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Attenuation of hemodynamic pressor response to laryngoscopy and endotracheal intubation by intravenous fentanyl in elective surgery under general anesthesia: A randomized controlled trial using three different doses

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ABSTRACT

Background: Direct laryngoscopy and endotracheal intubation elicit hemodynamic pressor responses which may be hazardous in high risk patients. Fentanyl, a low cost synthetic opioid, when used judiciously, may be a good option to attenuate this stress response. **Aims and Objectives:** The present study has been conducted to compare the efficacy of three different doses of intravenous fentanyl in attenuation of hemodynamic pressor response to laryngoscopy and endotracheal intubation in elective surgery under general anesthesia. **Materials and Methods:** It was a double-blinded randomized controlled trial. A total of 90 patients of American Society of Anesthesiologists physical status I and II, 55 male and 35 female, aged between 20 and 55 years, were randomized into three groups receiving 2, 3, and 4 μg/kg of injection fentanyl, respectively, administered intravenously 5 min before direct laryngoscopy and endotracheal intubation. **Results:** There were significant differences in hemodynamic variables among all three groups at 1, 3, 5, and 10 min after endotracheal intubation. Just after endotracheal intubation; heart rate, mean arterial pressure, and diastolic arterial pressure – all these variables showed significance between 3 μg/kg and 4 μg/kg groups only. Incidence of nausea/vomiting showed statistical significance between 2 μg/kg and 4 μg/kg groups only. **Conclusion:** In our double-blinded randomized controlled trial, 4 μg/kg of injection fentanyl administered 5 min before laryngoscopy and intubation, has showed superior efficacy in suppressing hemodynamic stress responses associated with it. Further, larger trials are needed to confirm our findings.

Key words: Fentanyl; Direct laryngoscopy; Endotracheal intubation; Hemodynamic pressor response

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INTRODUCTION

Laryngoscopy and endotracheal intubation are the cornerstones of balanced general anesthesia and resuscitative measures in intensive care units. During laryngoscopy, the blade of direct laryngoscope either presses against the vallecula (base of tongue) to lift up the epiglottis (Macintosh or McCoy type) or, directly presses against the epiglottis and lifts it up (Miller type). Lifting up the epiglottis results in exposure of the vocal cords, through which endotracheal tube is inserted (endotracheal intubation). It is a depth-of-anesthesia-dependent noxious stimulus,

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which can trigger adverse cardiovascular, respiratory and other physiological responses.[1] Significant changes in blood pressure (BP) and heart rate (HR) are common, particularly during induction[2] and after endotracheal intubation.[3] Both sympathetic and parasympathetic responses may be seen. In contrary to adults, parasympathetic responses predominate in pediatric population.[3] Increased plasma catecholamine concentrations generally accompany sympathetic pressor responses.[4]

Reid and Brace in 1940 first described the hemodynamic pressor response to laryngoscopy and endotracheal intubation.[5] Since then various studies have been conducted on hemodynamic pressor responses to intubation in different group of patients, both with and without cardiac illnesses. The tachycardia, arrhythmias, and hypertension resulting from stress response can be deleterious in patients with preexisting cardiac disease and may lead to complications such as myocardial infarction (MI) and cardiovascular accidents.[6] Anesthetic induction agents alone are not sufficient to suppress this hemodynamic pressor response following laryngoscopy and endotracheal intubation. Various pharmacological agents such as volatile anesthetics, topical and intravenous lignocaine, beta-blockers, calcium channel blockers, opioids, alpha-2 agonists, sodium nitroprusside, and nitroglycerine are often used to supplement anesthetic induction. Fentanyl citrate, a synthetic opioid, has been found effective in this aspect. It attenuates hemodynamic pressor response to laryngoscopy and intubation with different potency and dose titration.[7] Besides blunting the airway reflexes, it is a potent analgesic and allows the patient to wake up from anesthesia without feeling existential pain in the recovery room. Serious side effects of fentanyl such as respiratory depression and chest wall rigidity can effectively be minimized with adequate dose titration.

Aims and objectives

The present study was designed in a prospective, randomized, double-blind fashion to compare the effects of three different doses of intravenous fentanyl in attenuation of hemodynamic pressor response to laryngoscopy and endotracheal intubation during elective surgery under general anesthesia.

MATERIALS AND METHODS

After approval from institutional ethical committee and obtaining written informed consent of the patients, this study was conducted in Nilratan Sircar Medical College and Hospital, a tertiary care medical college hospital in eastern India, over a period of 18 months. 90 patients of American Society of Anesthesiologists (ASA) physical status I and II, aged between 20 and 55 years of both the sexes scheduled for elective surgery under general anesthesia were enrolled in this study. Power calculations suggested that a minimum of 16 subjects per group were required to detect 10% difference in HR between groups (taking type I or α error of 5%, type II or β error of 20% and Standard Deviation=10). To be on a safer side, 30 patients were included in each group (n=30). Patients with morbid obesity; having arrhythmia, heart failure, significant respiratory dysfunction, hyperkalemia, myopathies, psychiatric illnesses, allergy, or any contraindication to drugs used, were excluded from the study. Patients concomitantly taking clonidine, methyl dopa, beta blockers, calcium channel blockers, benzodiazepines, and mono amine oxidase inhibitors; patients having difficult airway or intubation taking more than 15 s or more than 2 attempts were also excluded from the study. During pre-anesthetic checkup, patients were examined and interviewed. On arrival in the preoperating room, an 18 gauge peripheral venous cannula was inserted after proper application of local anesthetic. All patients were premedicated with 0.2 mg injection glycopyrrolate and 4 mg injection ondansetron. On arrival in the operation theatre, monitors were attached and baseline parameters such as HR, non-invasive BP, oxygen saturation, and Electrocardiogram were recorded. Immediately before induction, patients were randomly divided into three equal groups (n=30) using sealed envelopes chosen by the patients. The groups were:

i. Group F2 – received 2 μg/kg injection fentanyl
ii. Group F3 – received 3 μg/kg injection fentanyl; and
iii. Group F4 – received 4 μg/kg injection fentanyl.

Total volume of the study drug was adjusted to 10 ml by diluting with normal saline and administered over a period of 1 min before induction. The preparation, labeling, and administration of the study drugs were done by an anesthesiologist who was not involved in this study (so this was a prospective, randomized, and double-blinded study). After recording of baseline vital parameters and administration of study drugs over the next 1 min, pre-oxygenation done for 3 min with 100% oxygen, and then anesthesia was induced in a standard anesthetic protocol with injection etomidate 0.2–0.4 mg/kg in titrating dose till loss of eyelash reflex. One minute after administration of injection succinyl choline (and 5 min after administration of study drugs), laryngoscopy and intubation was initiated. Intubation was done with appropriately sized endotracheal tube. Anesthesia was maintained by nitrous oxide (N_2O): Oxygen (O_2): Sevoflurane (66:33:1) with controlled ventilation. Fentanyl and vecuronium were used in incremental doses every 20 min. Ventilation was adjusted to maintain normocarbia (End Tidal Carbon Dioxide was maintained between 25 and 40 mm Hg). During surgery, Ringer's lactate solution was administered in maintenance dose as per Holiday Segar formula. Arterial pressures and

HRs were measured at baseline, before induction (i.e., after administration of study drugs), just after endotracheal intubation (T0), and then at 1 (T1), 3 (T3), 5 (T5), and 10 (T10) min after intubation. At the end of the surgery residual neuro-muscular blockade was antagonized with injection neostigmine 0.05 mg/kg and injection glycopyrrolate 0.01 mg/kg. The anesthesiologist who measured the arterial pressures and HRs was unaware of the study. Hypotension and hypertension were defined as systolic arterial pressure ≤20% and ≥25% of baseline value, respectively. Similarly, bradycardia and tachycardia were defined as HR ≤20% and ≥25% of baseline value, respectively.

Statistical analysis

Data were expressed as mean and standard deviation (Mean±SD). Normality of the distribution in each group was checked by the Shapiro–Wilk normality test. The homogeneity in three groups of mean and SD was analyzed using SPSS software version 20.0 (SPSS Inc., Chicago, Illinois, USA). Inter-group comparisons were done using one way analysis of variance (ANOVA). *Post hoc* Tukey test was followed where ANOVA values were significant. Categorical data were compared using Chi-square test. $P<0.05$ was considered as statistically "significant" ($P<0.05$) (Figure 1).

RESULTS

There were no significant differences between the three groups with regard to demographic data such as age, sex, body mass index, and ASA grade (Table 1). Pre-operative baseline vital parameters were compared among the three groups of patients and no significant difference was found (Table 2). Hemodynamic variables recorded in three groups at specified timings as mentioned in methodology are shown in Tables 3-6. No patient was excluded from the study.

There were significant differences in hemodynamic variables among all three groups at T1, T3, T5, and T10 (i.e., 1, 3, 5, and 10 min after endotracheal intubation, respectively). At T0, that is, just after endotracheal intubation; HR, mean arterial pressure, and diastolic arterial pressure – all these variables showed significance between Group F3 and Group F4 only. Comparison of the three groups with regard to side effects profile, namely, nausea/vomiting, hypotension, and bradycardia is shown in Table 7. Incidence of nausea/vomiting showed statistical significance between Group F2 and Group F4 only.

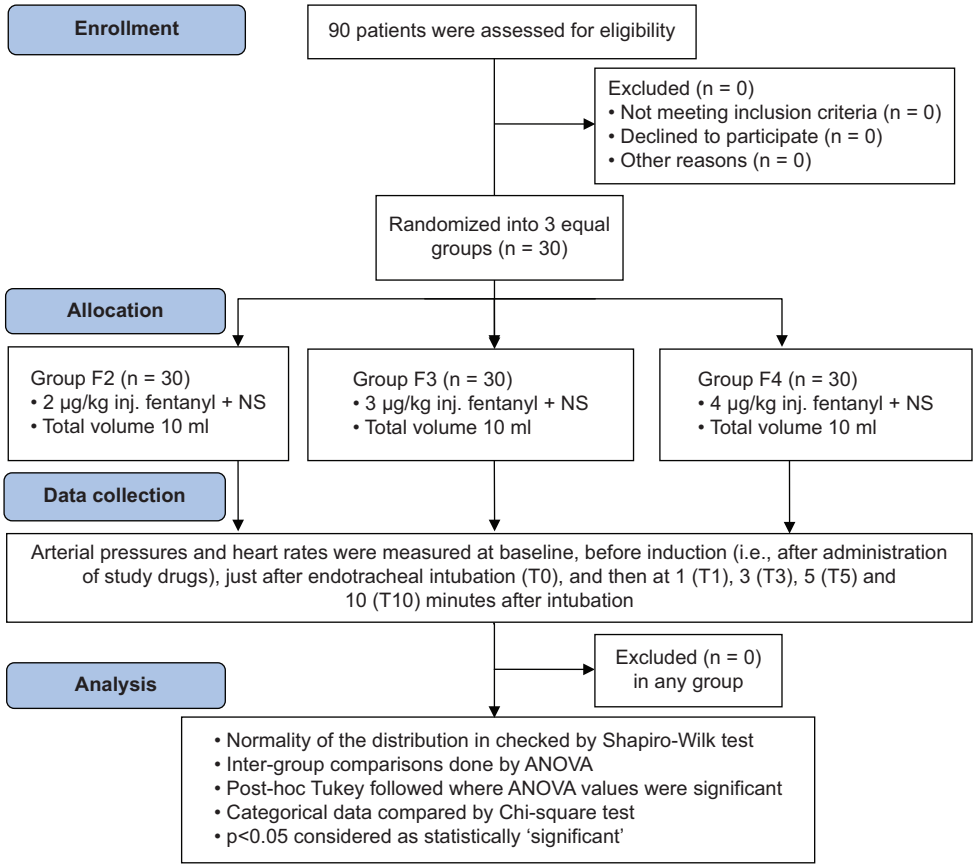

Figure 1: The CONSORT flow diagram of the study design

Table 1: Demographic profile (Mean±SD)

Demographic profile	Group F2	Group F3	Group F4	P-value
Age (years)	36.87±9.00	37.20±9.90	39.00±10.30	0.662
Sex (M: F)	16: 14	18: 12	21: 09	0.411
Weight (kg)	52.38±7.788	62.55±9.687	63.10±10.275	0.87
BMI	23.46±1.94	23.64±2.11	23.98±2.20	0.620
ASA-PS (I: II)	13: 17	17: 13	17: 13	0.490

ASA-PS: ASA physical status, BMI: Body mass index

Table 2: Pre-operative baseline vital parameters (Mean±SD)

Baseline parameters	Group F2	Group F3	Group F4	P-value
Heart Rate (bpm)	89.80±9.89	91.20±7.90	87.78±10.30	0.372
SAP (mm Hg)	126±11.15	122±8.75	127±13.35	0.196
MAP (mm Hg)	92.58±7.98	89.15±9.62	93.10±11.37	0.240
DAP (mm Hg)	79.43±8.67	80.13±12.78	82.76±13.65	0.523

SAP: Systolic arterial pressure, MAP: Mean arterial pressure, DAP: Diastolic arterial pressure

Table 3: Comparison of three groups with regard to heart rate (Mean±SD)

Time	Group F2	Group F3	Group F4	P-value
Pre-induction	93.23±15.93	92.83±22.44	93.00±15.35	0.996
T0	102.17±21.93	108.23±19.66	98.13±12.88†	0.111
T1	119.03±20.39	99.33±8.28*	90.63±9.48*†	<0.001
T3	101.33±17.47	89.67±7.57*	83.57±8.19*†	<0.001
T5	91.80±9.39	84.17±7.12*	79.23±6.88*†	<0.001
T10	85.80±7.24	81.07±7.42*	74.87±7.09*†	<0.001

Symbols represent a significant difference (P<0.05) compared with group F2 (*) or between group F3 and F4 (†), as determined using a one-way ANOVA with a *post hoc* Tukey test

Table 4: Comparison of three groups with regard to systolic arterial pressure (Mean±SD)

Time	Group F2	Group F3	Group F4	P-value
Pre-induction	132.53±10.80	134.37±11.56	133.27±9.90	0.802
T0	137.47±17.31	137.00±13.61	140.33±8.77	0.596
T1	160.10±17.96	146.77±6.89*	140.07±6.00*†	<0.001
T3	146.60±16.66	137.20±6.09*	131.43±7.89*†	<0.001
T5	137.03±11.24	129.10±7.28*	124.40±7.22*†	<0.001
T10	132.00±10.15	124.70±7.43*	119.13±7.94*†	<0.001

Symbols represent a significant difference (P<0.05) compared with group F2 (*) or between group F3 and F4 (†), as determined using a one-way ANOVA with a *post hoc* Tukey test

Table 5: Comparison of three groups with regard to mean arterial pressure (Mean±SD)

Time	Group F2	Group F3	Group F4	P-value
Preinduction	95.80±8.46	96.97±9.46	98.33±7.02	0.506
T0	102.00±15.90	100.60±10.99	106.27±6.81†	0.160
T1	120.72±12.64	108.57±9.36*	99.47±5.34*†	<0.001
T3	106.93±11.32	98.67±5.74*	91.37±5.12*†	<0.001
T5	99.82±8.71	93.27±5.59*	86.13±4.33*†	<0.001
T10	97.07±6.88	91.20±5.15*	80.40±4.47*†	<0.001

Symbols represent a significant difference (P<0.05) compared with group F2 (*) or between group F3 and F4 (†), as determined using a one-way ANOVA with a *post hoc* Tukey test

DISCUSSION

Since 1940, occurrence of hemodynamic pressor response during laryngoscopy and intubation have been known and extensively studied.[5] Although both direct laryngoscopy and endotracheal intubation discretely may indulge in sympathetic stimulation (with an exception of pediatric population where vagal mediated parasympathetic response may predominate[3]), the catecholamine rise associated with intubation far exceeds that with laryngoscopy alone.[8] Endotracheal intubation is even noxious than surgical incision. The depth of anesthesia required to attenuate hemodynamic pressor response to intubation is much higher (1.3 MAC, Minimum Alveolar

Table 6: Comparison of three groups with regard to diastolic arterial pressure (Mean±SD)

Time	Group F2	Group F3	Group F4	P-value
Preinduction	81.47±6.36	83.47±7.32	83.60±6.51	0.394
T0	88.27±13.34	91.00±13.14	91.80±8.77†	0.489
T1	104.70±11.62	94.57±6.97*	88.43±4.58*†	<0.001
T3	97.67±9.32	86.67±4.96*	82.63±4.25*†	<0.001
T5	86.63±8.81	81.53±7.61*	78.23±4.33*†	<0.001
T10	83.77±6.60	80.40±6.09*	75.07±4.86*†	<0.001

Symbols represent a significant difference (P<0.05) compared with group F2 (*) or between group F3 and F4 (†), as determined using a one-way ANOVA with a *post hoc* Tukey test

Table 7: Comparison of three groups with regard to side effects

Side effects (no. of patients)	Group F2	Group F3	Group F4	P-value
Nausea/vomiting (present: absent)	1: 29	2: 28	7: 23*	0.031
Hypotension (present: absent)	0: 30	0: 30	0: 30	NA
Bradycardia (present: absent)	0: 30	1: 29	0: 30	NA

Symbols represent a significant difference (P<0.05) compared with group F2 (*) or between group F3 and F4 (†), as determined using a one-way ANOVA with a *post hoc* Tukey test

Concentration) than that required to attenuate the response following surgical incision.[9] These hemodynamic pressor responses may well be tolerated in healthy young patients, but there may be increased risks of morbidity and mortality in patients predisposed with coronary artery disease, recent MI, hypertension, preeclampsia, etc.[10] In general, the pressor response starts within 5 s, maximizes at 60 s, and stabilizes within 10 min.[11] Because endotracheal intubation is a must for major surgical procedures and resuscitative measures to secure airway, the effort to reduce the sympathetic stimulation is now being aimed towards minimizing the stretching of tissues in the oropharynx and laryngo-pharynx during direct laryngoscopy.[12] McCoy and Macintosh blades may be more useful in this regard than Miller laryngoscopy blades.[13]

To suppress hemodynamic pressor response during intubation, different methods such as topical or intravenous application of local anesthetic agents, infiltration or nerve blocks, volatile anesthetic agents, beta-blockers, calcium channel blockers, opioids, α adrenergic blockers, and vasodilators have been studied till date. However, cost and relative advantage of using a particular drug is of great importance in day to day anesthesia practice.[14] For this reason, fentanyl still remains a commonly administered opioid for suppression of hemodynamic pressor responses during various invasive and surgical procedures including endotracheal intubation. Channaiah et al., opined that though single preinduction 2 μg/kg injection fentanyl successfully attenuates, but it "does not suppress," the hemodynamic pressor response to laryngoscopy and endotracheal intubation in ASA physical status I and II adults aged between 18 and 60 years.[14] Also, side effects were minimal at this dose. For this reason, we used three different doses of fentanyl in our study- 2 μg/kg, 3 μg/kg, and 4 μg/kg.

Mohite et al., concluded that lower 1 μg/kg dose of fentanyl was not as effective as 2 μg/kg dose.[15] For this reason, we also did not use fentanyl at the lower doses in our study.

Hosalli et al., opined that both 3 μg/kg and 5 μg/kg fentanyl were equally effective in blunting HR response, but 5 μg/kg fentanyl was more effective in blunting arterial pressure response.[16] We also observed similar findings where 4 μg/kg fentanyl was more effective in blunting both HR and arterial pressure responses than lower dose groups.

Iyer and Russell opted for 3 μg/kg as ideal dose of fentanyl in cardiac patients, as higher doses were associated with fall in mean arterial pressures. But they also opined that at least 10 μg/kg dose of fentanyl was needed to keep HR below 100/min.[17] In our study, 4 μg/kg dose was associated with significant lower HR and arterial pressures than lower 3 μg/kg and 2 μg/kg doses. Tachycardia in the lower doses of fentanyl in the study of Iyer and Russell may be attributed to the concomitant use of pancuronium.

Karliczek et al., studied the effects of two doses of fentanyl (3 μg/kg and 6 μg/kg) and infusion of etomidate.[18] They found that 3 μg/kg dose group was associated with tachycardia and hypertension after intubation while hypotension was seen with 6 μg/kg dose group. They concluded that safe dose range of injection fentanyl is very narrow. Here, we have also used injection fentanyl within this narrow range. We did observe increase in HR and arterial pressures after intubation with attenuation following incremental doses of fentanyl used, but hypotension was not associated. There was a single episode of bradycardia in 3 μg/kg dose group which was managed with injection atropine 0.6 mg in intravenous route. One patient in 2 μg/kg dose group, 2 patients in 3 μg/kg dose group, and 7 patients in 4 μg/kg dose group experienced

nausea/vomiting and were managed with injection ondansetron 8 mg in slow intravenous route.

Kovac concluded that in short surgical procedures, fentanyl of 5 μg/kg and 8 μg/kg dosage caused respiratory depression and delayed awakening, respectively.[3] In young healthy patients, fentanyl 5–6 μg/kg is effective in attenuating both BP and HR during laryngoscopy and intubation, while in geriatric patients, fentanyl 1.5–3 μg/kg given 3–4 min before laryngoscopy and intubation is sufficient. In our study, three different doses of fentanyl (2, 3, and 4 μg/kg) were administered 5 min before direct laryngoscopy and endotracheal intubation, and 4 μg/kg dose was most effective in attenuating hemodynamic pressor response with minimal side effects (nausea/vomiting).

Limitations of the study

There were several limitations of this study like small sample size, single-center design and selected study population (pediatric, elderly and ASA III-IV patients including those with cardiac problems were excluded). Also we didn't use relatively higher doses of injection fentanyl (>5 μg/kg, as often used in cardiac patients) and there was no control group. Further large scale multicentric study is required to better delineate our findings.

CONCLUSION

In our double-blinded randomized controlled trial, administration of 4 μg/kg of injection fentanyl 5 min before has effectively attenuated hemodynamic pressor response associated with direct laryngoscopy and endotracheal intubation without any potential side effects. Further, larger trials with higher doses may be needed to confirm our findings.

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