Journal of Pharmaceutical Research International

33(60A): 541-551, 2021; Article no.JPRI.81349
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Comparative Study of Safety and Efficacy of Three Different Doses of Fentanyl on Hemodynamic Response to Laryngoscopy and Tracheal Intubation in Patients under General Anaesthesia

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i60A34517

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/81349

Original Research Article

Received 15 October 2021
Accepted 18 December 2021
Published 20 December 2021

ABSTRACT

Aim of Study: Laryngoscopy and endotracheal intubation are the commonest method for securing a definitive airway for general anaesthesia. It is one of the most invasive and painful stimuli in anaesthesia producing clinically relevant changes in the hemodynamic variables.
This study has been designed to compare the safety and efficacy of three different doses of fentanyl (2µg/kg, 3µg/kg and 4µg/kg) in attenuating hemodynamic response, following laryngoscopy and endotracheal intubation.
Materials and Methods: In this observational study, three groups of 90 patients belonging to ASA grade I and II, aged between 18 to 65
years, including either gender, posted for elective surgery under GA with informed consent. Baseline vital hemodynamic parameters and the serial heart rate, arterial pressures, SpO2 and respiratory rate were noted at five minutes after intravenous fentanyl administration, during laryngoscopy & intubation and at 1-, 3-, 5-, 10- and 20-minutes after laryngoscopy. Ramsay

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sedation scores were also noted at five minutes after intravenous fentanyl administration, during extubation and at 10-, 20- and 30-minutes after extubation.
Results: There was substantial difference in mean HR, SBP, DBP & MAP values post 5 minutes after intravenous fentanyl administration, during laryngoscopy, at 1, 3-, 5-, 10- and 20-minutes following laryngoscopy and intubation between the three groups. Patients' behaviour belonging to group C (IV fentanyl 4µg/kg), followed by the patients of group B (IV fentanyl 3µg/kg) presented considerable amount of attenuation of all the hemodynamic stress parameters effectively, with statistically significant results when compared to group A (IV fentanyl 2µg/kg).
Conclusion: Intravenous fentanyl 4µg/kg and 3µg/kg are better at attenuating the laryngo-tracheal stress response, in comparison to intravenous fentanyl 2µg/kg.

Keywords: Fentanyl; hemodynamic response; laryngoscopy; endotracheal intubation.

1. INTRODUCTION

Laryngoscopy and endotracheal intubation are considered as strong noxious stimuli, producing clinically relevant changes in hemodynamic variables such as tachycardia and hypertension, most commonly [1-3]. This hemodynamic response is precipitated via a sympathoadrenal stimulation. Sympathetic stimulation leading to raised plasma catecholamine levels during the act of laryngo-tracheal manipulation has been advocated as the major cause for this hemodynamic response [4]. It is short-lived, occurring 30 seconds after starting laryngoscopy and lasting for less than 10-15 minutes. Often well tolerated by healthy individuals but can be detrimental to individuals with cardiopulmonary compromised conditions.

Various studies carried out with different analgesic doses of fentanyl, ranging from 1.5µg/kg to 8µg/kg, presented with equally varying results for attenuating the hemodynamic response to laryngoscopy and tracheal intubation [5-8]. Though higher dose of fentanyl is known to be associated with pruritis, nausea and vomiting, hypotension, postoperative somnolence, respiratory depression and chest rigidity.

Over the years various modalities of pharmacological and non-pharmacological methods have been devised in order to attenuate this physiological response. Our study is an endeavour to compare the safety and efficacy of three different dosage of fentanyl (2µg/kg, 3µg/kg and 4µg/kg) in attenuating hemodynamic response, oxygen saturation (SpO2) and respiratory rate (RR) following laryngoscopy and endotracheal intubation.

2. MATERIALS AND METHODS

After detailed pre-anesthetic evaluation, routine and specific investigation, each patient was informed regarding the nature and purpose of the study. Preoperative adequate fasting hours (6–8 hrs) were confirmed. Patients were prepared by securing 20 G intravenous (IV) cannula, applying basic monitoring like pulse oximetry, non-invasive blood pressure and standard 3-lead electrocardiography (ECG). The patients were randomized into three groups using the equal group random allocation method. Baseline vital parameters such as systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP), SPO2 and respiratory rate will be recorded (baseline).

Patients were pre-medicated with Inj. Glycopyrrolate 0.2mg I.V, Inj. Midazolam 1mg I.V., followed by Inj. Fentanyl as per the following groups:

Group A: Inj. Fentanyl 2mcg/kg diluted up to 10ml with NS IV given 5 minutes prior to intubation.
Group B: Inj. Fentanyl 3mcg/kg diluted up to 10ml with NS IV given 5 minutes prior to intubation.
Group C: Inj. Fentanyl 4mcg/kg diluted up to 10ml with NS IV given 5 minutes prior to intubation.

All patients were induced with propofol 2 mg/kg IV, followed by Inj. succinylcholine 2mg/kg. After an interval of one minute, laryngoscopy and intubation were performed. Inj. vecuronium bromide 0.1mg/kg IV was given to all patients.

All hemodynamic measurements like HR, SBP, DBP, MAP, SpO2 & RR were recorded at baseline, 5 minutes after intravenous fentanyl, during laryngoscopy & intubation, 1 minute, 3 minutes, 5 minutes, 10 minutes & 20 minutes after intubation.

Furthermore, the patient was maintained on O2 /N2O / Isoflurane or Sevoflurane and intravenous

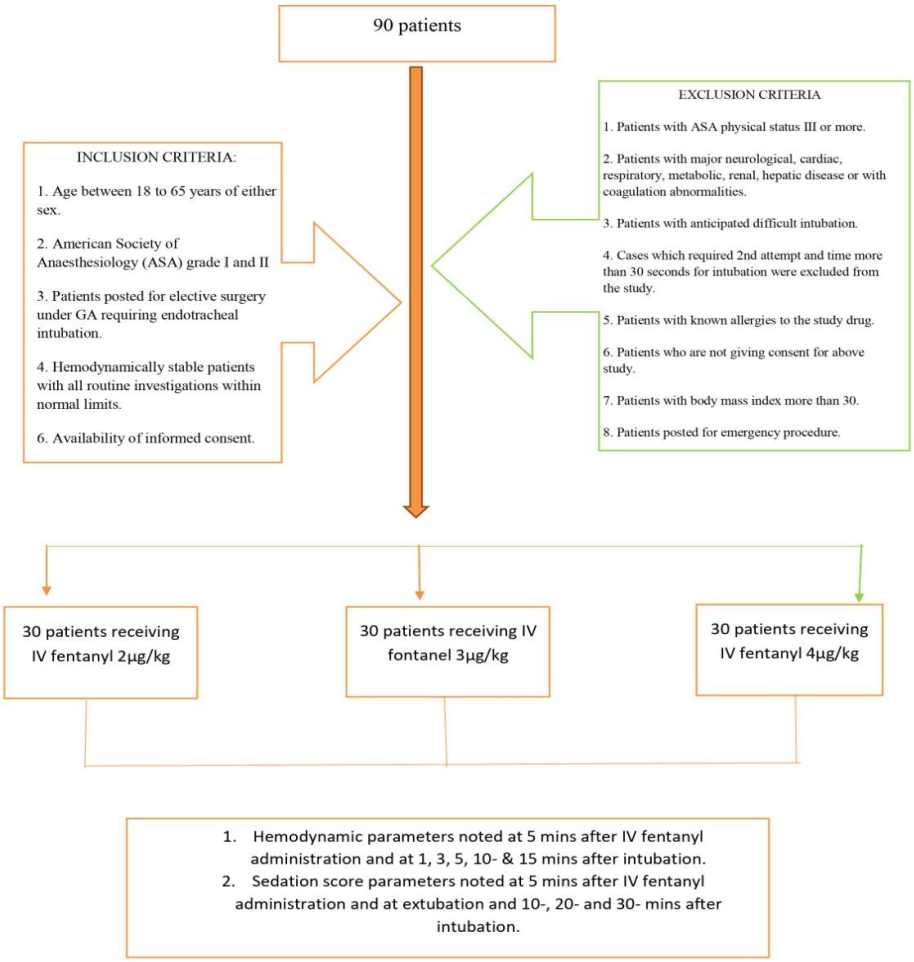

Fig. A. Flowchart shows how Institute Ethics Committee Clearance was obtained before start of study

vecuronium increments were given as and when required, and patients' vitals were monitored continuously intra-operatively.

Sedation score was noted at the time of extubation. Then patient will be shifted to recovery room and sedation score was again be noted at 10, 20 and 30 minutes after extubation

Sedation score is denoted as per the Ramsay sedation assessment scale.

The patients were also monitored for any adverse effects of the drugs.

2.1 Statistical Data

The one-way analysis of variance (ANOVA) was used to determine whether there are any statistically significant differences between the means of the three independent groups.

Chi-square test was used to test whether distributions of categorical variables differ from each other. P value was considered as significant if less than 0.05 at 95% confidence interval.

3. RESULTS

The demographic profile was comparable in all three groups.

Table 1 shows Demographic profiles in both the three groups were found to be comparable, with any statistical significance.

Table 2 shows Baseline values of the basic hemodynamic parameters.

There was no statistically significant difference between the study groups with respect to their baseline values for the parameters of heart rate (HR), systolic blood pressure (SBP), diastolic

blood pressure (DBP), mean arterial pressure (MAP), SpO2 and respiratory rate (RR).

There was substantial difference in mean HR, SBP, DBP & MAP values post 5 minutes after intravenous fentanyl administration, during laryngoscopy, as well as at 1, 3-, 5-, 10- and 20-minutes following laryngoscopy and intubation between the three groups.

Table 3 shows HR, SBP, DBP & MAP values post fentanyl injection & during laryngo-tracheal manipulation.

Fig. 1. depicts change in heart rate pre- and post-fentanyl injection & during laryngo-tracheal manipulation.

Fig. 2. depicts change in SBP, DBP & MAP pre- and post-fentanyl injection & during laryngo-tracheal manipulation.

Table 4 shows HR, SBP, DBP & MAP values at 1-, 3-, 5-, 10- and 20-minutes after endotracheal intubation.

Five minutes after intravenous fentanyl administration there is a fall in HR from the baseline values in all three groups, showing a 6.28% decrease in group A and 6.34% decrease in group B, in comparison to 17.84% fall in HR from baseline in group C. But during laryngoscopy and endotracheal intubation, there was 2.94% increase in mean HR from the baseline values in group A, but the mean HR remains settled without any significant increase in group B and group C.

In the SBP, DBP and MAP values recorded for 5 minutes after intravenous fentanyl administration there is a fall in blood pressure from the baseline values in all three groups. There was a 5.00 % decrease in group A and 7.24 % decrease in group B, in comparison to a 19.95 % fall in SBP from baseline values in group C.

Mean DBP five minutes after fentanyl administration showed a 1.11% decrease in group A, a 4.65 % decrease in group B in comparison to 29.85 % fall in DBP from baseline in group C. Also, in the values recorded for 5 minutes after intravenous fentanyl administration the mean MAP values, depicting a 2.52 % decrease in group A, 5.54 % decrease in group B and 25.26% decrease in group C from mean baseline values.

During laryngoscopy and endotracheal intubation, there was 2.94% increase in mean HR from the baseline values in group A, but the mean HR remains settled without any significant increase in group B and group C. Similarly, we see a marked increase in blood pressures values in group A, 10.23% increase in SBP, 7.58% increase in DBP and 8.74 % increase in MAP form their respective baseline values during laryngoscopy and tracheal intubation, unlike in group B and group C.

Post-intubation in group A, 1-, 3-, 5-, 10- and 20-minute we see a steady rise in mean blood pressures (SBP, DBP and MAP) from the baseline values, which is not seen in group B and group C.

Hence patients belonging to group C showed considerable amount of attenuation of all the hemodynamic stress parameters effectively, with statistically significant values when compared to other groups.

Table 5 shows Ramsay Sedation Score after fentanyl administration, during extubation and 10-, 20-, and 30-minutes after extubation.

Fig. 3. depicts ramsay sedation score after fentanyl administration, during extubation and 10-, 20-, and 30-minutes after extubation.

Ramsay sedation assessment score post 5 minutes of intravenous fentanyl administration was taken as the baseline value and the recorded mean for group A were 1.80 ± 0.71, group B 2.63 ± 0.67 and group C 2.73 ± 0.45 respectively, was found to be statistically significant.

Post-extubation and at 10-, 20- and 30-minute post-extubation, the average sedation score in group A and group B was 2. Whereas in group C, immediately post-extubation average sedation score was 3, which gradually decreased over the course of 10-, 20- and 30-minutes to an average score of 2.

Total two patients, one each from group B and group C complained of nausea. In group C, two patients had complaints of somnolence. However, the side effects observed were minimal and not statistically significant.

Table 1. Demographic profile of the three groups

Parameter		Group A	Group B	Group C	P value	Inference
Age (years)		40.47 ± 13.28	38.73 ±15.61	38.30 ±14.84	0.6437	Not significant
Weight (kg)		60.53 ± 12.20	58.73 ±11.35	58.73 ±11.61	0.5564	Not significant
Gender	Male	16 (53.33)	19 (63.33)	15 (50.00)		
	Female	14 (46.67)	11 (36.67)	15 (50.00)	0.4321	Not significant
	I	15 (50.00)	14 (46.67)	18 (60.00)		
ASA	II	15 (50.00)	16 (53.33)	12 (40.00)	>0.9999	Not significant

This table depicts the mean distribution of the basic demographic profiles of the three studygroups, which were found to have no significant statistical differences

Table 2. Baseline values of the basic hemodynamic parameters (HR, SBP, DBP, MAP, RRand SpO_2) for all three groups

Parameters (baseline)	Group A	Group B	Group C	P value
Heart rate (beats/min)	82.77 ± 12.70	87.73 ± 15.14	80.37 ± 12.59	0.1053
Systolic blood pressure (mm of Hg)	122.50 ± 12.38	121.17 ± 13.67	122.83 ± 12.42	0.8690
Diastolic blood pressure (mm of Hg)	78.20 ± 9.90	76.53 ± 10.41	76.93 ± 8.74	0.7855
Mean arterial blood pressure (mm of Hg)	92.97 ± 9.53	91.01 ± 10.22	92.32 ± 8.81	0.7207

This table depicts the mean distribution of the baseline hemodynamic parameters of the threestudy groups, which were found to have no significant statistical differences

Table 3. HR, SBP, DBP & MAP values post fentanyl injection & during laryngo-trachealmanipulation

Parameters		Group A	Group B	Group C	P value
Heart rate	5 mins after fentanyladministration	77.57 ± 10.69	82.17 ± 16.93	66.03 ± 8.95	0.0001*
(Beats/min)	During laryngoscopy &intubation	85.20 ± 10.94	85.23 ± 15.53	77.43 ± 9.46	0.0210*
SBP (mm of Hg)	5 mins after fentanyl administration	116.37 ± 12.21	112.40 ± 14.46	98.33 ± 7.12	0.0000*
	During laryngoscopy & intubation	135.03 ± 9.35	120.00 ±17.18	114.23 ± 9.84	0.0000*
DBP (mmof Hg)	5 mins after fentanyladministration	77.33 ± 8.30	72.97 ± 11.77	53.97 ± 4.63	0.0000*
	During laryngoscopy &intubation	84.13 ± 5.85	77.00 ± 10.93	73.13 ± 8.41	0.00001*
MAP (mmof Hg)	5 mins after fentanyladministration	90.63 ± 8.09	85.97 ± 11.57	69.00 ± 4.62	0.0000*
	During laryngoscopy &intubation	101.10 ± 6.01	90.69 ± 12.23	86.82 ± 7.93	0.0000*

This table depicts the mean distribution of the basic demographic profiles of the three study groups five minutes after I.V. Fentanyl administration, which showed statistically significantblunting of hemodynamic parameters like HR, SBP, DBP and MAP in all three groups, withthe decrease in these parameters being more prominent in group B and C in comparison to group A

Table 4. HR, SBP, DBP & MAP values at 1-, 3-, 5-, 10- and 20-minutes after endotrachealintubation

Parameters		Group A	Group B	Group C	P value
Heart rate (beats/min)	1 minute	79.47 ± 9.95	85.70 ± 17.00	72.57 ± 8.20	**0.0004***
	3 minutes	79.60 ± 9.60	85.57 ± 14.10	73.77 ± 7.87	**0.0003***
	5 minutes	81.07 ± 12.72	86.17 ± 14.48	73.53 ± 5.49	**0.0002***
	10 minutes	82.57 ± 13.51	84.63 ± 12.02	75.23 ± 8.44	**0.0055***
	20 minutes	84.47 ± 9.16	85.03 ± 12.43	75.33 ± 8.18	**0.0003***
SBP (mm ofHg)	1 minute	129.50 ± 8.18	118.30 ± 15.75	117.20 ± 12.72	**0.0003***
	3 minutes	128.13 ± 7.76	113.47 ± 17.41	116.80 ± 12.95	**0.0001***
	5 minutes	126.63 ± 7.54	114.30 ± 17.08	117.13 ± 15.37	**0.0025***
	10 minutes	126.13 ± 7.26	116.43 ± 14.85	115.70 ± 15.15	**0.0034***
	20 minutes	125.90 ± 10.17	116.80 ± 12.67	116.00 ± 10.89	**0.0013***
DBP (mmof Hg)	1 minute	79.77 ± 5.61	74.20 ± 10.23	74.07 ± 10.12	**0.0218***
	3 minutes	78.20 ± 5.52	71.67 ± 10.03	69.73 ± 7.31	**0.0001***
	5 minutes	77.13 ± 5.49	72.67 ± 9.90	70.33 ± 4.87	**0.0014***
	10 minutes	76.10 ± 5.05	72.80 ± 9.13	69.80 ± 5.31	**0.0022***
	20 minutes	79.47 ± 5.77	75.53 ± 10.47	69.53 ± 6.19	**0.00001***
MAP (mmof Hg)	1 minute	96.33 ± 5.64	88.40 ± 11.79	88.43 ± 9.67	**0.0013***
	3 minutes	94.82 ± 5.67	85.47 ± 12.09	85.56 ± 7.41	**0.00004***
	5 minutes	93.24 ± 6.32	86.34 ± 10.96	85.09 ± 7.47	**0.0006***
	10 minutes	93.03 ± 5.43	87.04 ± 10.10	85.53 ± 7.17	**0.0008***
	20 minutes	94.94 ± 6.92	89.09 ± 11.20	84.66 ± 5.99	**0.00003***

This table depicts the mean distribution of the basic demographic profiles of the three studygroups during laryngoscopy and intubation and after 1-, 3-, 5-, 10- & 20-minutes after intubation, which showed statistically significant rise of hemodynamic parameters like HR, SBP, DBP and MAP in group A in comparison to minimal or no raise in HR, SBP, DBP andMAP in group B and C respectively

Table 5. Ramsay Sedation Score at 5 minutes after fentanyl administration, during extubationand 10-, 20-, and 30-minutes after extubation

Sedation score		Fentanyl 2mcg (Group A)	Fentanyl 3mcg (Group B)	Fentanyl 4mcg (Group C)	p value
		Mean ± SD	Mean ± SD	Mean ± SD	
5 min after fentanyl(pre induction value)		1.80 ± 0.71	2.63 ± 0.67	2.73 ± 0.45	0.0000*
During extubation		2.47 ± 0.51	2.40 ± 0.62	3.00 ± 0.00	0.0000*
After extubation (min)	10	2.10 ± 0.31	2.37 ± 0.49	2.37 ± 0.49	0.0262*
	20	2.00 ± 0.00	2.20 ± 0.41	2.00 ± 0.00	0.0013*
	30	2.00 ± 0.00	2.03 ± 0.18	2.00 ± 0.00	0.4380

This table depicts the ramsay sedation score of the three study groups five minutes after I.V.Fentanyl administration, at the time of extubation and at 10-, 20-minutes after extubation, which showed statistically significant sedation scores in the group C followed by group B &A. Whereas sedation scores for all three groups at 30-minutes post extubation was not statistically significant

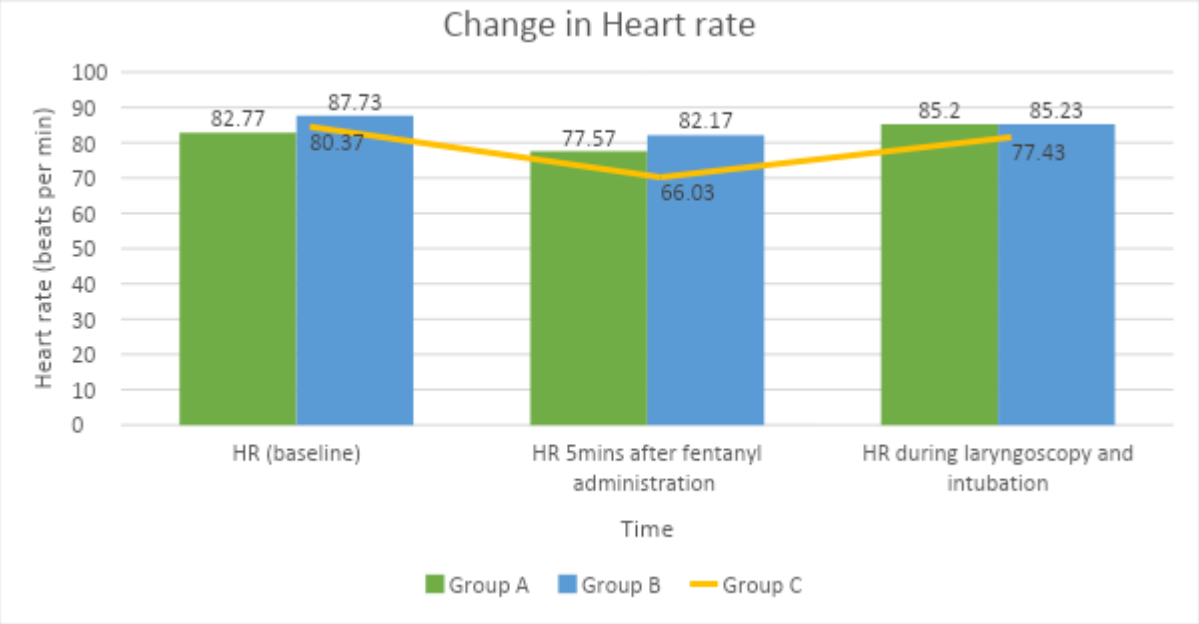

Fig. 1. Graph showing change in heart rate pre- and post-fentanyl injection & during laryngo-tracheal manipulation

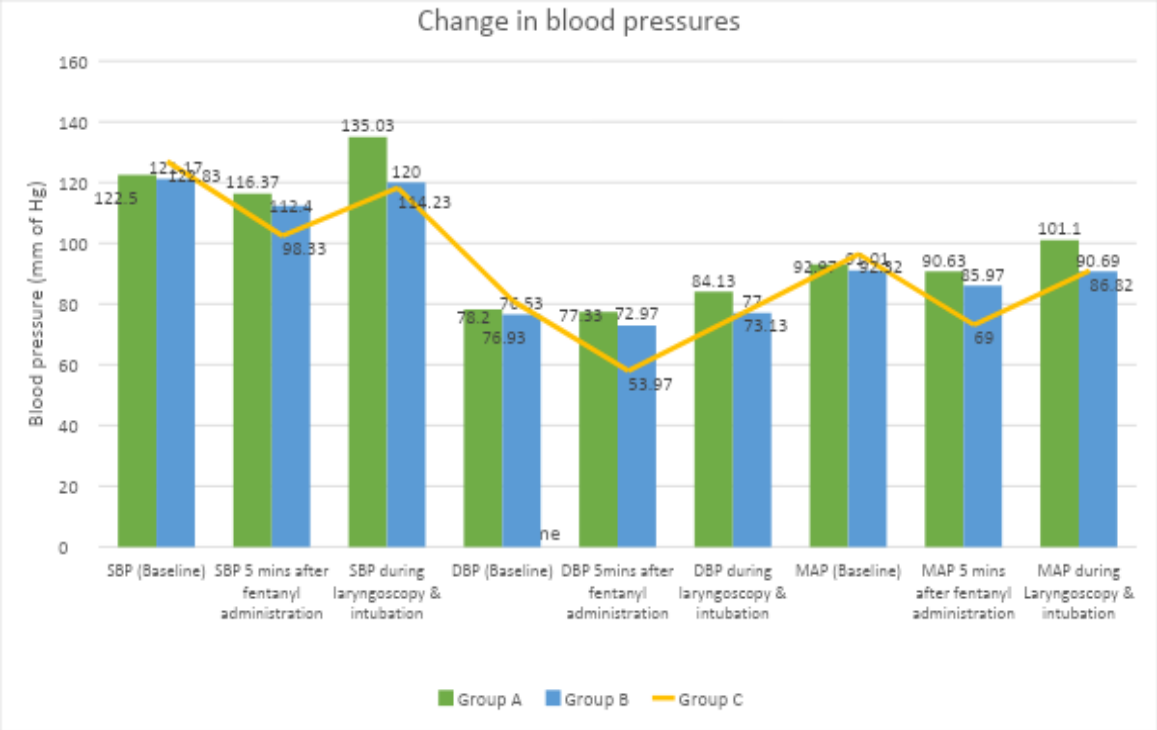

Fig. 2. Graph showing change in SBP, DBP & MAP pre- and post-fentanyl injection & during laryngo-tracheal manipulation

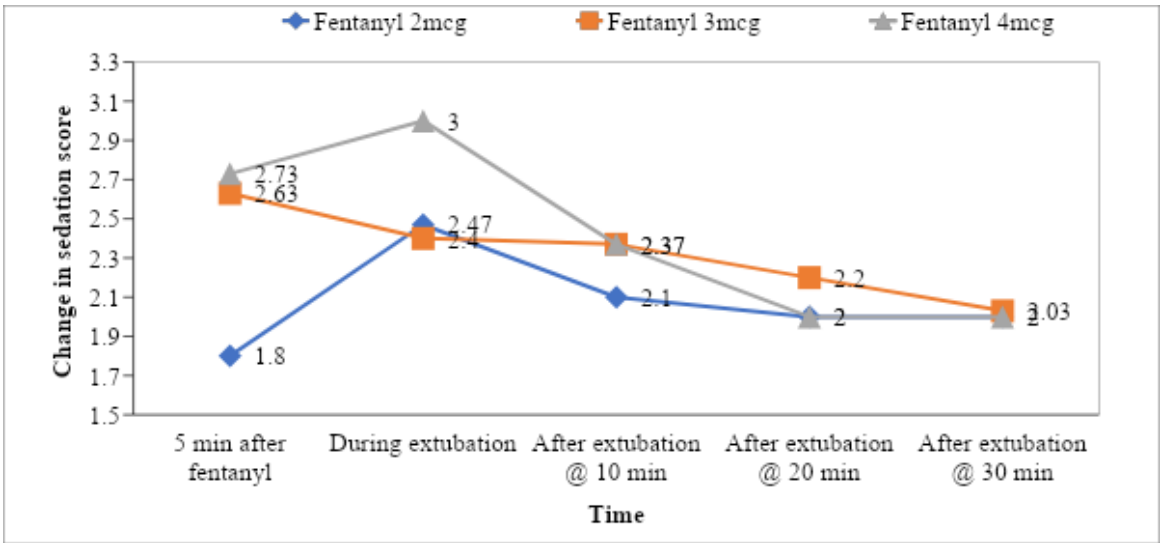

Fig. 3. Graph showing ramsay sedation score after fentanyl administration, during extubation and 10-, 20-, and 30-minutes after extubation

4. DISCUSSION

The act of laryngoscopy and endotracheal intubation are painfully potent stimuli and therefore presents a period of extreme hemodynamic stress, which is associated with increased sympathetic activity clinically manifesting as tachycardia and hypertension. Such sympathoadrenal stimulation may precipitate left ventricular failure, myocardial ischemia, cerebral haemorrhage, especially in patients of coronary or cerebral atherosclerosis, or hypertension and even convulsions.

Till date a variety of pharmacological as well as non-pharmacological methods have been

utilised, with varying degrees of success, in order to attenuate or blunt this hemodynamic pressor response, without a definitive answer.

Fentanyl is administered as a premedication to attenuate the laryngo-tracheal pressor responses. It causes an increase in parasympathetic tone and decreased sympathetic tone [9]. Multiple studies have suggested that fentanyl acts mainly on two receptors- i.e., opioid receptors and μ receptors. Intravenous administration of fentanyl 5 minutes prior to laryngoscopy and intubation is considered as the optimal time to produce effective attenuation of the pressor response [10].

This act of blunting the sympathoadrenal response with fentanyl is found to be dose dependent. Administration of fentanyl 2μg/kg only significantly reduces the physiological hemodynamic response to laryngoscopy and endotracheal intubation, whereas fentanyl 6μg/kg, completely abolishes the pressor response as per the studies carried out by Splinter WM et al [11].

In each group, 30 patients were selected after considering the inclusion and exclusion criterions. Patients in all three groups did not show any significant statistical differences with respect to age, gender and ASA- grade distribution. In our study, the baseline values (prior to fentanyl administration) of HR, arterial blood pressures were comparable in all three groups i.e., p value was not statistically relevant.

Five minutes following intravenous fentanyl administration there is a significant fall in HR, SBP, DBP and MAP, noted in all three groups.

However, 2.94% increase mean HR is seen in group A during laryngo-tracheal manipulation, followed by a steady increase in the HR values post intubation at 1-, 3-, 5-, 10- and 20-minutes by a 2.05% rise above the baseline values, which too proved to be statistically significant, as no such comparative increase was noted in group B and group C.

V. Iyer et al [12] in 1988 had concluded in their study with four different doses of fentanyl, 2 μg/kg, 5 μg/kg, 10 μg/kg and 15 μg/kg, that for attenuation of the stress response to tracheal intubation, that fentanyl dose 5 μg/kg and greater, produced minimal to no increase in the mean HR and blood pressure values.

In a similar study conducted by Splinter WM et al [11] in 1989, comparing stress responses to laryngoscopy and endotracheal intubation with intravenous fentanyl, they too noted that 2μg/kg fentanyl only attenuates the heart rate and arterial pressures by very small margin with subsequent increase during laryngoscopy and intubation.

In the SBP, DBP and MAP values recorded for 5 minutes after intravenous fentanyl administration there is a fall in blood pressure from the baseline values in all three groups. However, we see a marked increase in blood pressures values in group A, 10.23% increase in SBP, 7.58% increase in DBP and 8.74 % increase in MAP form their respective baseline values during laryngoscopy and tracheal intubation, unlike in group B and group C.

Post-intubation in group A, 1-, 3-, 5-, 10- and 20-minutes we see a steady rise in mean blood pressures (SBP, DBP and MAP) from the baseline values, which is not seen in group B and group C.

A study conducted by S Vijayaragavan et al [13] to assess the effect of IV fentanyl 2μg/kg and 5μg/kg for suppression of the hemodynamic pressor response during induction and intubation. They concluded that at a dose of fentanyl 5 μg/kg attenuated the pressor response to intubation.

A.S. Karande et al [14] conducted a study to compare the effectiveness of 2μg/kg fentanyl and 3 μg/kg fentanyl, administered prior to laryngo-tracheal manipulation in order to blunt the hemodynamic stress response. No significant rise in mean SBP values was seen during laryngo-tracheal manipulation, as well as post intubation following administration of 3μg/kg fentanyl.

A study conducted by Kumar M & Tripathi DC et al [3] in 2017 to clinically evaluate the efficacy of three different dosages of fentanyl 2μg/kg, 3μg/kg and 4μg/kg to suppress the laryngo-tracheal pressor response. They found that fentanyl 3μg/kg is the most adequate dose suppressing the stress response during laryngo-tracheal manipulation.

Ramsay sedation assessment score recorded post 5 minutes of intravenous fentanyl administration was taken as the baseline value and the recorded mean for group A were 1.80 ±

0.71, group B 2.63 ± 0.67 and group C 2.73 ± 0.45 respectively, was found to be statistically significant. Post-extubation and at 10-, 20- and 30-minute post-extubation, the average sedation score in group A and group B was 2. Whereas in group C, immediately post-extubation average sedation score was 3, which gradually decreased over the course of 10-, 20- and 30-minutes to an average score of 2.

Our study results also showed in similar results as the study conducted by Jean-Marc Bernard et al [15] on the pharmacokinetics of intravenous fentanyl, with regards to blood pressure, plasma clearance, elimination rate of fentanyl along with associated hypotension, opioid associated respiratory depression, nausea vomiting and dose-dependent sedation. According to the sedation scale used in the study (2 = arousal by verbal stimuli for more than 20 s; 3 = arousal by verbal stimuli for less than 20 s), the no significant differences was seen in the sedation scores between the fentanyl 3µg/kg group and the clonidine-fentanyl group (2.3 ± 0.2 and 2.4 ± 0.2 respectively).

One patient from group B and group C had complains of postoperative nausea, which subsided following administration of inj. Ondansetron 4mg IV. In group C, two patients had developed opioid induced somnolence and were observed in PACU (Post-operative Anaesthesia Care Unit) for 2-3 hours postoperatively. They were shifted to their respective wards post 3 hours observation in PACU.

No incidence of chest rigidity or respiratory depression was reported from any of the groups during the study. All the side effects observed and documented were also not statistically relevant.

The major drawback of our study is that we did not test stress mediators involved during the pressor response period. The catecholamine release in response to the noxious stimuli of laryngoscopy and intubation is considered to be in highest amount in central venous samples in comparison to peripheral venous or arterial samples. However, as our study was conducted in ASA I & II patients undergoing moderate duration surgeries lasting for1-3 hours, we therefore refrained from central venous catheterization insertion in our patients, as it is known to be non-ethical in non-supra-major surgeries.

Also, as our study group comprised of ASA I and II grade patients with ages ranging from 18-65 years undergoing non cardiac surgeries. So, this study doesn't include the effects of the various dosage of fentanyl on geriatric patients and patients with compromised cardiac function. Hence, we can suggest further studies to overcome the above stated limitations to recommend its use in such high-risk patients.

5. CONCLUSION

Based on the current clinical study, intravenous fentanyl 4µg/kg and 3µg/kg are better at attenuating the laryngo-tracheal stress response, in comparison to intravenous fentanyl 2µg/kg. We can hence, reasonably conclude that higher dosage of fentanyl can be used safely to acquire maximum obtundation of the laryngo-tracheal pressor response for a reasonable duration without any significant opioid associated side effects.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

As per international standard or university standard, respondents' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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