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Original Research Article

Evaluation of Different Doses of Fentanyl in Laparoscopic Surgeries for Attenuation of Stress Response to Laryngoscopy and Intubation

Dr. Amulya N.1, Dr. Gundapuneni Akhila. 2, Dr. S. Chendraya Perumal.3, Dr. Dhananjaya Kumar S.M. 4

1 Senior Resident, Department of Cardiac Anesthesiology, Sri Jayadeva Institute of Cardiovascular Sciences and Research Center, Bangalore, Karnataka, India.

2 Junior Resident, Department of Heart and Lung Transplant, Krishna Institute of Medical Sciences, Secunderabad, Hyderabad, India.

3 Junior Resident, Department of Heart and Lung Transplant, Krishna Institute of Medical Sciences, Secunderabad, Hyderabad, India.

4 Assistant Professor, Department of Anaesthesia, Kodagu Institute of Medical Sciences, Madikeri, Karnataka, India.

Corresponding Author

Dr. Dhananjaya Kumar S.M., Assistant Professor, Department of Anaesthesia, Kodagu Institute of Medical Sciences, Madikeri, Karnataka, India.

ABSTRACT

Background

Inadequate plane of anesthesia while doing laryngoscopy and intubation result in significant hemodynamic response. Fentanyl citrate suppresses upper airway reflexes and is effective in blunting the response while laryngoscopy and intubation. This study was carried out to compare three different doses of fentanyl (2, 3 and 4μg/kg) for attenuation of stress response to laryngoscopy and intubation.

Methods

Study design: Randomized double-blind study conducted at Krishna Institute of Medical Sciences Ltd. Secunderabad from November 2018 to January 2020.Total sample size was 111. The patients were randomly allocated in a double-blind fashion using computer Generated randomization table and divided in to three groups. Group -A received inj. FENTANYL 2 μg/kg IV, Group - B received inj. FENTANYL3 μg/kg IV, and Group--C received inj. FENTANYL 4 μg/kg IV5 min before induction of anesthesia.

Results

The difference between the groups was found to be highly significant at the time of intubation (p value < 0.001), 1 minute after intubation (p value <0.001), 3 minutes after Intubation (p value < 0.001), 5 minutes after intubation (p value < 0.001).Attenuation of Heart rate and systolic blood pressure at various time intervals was found to be highly significant with Group C (Fentanyl 4 mcg/kg) when compared to Group A (2 mcg/kg)and Group B(3mcg/kg).

Conclusion

This study showed that fentanyl 4 μg/kg resulted in better attenuation of stress response when compared to 3μg/kg fentanyl, 2μg/kg fentanyl to laryngoscopy and intubation in laparoscopic surgeries.

Keywords: Intravenous fentanyl, laryngoscopy, intubation, stressor response,

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Introduction

Inadequate plane of anesthesia while doing laryngoscopy and intubation result in significant increase in blood pressure and heart rate [1-4]. These changes occur from reflex sympathetic discharge resulting from pharyngealandlaryngotracheal stimulation which result in increased plasma concentration of epinephrine and norepinephrine. These hemodynamic responses are not completely attenuated by routine premedication [5]. Fentanyl citrate has been identified as an effective agent in this regard [6-12].

Fentanyl citrate suppresses upper airway reflexes and is effective in blunting the Sympathetic response to laryngoscopy and intubation, having different potency with Varying dose titration [13-17].

The present study was carried out to compare three different doses of fentanyl (2, 3 And 4 μg/kg) for attenuation of stress response to laryngoscopy and intubation during Laparoscopic surgeries.

AIMS AND OBJECTIVES

Aim: Evaluation of three different doses of fentanyl for laparoscopic surgeries.

Primary Objective:
To compare the effectiveness of three different doses of fentanyl in attenuation of sympathetic response to laryngoscopy and endotracheal intubation in Laparoscopic surgeries.

Secondary Objectives:
To measure requirement of propofol during induction.
Intraoperative requirement of inhalation agent (sevoflurane) with 3 different doses of fentanyl.
Incidence of postoperative nausea and vomiting in 3 different groups

MATERIALS AND METHODS

Study design: Randomized double-blind study
Study setting: Krishna Institute of Medical Sciences Ltd. Secunderabad
Study duration: November 2018 to January 2020.
Sample size: 111 (3 groups, 37 each)
Sample size calculation:

$$N = \frac{[\ (SD1^2+SD2^2)\ (Za +Zb)\ 2]}{\Delta mean^2}$$

Za= 1.96 at 95% CI, Level of significance 5 %
Zb=1.28
Δ mean = mean difference= 77.83-75.41=2.42
SD1=5.29
SD2= 5.74(based on study done by Thakur et al output variable heart
Rate mean and standard deviation during intra operative period is
Considered for sample size calculation)
N= (5.29×5.29 +5.74×5.74) (1.96 +1.28)2 / 2.42×2.42
N=110.361

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Total sample size 111. Based on 1:1 ratio sample size considered in
Each group 37 for 3 groups
Sample size taken as 40 for each group for 3 groups to avoid dropouts.

Inclusion criteria
1. ASA Grade 1 and 2
2. Age between 18 to 50 years
3. Patients undergoing laparoscopic cholecystectomy
4. Surgery duration less than 1 hour

Exclusion criteria
1. ASA grade 3 and above
2. Morbid obesity and those with OSA
3.Patients with cardiac, renal, hepatic, respiratory disorders and
Hypertensive status
4. Patients with endocrine disorders
5. Pregnant and lactating patients
6. Patients with known hypersensitivity to fentanyl
7. Patients with history of postoperative nausea and vomiting
8. Patient refusal

The patients were randomly allocated in a double-blind fashion using computer
Generated randomization table and divided in to three groups as below:
GROUP A(n=40) -inj. FENTANYL 2 μg/kgIV
GROUP B (n=40) -inj. FENTANYL 3 μg/kgIV
GROUP C (n=40) - inj. FENTANYL 4 μg/kgIV

A thorough preanesthetic evaluation was performed by taking history and clinical
Examination. In all patients age, weight, Systolic blood pressure, Diastolic blood
Pressure and Heart rate were recorded. All patients were investigated thoroughly to
Rule out cardiac, renal, hepatic and endocrine problems

On arrival in the operation theatre, monitors were attached and baseline preoperative parameters such as heart rate, systemic arterial pressure and oxygen Saturation were noted down. Intravenous line was secured with 18-gauge cannula.Patients were premedicated with inj. Glycopyrrolate, inj. 0.2 mg IV, inj. Midazolam0.02 mg/ kg IV and Inj. Ondansetron 0.08mg/kg IV.

Group -A received inj. FENTANYL 2 μg/kg IV in 10 ml of 0.9% normal saline 5min before Induction of anesthesia whereas Group - B received inj. FENTANYL3 μg/kg IV in 10ml of 0.9% normal saline 5min before induction of anesthesia and Group--C received inj. FENTANYL 4 μg/kg IV in 10 ml of 0.9% normal saline 5 min before induction of anesthesia.

Patients were induced with inj. propofol 1 - 2 mg/kg IV and the dose at which loss of verbal response is noted. Endotracheal intubation was facilitated by inj. vecuronium bromide 0.1mg/kg IV. Anesthesia was maintained with 33%oxygen and 66 % air, sevoflurane (1-2%) and inj.vecuronium bromide 0.02mg/kg IV, Intermittent positive pressure ventilation was continued bymechanical ventilator and ETCO2 was maintained between 35 - 40 mmHg.

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Monitoring of pulse rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, ETCO2 was done and recorded at the time of induction, intubation and thereafter 1 min,3 min, 5 min after intubation. At the end of surgeryall patients were reversed with inj. Glycopyrrolate 0.01mg/kg IV and inj.Neostigmine 0.05mg/kg IV. Extubation was performed after return of reflexes and consciousness, then patients were transferred to recovery room.

Following parameters were observed and recorded

1. Systemic arterial pressure including the systolic, diastolic mean arterial pressure,heart rate, oxygen Saturation, end tidal carbon dioxide and electrocardiographywere recorded at the following points of time: Base line, before induction, at the time of intubation, 1 minute after intubation, 3 minutes after intubation, 5minutes after intubation
2. Induction dose of propofol required.
3. Volume of inhalational agent (sevoflurane) required was noted (using carestation 620).
4. Postoperative monitoring of nausea and vomiting was done at 6th hour and 24thhour postoperatively.

Post operative period

Patients were monitored post operatively for any adverse effects like bradycardia,nausea, vomiting, respiratory depression and any other side effects

Statistical Analysis

In total 120 patients, 40 patients were allocated to each group. At the end of study, all data was analyzed using SPSS 19.0version. Descriptive data presented as mean ± SD. Quantitative data were analyzed by ANOVA followed by unpaired‘t’ test. Qualitative data were analyzed using chi square test. Within the group, changes in hemodynamic parameters with respect to baseline were compared using paired‘t’ test.

Inter group comparisons of percentage change of hemodynamic parameters compared to baseline were done by repeated measure ANOVA followed by unpaired ‘t' test with Bonferroni’s correction. P value < 0.05 was taken as statistically significant. P value <0.001 was taken as statistically highly significant

Results

ANALYSIS OF HEMODYNAMIC VARIABLES

Table 1: Heart Rate

HR	Group A	Group B	Group C	P Value
Base Line	83.25 ± 6.356	84.48 ± 5.931	85.53 ± 3.194	0.168
Before Induction	81.85 ± 6.562	82.75 ± 6.299	83.45 ± 3.374	0.443
At the time of Intubation	95.58 ± 4.95	88.28± 7.186	82.75 ±3.28	< 0.001
1min after intubation	93.05 ± 3.493	84.23 ± 7.17	81.15 ± 4.828	< 0.001
3min after intubation	90.78 ± 3.765	80.33 ± 6.933	79.25 ± 3.998	< 0.001
5mins after intubation	90.08 ± 4.041	76.4 ± 6.308	75.3 ± 4.298	< 0.001

The difference between the groups was found to be **highly significant** at the time of intubation (p value < 0.001), 1 minute after intubation (p value <0.001), 3 minutes after Intubation (p value < 0.001), 5 minutes after intubation (p value < 0.001).

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Attenuation of Heart rate at various time intervals was found to be highly significant with Group C (Fentanyl 4 mcg/kg) compared to Group A (2 mcg/kg) and Group B (3mcg/kg).

Table 2: Systolic Blood Pressure

SBP	Group A	Group B	Group C	P Value
Base Line	127.55 ± 5.354	127.88 ± 4.625	130.18 ± 2.925	0.017
Before Induction	123.28 ± 4.793	124.08 ± 4.503	124.15 ± 5.545	0.684
At the time of Intubation	127.8 ± 4.921	127.03 ± 3.99	119.25 ± 5.212	< 0.001
1min after intubation	125.1 ± 3.901	122.28 ± 4.674	114.18 ± 5.043	<0.001
3min after intubation	121.35 ± 3.807	118.25 ± 4.684	109.7 ± 5.07	< 0.001
5mins after intubation	119.35 ± 3.718	114.88 ± 4.256	107.43 ± 5.007	< 0.001

The values were analyzed and were found to be **highly significant** at the time of intubation (P value < 0.001), 1 minute after intubation (p value <0.001), 3minutes after intubation (p value<0.001), 5 minutes after intubation (p value < 0.001). Attenuation of systolic blood pressure at various time intervals was found to be highly significant with Group C (Fentanyl 4 mcg/kg) compared to Group A (2 mcg/kg) and Group B(3mcg/kg).

Table 3: Diastolic Blood Pressure

DBP	Group A	Group B	Group C	P Value
Base Line	81.15 ± 3.813	82.95 ± 2.087	82.53 ± 2.631	0.019
Before Induction	78.88 ± 3.524	80.08 ± 2.325	79.63 ± 2.798	0.184
At the time of Intubation	84.08 ± 3.133	82.25 ± 2.539	78.23 ± 2.722	< 0.001
1min after intubation	83.53 ± 2.97	81.7 ± 2.554	74.93 ± 2.683	< 0.001
3min after intubation	82.03 ± 3.214	80.4 ± 2.629	73.2 ± 3.283	< 0.001
5mins after intubation	81.58 ± 3.948	78.25 ± 2.696	70.78 ± 3.117	< 0.001

The values were analyzed and were found to be **highly significant** at the time of intubation (P value < 0.001), 1 minute after intubation (p value < 0.001), 3 minutes after intubation (p value < 0.001), 5 minutes after intubation (p value <0.001). Attenuation of diastolic blood pressure at various time intervals was found to be highly significant with Group C (Fentanyl 4 mcg/kg) compared to Group A (2mcg/kg) and Group B(3mcg/kg).

Table 4: Mean arterial pressure

MAP	Group A	Group B	Group C	P Value
Base Line	95.93 ± 3.261	96.53 ± 2.025	96.73 ± 2.05	0.337
Before Induction	92.73 ± 3.13	94.5 ± 2.276	93.55 ± 6.021	0.162
At the time of Intubation	98.23 ± 2.326	93.3 ± 9.216	93.23 ± 1.993	< 0.001
1min after intubation	96.13 ± 2.162	95.4 ± 2.24	91.23 ± 4.833	< 0.001
3min after intubation	94.8 ± 2.672	92.33 ± 2.269	88.6 ± 2.898	< 0.001
5mins after intubation	93.93 ± 3.133	90.18 ± 2.459	82.7 ± 3.023	< 0.001

The values were analyzed and were found to be **highly significant** at the time of intubation (P value < 0.001), 1 minute after intubation (p value <0.001), 3 minutes after intubation (p value < 0.001), 5 minutes after intubation (pvalue< 0.001). Attenuation of Mean arterial pressure at

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various time intervals was found to be highly significant with Group C (Fentanyl 4 mcg/kg) compared to Group A (2 mcg/kg) and Group B(3mcg/kg).

INDUCTION DOSE OF PROPOFOL

The results were analyzed and the difference was found to be **highly significant** (p value <0.001). Group C receiving 4 mcg/kg fentanyl showed significantly lower requirement of propofol compared to Group A (2mcg/kg) and Group B (3mcg/kg).

Graph 1: Graphical representation of Mean dose of propofol required during Induction.

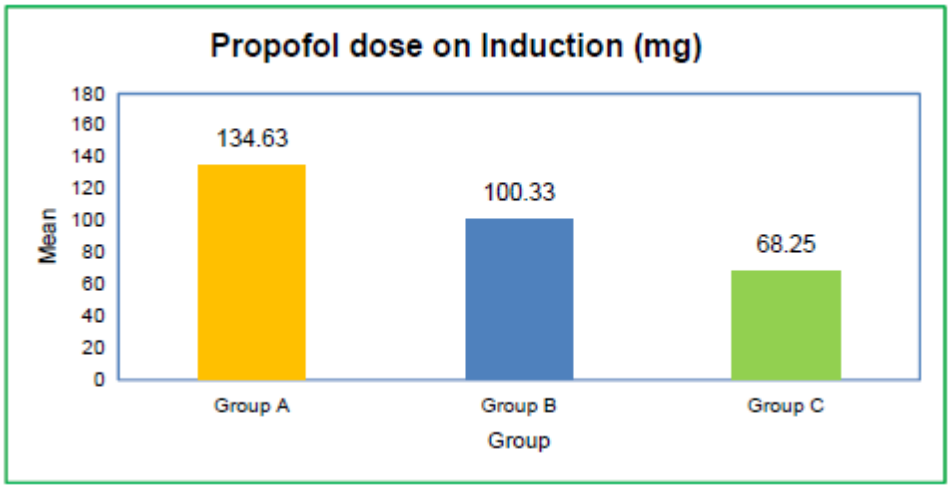

Table 5: Inhalational agent required

Group	Inhalational agent required (sevoflurane) (ml)		P Value (ANOVA)
	Maan	Std. Deviation	
Group A	30.2	1.305	<0.001
Gropu B	29.5	1.281	
Group C	24.13	1.667	

The values were analyzed and the difference was found to be **highly significant** (p value < 0.001). Group A receiving (2mcg/kg) fentanyl showed significantly higher requirement of Sevoflurane compared to Group B (3mcg/kg) and Group C 4mcg/kg) . Graphical representation of mean of inhalational agent (Sevoflurane) required in 3 groups

Graph 2: Inhalational agent required

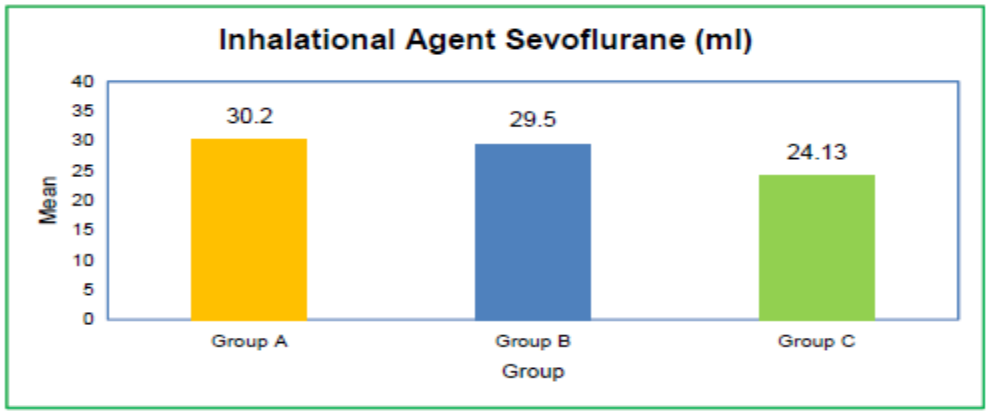

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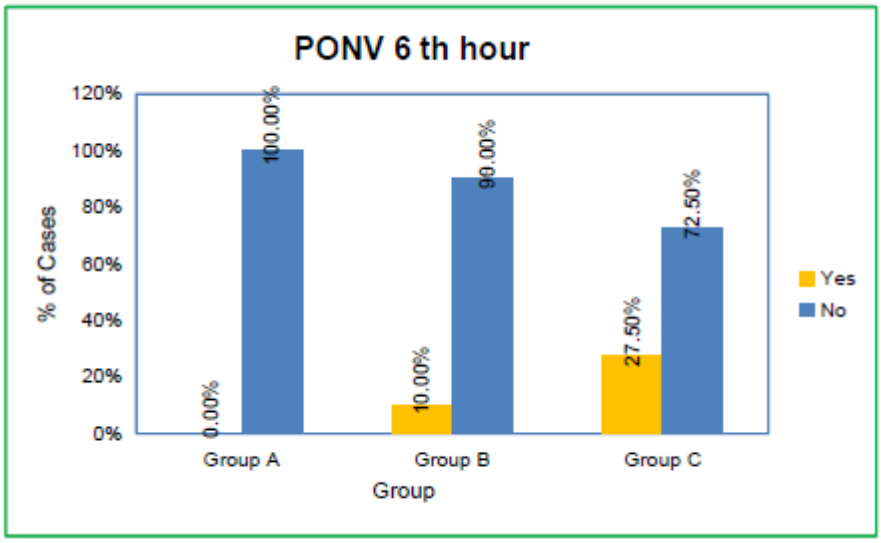
Table 6: Post operative nausea and vomiting (PONV)

PONV 6th hour	Group			Total
	Group A	Group B	Group C	
Yes	0	4	11	15
No	40	36	29	105
Total	40	40	40	120

P value (Chi-Square) test - <0.001

The above table summarizes the postoperative nausea and vomiting at 6th hour. The difference between the groups was found to be **highly significant** (p value <0.001).



Graphical representation of incidence of postoperative nausea andvomiting in 6th hour.

DISCUSSION

Fentanyl has been tried in various bolus doses for control of hemodynamic changes of laryngoscopy. Black et al[18] and Kay et al[19]found completeattenuation of hemodynamic response with 5 µg/kg of fentanyl. Low doses offentanyl were employed because large dose produces muscular rigidity,bradycardia, nausea and vomiting. Large doses may also cause postoperativerespiratory depression; especially in surgery with short duration of less than 1 hour.The present study was conducted on laparoscopic surgeries and these surgeriesare of intermediate duration around 2 hrs.

Heart rate:

The difference between the groups was found to be **highly significant** at the time of intubation (p value < 0.001), 1 minute after intubation (p value <0.001), 3 minutes after Intubation (p value < 0.001), 5 minutes after intubation (p value < 0.001).So, in the present study there was complete attenuation of tachycardia response to laryngoscopy and intubation with fentanyl 4µg/kg (group C) compared to fentanyl3µg/kg (group B) and 2µg/kg (group A).

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Splinter WM et al (20) studied effects of fentanyl 1.5 μg/kg and 3 μg/kg forhemodynamic responses to laryngoscopy and tracheal intubation in geriatricpatients. They concluded that by increasing the dose of fentanyl attenuation oftachycardia response to intubation was better.
Patients receiving 2 microgram/kg (Group A) , 3microgram/kg (Group B) showed increase in Systolic blood pressure response tobase line whereas the response to intubation was totally attenuated in patientsreceiving 4 microgram/kg fentanyl (Group C).**Kautto UM et al(21)** concluded that supplementation of anesthetic induction withfentanyl 2 μg/kg significantly attenuated the increase in SBP after laryngoscopy andintubation and fentanyl 6 μg/kgcompletely abolished pressure responses. Theyconcluded that increasing doses of fentanyl completely abolishes pressorresponsefor intubation.

Patients receiving 2 microgram/kg (Group A), 3microgram/kg (Group B) showed increase in Diastolic blood pressure response to base line whereas the response to intubation was totally attenuated in patientsreceiving 4 microgram/kg fentanyl (Group C).

Patients receiving 2 microgram/kg (Group A), 3 microgram/kg(Group B) showed increase in Mean arterial pressure response to base linewhereas the response to intubation was totally attenuated and did not show anyrise in MAP and is continuously below basal line throughout studyinpatientsreceiving 4microgram/kg fentanyl (Group C).

Hosalli V et al(22) found that in patients receiving fentanyl 3 μg/kg MAP isincreased at the time of intubation and returned to below basal line after 3 minutes of intubation and in patients who received fentanyl 5 μg/kg MAP remained belowbaseline throughout the study. They concluded that increasing doses of fentanylcompletely abolishes MAP response for intubation.administering fentanyl 5 min prior to propofolcausedmarked reduction in the dose requirement of the latter along with a significantlydecreased incidence of hypotension, unwanted movements, vocalization andbucking during induction.

Thomas VL et al(23)administered 100 mcg of fentanyl 1- - 5 min before inductionwithpropofol in patients undergoing day care gynecologic procedures.Comparedtothe control group, there were significant decreases in induction time, propofoldoseand mean blood pressure with the use of fentanyl.

Group A patients receiving(2mcg/kg) fentanyl showedsignificantly higher requirement of inhalational agent(Sevoflurane) compared toGroup B(3mcg/kg) and Group C(4 mcg/kg) **(p value < 0.001 - highly significant)**Postoperative incidence of Nausea and Vomiting is higher withfentanyl 4mcgs/kg (Group C) compared to Group A(2mcgs/kg) and Group B(3mcgs/kg)

CONCLUSION:

The present study showed that fentanyl 4 μg/kg resulted in better attenuation ofhaemodynamic response when compared to 3μg/kg fentanyl, 2μg/kg fentanyl forattenuation of stress response to laryngoscopy and intubation in laparoscopicsurgeries.Administering fentanyl 5min prior to propofol causes marked reduction in the doserequirement of the latter along with a significantly decreased incidence ofhypotension, unwanted movements, vocalization and bucking during induction.Postoperative incidence of Nausea and Vomiting is higher with increasing doses offentanyl. Therefore usage of higher dose of fentanyl in Patients with known historyof postoperative nausea and vomiting requires further evaluation.The intraoperative requirement of Inhalational agent was significantly decreasedwith increasing doses of fentanyl.

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