Original Research Article

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

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 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**.**

INTRODUCTION:

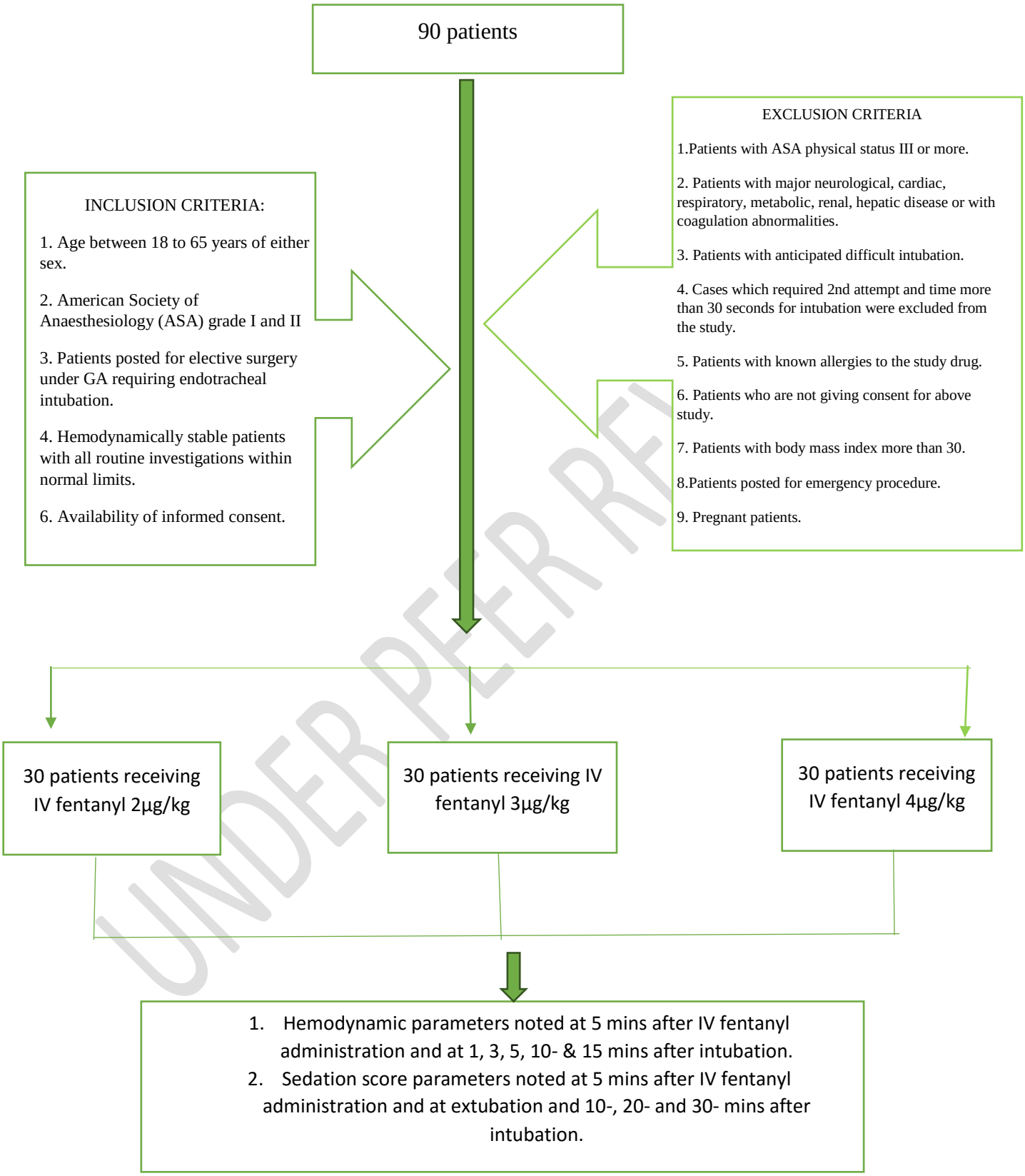
Laryngoscopy and endotracheal intubation are considered as strong noxious stimuli, producing clinically relevant changes in hemodynamic variables such as tachycardia and hypertension, most commonly.[1,2,3] This hemodynamic response is precipitated via a sympathoadrenal stimulation. Sympathetic stimulation 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 equally varying results for attenuating the hemodynamic response to laryngoscopy and tracheal intubation.[5,6,7,8] 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.

MATERIALS AND METHODS

Chart 1: Institute Ethics Committee Clearance was obtained before start of study.



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 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.

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.

RESULTS:

The demographic profile was comparable in all three groups.

<insert> Table 1: Demographic profile of the three groups. (Refer to Legends for tables, after references)

Demographic profile in both the three groups were found to be comparable, with any statistical significance.

<insert> Table 2: Baseline values of the basic hemodynamic parameters. (Refer to Legends for tables, after references)

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.

<insert> Table 3: HR, SBP, DBP & MAP values post fentanyl injection & during laryngo-tracheal manipulation. (Refer to Legends for tables, after references)

<insert> Fig 1: Graph showing change in heart rate pre- and post-fentanyl injection & during laryngo-tracheal manipulation. (Refer to Legends for figures, after references)

<insert> Fig 2: Graph showing change in SBP, DBP & MAP pre- and post-fentanyl injection & during laryngo-tracheal manipulation. (Refer to Legends for figures, after references)

<insert> Table 4: HR, SBP, DBP & MAP values at 1-, 3-, 5-, 10- and 20-minutes after endotracheal intubation. (Refer to Legends for tables, after references)

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.

<insert> Table 5: Ramsay Sedation Score after fentanyl administration, during extubation and 10-, 20-, and 30-minutes after extubation. (Refer to Legends for tables, after references)

<insert> Fig 3: Graph showing ramsay sedation score after fentanyl administration, during extubation and 10-, 20-, and 30-minutes after extubation. (Refer to Legends for figures, after references)

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.

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.

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 (opturation?) of the laryngo-tracheal pressor response for a reasonable duration without any significant opioid associated side effects.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. 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.

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Legends for tables:

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)	0.4321	Not significant
	Female	14 (46.67)	11 (36.67)	15 (50.00)		
ASA	I	15 (50.00)	14 (46.67)	18 (60.00)	>0.9999	Not significant
	II	15 (50.00)	16 (53.33)	12 (40.00)		

Table 2: Baseline values of the basic hemodynamic parameters

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

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

Parameters		Group A	Group B	Group C	P value
Heart rate (Beats/min)	5 mins after fentanyl administration	77.57 ± 10.69	82.17 ± 16.93	66.03 ± 8.95	**0.0001***
	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 (mm of Hg)	5 mins after fentanyl administration	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 (mm of Hg)	5 mins after fentanyl administration	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***

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

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 of Hg)	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 (mm of 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***
	1 minute	96.33 ± 5.64	88.40 ± 11.79	88.43 ± 9.67	**0.0013***

MAP (mm of Hg)	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***

Table 5: Ramsay Sedation Score at 5 minutes after fentanyl administration, during extubation and 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

Legends for Figures:

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

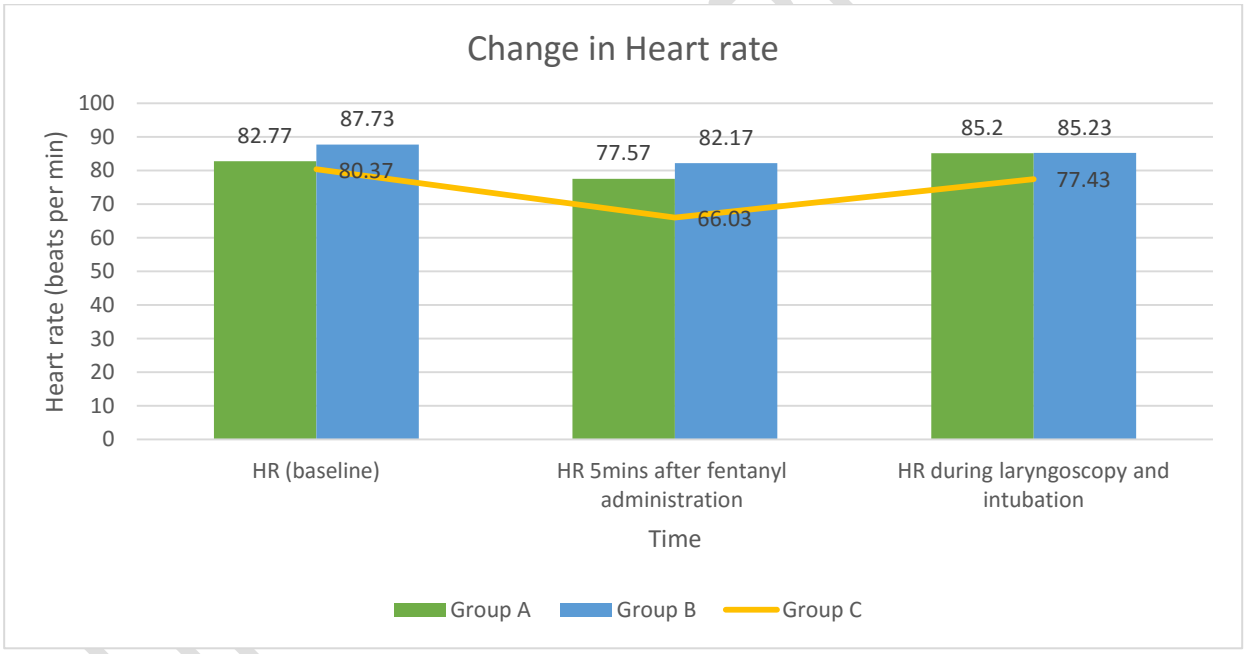

Fig 2: Graph showing change in SBP, DBP & MAP pre- and post-fentanyl injection & during laryngo-tracheal manipulation.

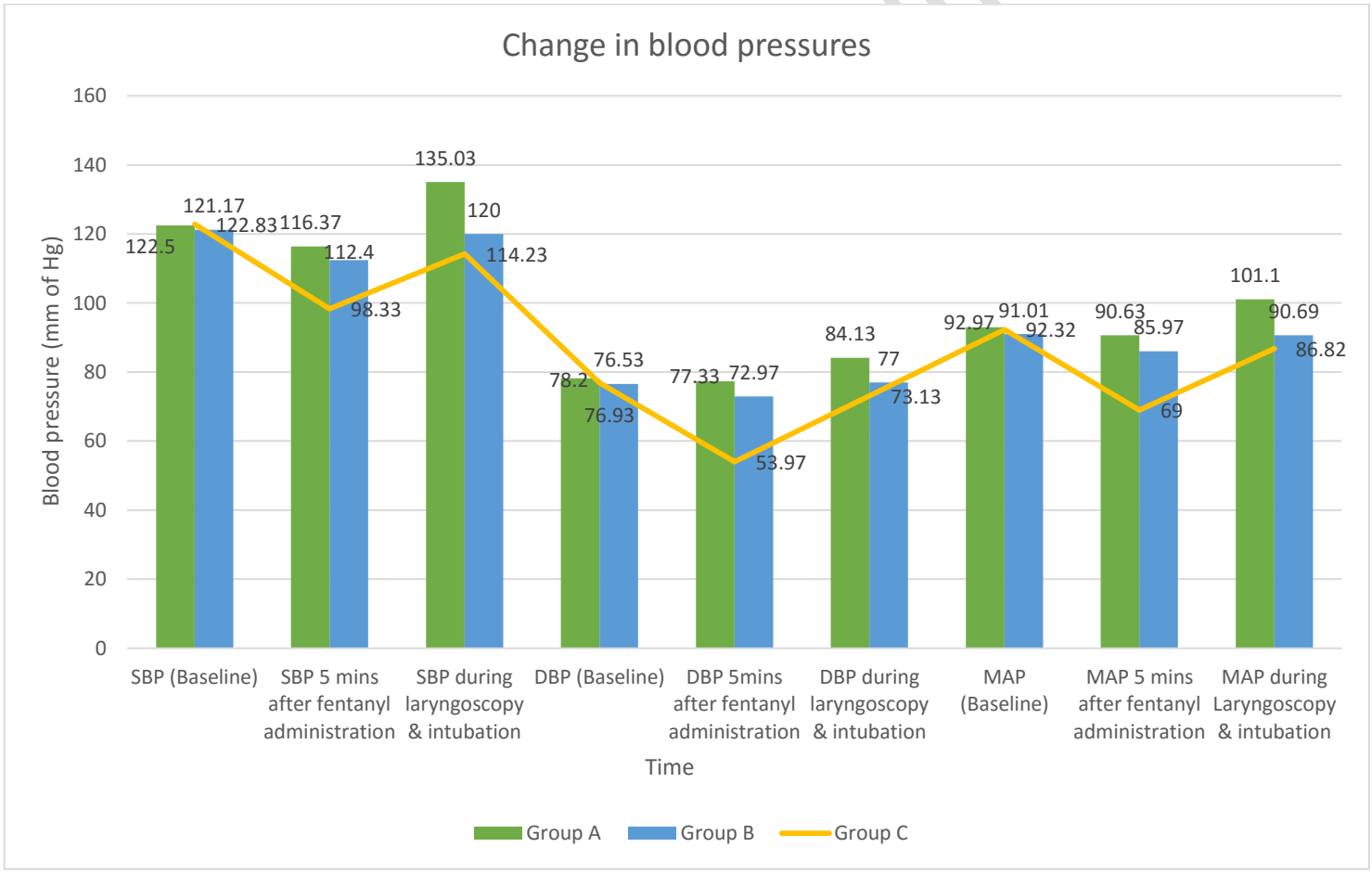

Fig 3: Graph showing ramsay sedation score after fentanyl administration, during extubation and 10-, 20-, and 30-minutes after extubation.