 min before tracheal intubation. They concluded that the most effective time to administer fentanyl to protect circulatory responses to laryngoscopy and tracheal intubation is 5 min before tracheal intubation. Fentanyl is often used to reduce the hemodynamic response to tracheal intubation. However, large doses may cause unwanted side effects. Administration of fentanyl at the optimal time reduces the dose required.[13,14,15] So, in our study we administered fentanyl citrate at 5 minutes before intubation and we got the maximum response.

JE Smith[9] studied the effect of fentanyl on the circulatory responses to orotrachealfiberoptic intubation and found that fentanyl 6 mcg/kg suppresses the hypertensive response to fiberopticintubation as effectively as it does to mcintosh intubation. It also attenuates tachycardia associated with intubation.[16–18] So, fentanyl 6 mcg/kg can be recommended as a simple and effective method of minimising the cardiovascular disturbances produced by orotrachealfiberopticintubation under general anesthesia.[19,20]

TE Black[5] had done had done a comparative study between alfentanyl and fentanyl in reducing the hemodynamic responses to tracheal intubation and laryngoscopy and conclude that alfentanyl in low-doses can be used as a supplement during induction to prevent the rise in blood pressure and heart rate associated with laryngoscopy and intubation. The use of fentanyl 5 mcg/kg or alfentanyl 15 mcg/kg were equally effective in preventing a rise in blood pressure but 30 mcg/kg of alfentanyl was required to prevent an increase in heart rate.[21,22] The apparent duration of effect of the induction combination was significantly shorter when using alfentanyl rather than fentanyl.

In our study, we had given the two dose of fentanyl citrate and compared the effects of both the doses in attenuation of hemodynamic responses. We found out that fentanyl citrate decreases the hemodynamic parameters sufficiently and prevent

any rise in parameters if given in sufficient doses and at optimum time interval

In our study, we have found out that in Group 1 who received the 2 mcg/kg dose shows some increase in hemodynamic parameters during intubation and it again came back to below baseline 1 minute after intubation. However, in Group 2 patients who received 4 mcg/kg dose did not show any rise in hemodynamic parameters and were continuously below base line throughout study period.

We follow our patients for 10 minutes after intubation and found out the mean decrease in heart rate in Group 1 is 7.77% while in Group 2 its 14%. In Group 1 there was transient rise in heart rate of approximately 3% and then start to decline after 1 minute. The decrease in heart rate was found to be 1% at 1min, 5% at 5 min and maximum 7% at 10 minutes in Group 1 patients. While in Group2 patients decrease in heart rate was sustained and in was 4% at 1 min, 8% at 3 min, 10% at 5 min and maximum at 14% at 10 minutes.[23–25]

Decrease in SBP was sustained throughout these 10 minutes. That is 5% at 1min, 15% at 5 min and 10 minutes as well in Group 1 patients while in Group 2 patients the decrease in SBP.was 11% at 1 min, 19% at 5 min and 21% at 10 minutes. Decrease in DBP was also sustained after initial rise during intubation in Group 1 patients. The maximum decrease in DBP noted was 12% in Group 1 and 20% in Group 2 patients. Decrease in MAP was also sustained in both the Groups and maximum decrease fond at 10^{th} minutes was around 12% in Group 1 and 20% in Group 2 patients. The rate pressure product which is a measure of myocardial oxygen demand was decrease upto 20% in Group 1 and approximately 34% in Group 2 patients. No evidence of any myocardial insult was seen in any of the patients in any Group in our study except two patients showing transient hypotension and bradycardia in Group 2. None of our patients demonstrate the side effect postoperatively.

Conclusion

From our study we conclude that:

- Fentanyl citrate given 5 minutes before intubation produces most attenuation of the hemodynamic effects of stress response.
- Pretreatment with fentanyl citrate in every normal case would cause attenuation of hemodynamic effects of laryngoscopy and intubation. It will cause minimal change in heart rate, SBP, DBP, MAP, RPP during the first 10 minutes after intubation.
- Fentanyl citrate given in dose of 2 mcg/kg resulted in attenuation of response to laryngoscopy and intubation but transient rise in heart rate and blood pressure were noted in this group at the time of intubation. However, thereafter it successfully decreases the hemodynamic parameters.
- Fentanyl citrate given in dose of 4 mcg/kg resulted in complete attenuation of hemodynamic response during laryngoscopy and intubation and none of the recording were above baseline after intubation. So, 4 mcg/kg dose is more suitable and more effeicient in attenuating the stress response during intubation.
- None of our patients had any side effects postoperatively like chest wall rigidity, hypotension, bradycardia, arrhythmia and respiratory depression except for the two patients in Group 2 who developed bradycardia and hypotension transiently.
- So, fentanyl citrate in 2 mcg/kg significantly attenuate but fentanyl 4 mcg/kg completely attenuates the hemodynamic responses during laryngoscopy and intubation.

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