

# A Comparative Study of Labetalol and Fentanyl on the Sympathomimetic Response to Laryngoscopy and Intubation in Vascular Surgeries

Babita, Bhupendra Singh, Anjum Saiyed, Reema Meena, Indu Verma, Chand Kishan Vyas

Department of Anaesthesia, Sawai Man Singh Medical College and Hospital, Jaipur, Rajasthan, India

## Abstract

**Background:** Stress response to laryngoscopy and intubation causes autonomic or endocrine disturbance such as hypertension, tachycardia, and arrhythmias that may be potentially dangerous in cardiovascular disease patients. These changes are maximum at 1 min after intubation and last for 5-10 min. Labetalol is a selective  $\alpha_1$ - and nonselective  $\beta_1$ - and  $\beta_2$ -adrenergic antagonist. It lowers blood pressure (BP) by decreasing systemic vascular resistance by  $\alpha_1$ -blockade and reflex tachycardia attenuated by simultaneous  $\beta$ -blockade. Fentanyl is a potent synthetic opioid agonist with rapid onset and short duration of action. It blocks afferent nerve impulses resulting from stimulation of the pharynx and larynx during intubation. This is a prospective, randomized, control trial carried out to compare the effect of labetalol and fentanyl on sympathomimetic response to laryngoscopy and intubation in vascular surgeries. **Materials and Methods:** Eighty four patients [American Society of Anesthesiologists (ASA) grade I and II] scheduled for vascular surgeries were divided into three groups (28 each). Group A received fentanyl 2  $\mu\text{g}/\text{kg}$  intravenous (IV), Group B received labetalol 0.25  $\text{mg}/\text{kg}$  IV, and Group C received 10 mL saline IV. The groups were compared for heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and rate pressure product (RPP). **Results:** The groups were comparable as per their demographic data and preoperative vitals. All the vitals decreased significantly ( $P < 0.05$ ) in Group A and Group B from just before intubation (5 min after the study drug) to 15 min after intubation compared to the control group. Labetalol decreased SBP, DBP, and MAP significantly at 1 min and 3 min after intubation and RPP at 1 min and 15 min after intubation. In HR, the difference was not significant ( $P > 0.05$ ). The incidence of hypertension and tachycardia was higher in Group C. No hypotension, bradycardia, and abnormal electrocardiogram (ECG) were recorded in any group. **Conclusion:** In lower doses, labetalol is a better agent than fentanyl in attenuating the sympathomimetic response to laryngoscopy and intubation but the difference is not significant. However, both effectively blunt the pressure response.

**Key words:** Fentanyl, general anesthesia, labetalol, pressure response, tracheal intubation, vascular surgery

## INTRODUCTION

Despite the emergence of new airway devices in recent years, rigid laryngoscopy and tracheal intubation remain the gold standard in airway management. The hemodynamic changes stemming from airway instrumentation are due to sympathoadrenal discharge caused by epipharyngeal and parapharyngeal stimulations, which cause a significant rise in the catecholamine level that increases blood pressure (BP) and pulse.<sup>[1]</sup>

These hemodynamic changes may be dangerous in susceptible patients such as those with hypertension, coronary artery disease, cerebrovascular disease, and intracranial aneurysm

and may cause arrhythmias, myocardial infarction (MI), left ventricle failure, and rupture of aneurysm.<sup>[2]</sup>

Various pharmacological methods are used to suppress this response but not any of these is 100% effective. So, it is desirable to use a drug with rapidly recognizable and easily treatable adverse effects. The procedure should be simple so that it can be recommended as a routine practice. Fentanyl is a potent synthetic opioid agonist with rapid onset (3-5 min), short duration of action (30-60 min), and peak effect at 5-7 min.<sup>[3]</sup> It decreases BP and heart rate (HR) on account of its property of vasodilatation, depression of vasomotor, and stimulation of vagal center. Overdose is treated by naloxone.<sup>[4]</sup>

Fentanyl also has a combination of analgesic potency and acceptable profile of adverse effects matched by no other class of drugs.<sup>[5]</sup>

### Access this article online

#### Quick Response Code:



Website:  
[www.karnatakaanaesthj.org](http://www.karnatakaanaesthj.org)

DOI:  
10.4103/2394-6954.163081

#### Address for correspondence:

Dr. Babita,  
Babita d/o Mahilal, Behind Tehseel, Chamad Gali, Ward No. 6,  
Tehseel - Nagar, Bharatpur - 321 205, Rajasthan, India.  
E-mail: drbabita24@gmail.com

Labetalol is a unique oral and parenteral antihypertensive drug that is  $\alpha$ 1- and nonselective  $\beta$ 1- and  $\beta$ 2-adrenergic antagonist. It reaches its peak effect at 5-15 min after intravenous (IV) injection and rapidly redistributes (5.9 min redistribution half-life).<sup>[6]</sup>

It lowers BP by decreasing systemic vascular resistance ( $\alpha$ 1-blockade), whereas reflex tachycardia triggered by vasodilatation is attenuated by simultaneous  $\beta$ -blockade. Cardiac output remains unchanged.<sup>[7]</sup>

The aim of the present study is to assess and compare the hemodynamic parameters and side effects associated with laryngoscopy and intubation between the three groups.

## MATERIALS AND METHODS

This prospective randomized study was conducted between December 2012 and May 2013.

We studied 84 patients as per American Society of Anesthesiologists (ASA) grade I and II, either sex weighing 40-65 kg, aged 20-55 years, and scheduled for elective vascular surgery were enrolled after approval from the institutional ethics committee and written informed consent of the patient was obtained. Patients having compromised renal, pulmonary, and cardiac status, diabetes, anticipated difficult intubation, hypertension, compensatory tachycardia, baseline pulse <60 bpm, baseline systolic blood pressure (SBP) <100 mmHg, those on medicines with cardiovascular effects, and those having known allergy to the anesthetic agents used were excluded from the study. The research methodology was prospectively randomized with the help of chit-in-the-box method and the patients were divided into the following three groups:

Group A - fentanyl 2  $\mu$ g/kg (10 mL total volume); Group B - labetalol 0.25 mg/kg (10 mL total volume); and Group C - normal saline 0.9% (10 mL total volume).

In the operation theater, the patient's body weight, fasting, consent, and preanaesthetic check-up (PAC) were checked. Baseline parameters [pulse rate (PR), SBP, diastolic blood pressure (DBP), mean arterial pressure (MAP), and rate pressure product (RPP)] were recorded. Two IV lines were secured. All the patients were premedicated by midazolam injection of dosage 0.05 mg/kg, glycopyrrolate injection of dosage 0.005 mg/kg, ondansetron injection of dosage 0.1 mg/kg, and diclofenac injection of dosage 1.5 mg/kg intravenously. After 10 min, all the parameters were recorded and then the study drug was given in a double-blind fashion over 2 minutes, 5 min. before intubation. Then, preoxygenation was done for 3 min. Then, thiopentone injection of dosage 5 mg/kg was given slowly within 1 min followed by succinylcholine injection of dosage 2 mg/kg. The patient was ventilated with 100% oxygen for 45 s. The hemodynamic parameters were recorded just before intubation (5 min after the study drug). Then, intubation was done. Maintenance was done with 40% O<sub>2</sub> + 60% N<sub>2</sub>O + 0.4 vol% isoflurane. Muscle relaxation was provided by atracurium injection of dosage 0.5 mg/kg

loading dose and subsequent dose of 0.1 mg/kg. Hemodynamic parameters and any side effect were recorded at 1 min, 3 min, 5 min, 7 min, 10 min, and 15 min after intubation.

At the end of the surgery, neuromuscular block was reversed with neostigmine of dosage 0.05 mg/kg IV and glycopyrrolate of dosage 0.01 mg/kg IV.

We defined the following terms for study:

- Hypotension - defined as SBP <25% of baseline value or 90 mmHg, whichever is lower
- Hypertension - defined as SBP >25% of baseline value or 150 mmHg, whichever is higher
- Tachycardia - defined as HR >25% of baseline value
- Bradycardia - defined as HR <60 bpm
- An arrhythmia - any ventricular or supraventricular premature beat or any rhythm other than sinus.

## Statistical analysis

The differences between the mean values of the three groups were analyzed using one-way analysis of variance (ANOVA) test and within the groups, it was done using paired *t*-test. All the qualitative data were summarized in the form of proportions. Differences between the proportions were analyzed using Chi-square test. The levels of significance and  $\alpha$  error were kept 95% and 5%, respectively, for all statistical analyses.

$P < 0.05$  were considered as significant (S) and  $P > 0.05$  as statistically nonsignificant (NS).

## RESULTS

All quantitative data were summarized in the form of mean  $\pm$  standard deviation (SD). The three groups were comparable in patient characteristics with respect to age, gender, mean weight, and ASA physical status ( $P > 0.05$ ) [Table 1]. Mean baseline variables were comparable in the three groups [Table 2].

Figure 1 shows that just before intubation, PR decrease in Group A and Group B was due to effect of the drugs. The increase in HR after intubation was minimal in Group A and Group B as compared with Group C, which was statistically significant ( $P < 0.05$ ). In Group A, the PR significantly increased at 1 min and 3 min after intubation and returned to the baseline at 7 min after intubation and below the baseline at 10 min after intubation. Meanwhile, in Group B, PR increased significantly at 1 min, 3 min, and 5 min after intubation and returned to the baseline at 7 min and was below the baseline at 10 min after intubation. In Group C, there was a significant increase in PR at all points when compared to the baseline.

**Table 1: Demographic characteristics**

Variables	Group A	Group B	Group C	P
Age (years)	43.4 $\pm$ 11.4	43.5 $\pm$ 8.5	41.8 $\pm$ 10.4	$\geq$ 0.05
Gender (male/female)	23/5	21/7	23/5	$\geq$ 0.05
Weight (kg)	56 $\pm$ 6	56.7 $\pm$ 5.7	56.6 $\pm$ 5.5	$\geq$ 0.05
ASA grade (I/II)	23/5	23/5	24/4	$\geq$ 0.05

ASA: American society of anaesthesiologists

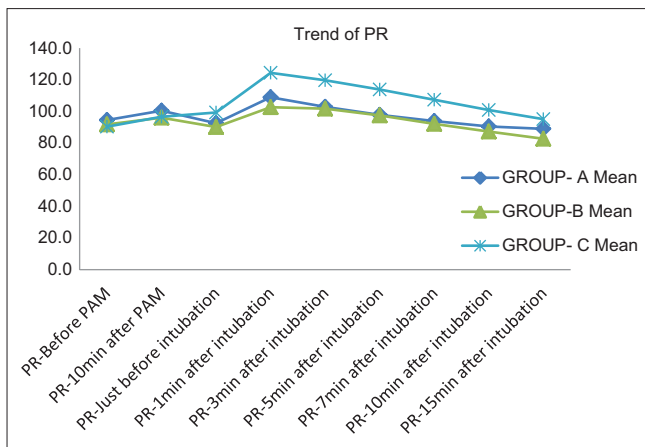


Figure 1: Comparison of PR between the three groups

Table 2: Comparison of mean baseline variables between the three groups

	Baseline PR (bpm)	Baseline SBP (mmHg)	Baseline DBP (mmHg)	Baseline MAP (mmHg)	Baseline RPP
Group A	94.6±13.9	123.5±5.7	82.4±4.5	96.1±4.1	11663.4±1698.8
Group B	91.8±10.3	123.5±7.7	80.3±4.5	94.7±4.8	11343.3±1568.5
Group C	90.3±10.5	124.8±7.1	79.6±5.7	94.7±3.8	11255.3±1294.6
P value	>0.05	>0.05	>0.05	>0.05	>0.05

PR: Pulse rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure, RPP: Rate pressure product

Figure 2 shows that in Groups A and B, SBP returned to the baseline at 7 min and was below the baseline after this but in Group A, it was not significant. Meanwhile, in Group B, the decrease was significant after 7 min below the baseline. In Group C, compared to the baseline, there was a statistically significant rise at all points.

Figure 3 shows that in Group A, DBP was comparable to the baseline at 7 min after intubation and significantly decreased 10 min after intubation. Meanwhile, in Group B it returned to baseline levels at 10 min after intubation. In group C DBP increase significantly upto 10 min after intubation and it returned to baseline at 15 min after intubation. DBP after intubation was significantly lower in the labetalol group than the fentanyl group at 1 min and 3 min after intubation. The differences were not significant at other times.

Figure 4 shows the mean arterial BP that was calculated from the recordings of SBP and DBP, which were recorded at various time intervals. In Group A, there was a significant fall in MAP 10 min after intubation while in group B, the decrease was significant at 15 min after intubation. In Group C, there was a significant increase after intubation up to 15 min.

MAP after intubation was significantly lower in the labetalol group than the fentanyl group at 1 min and 3 min after intubation. The differences were not significant at other times.

Figure 5 shows RPP, which was calculated from recordings of SBP and PR (formula:  $SBP \times HR$ ), which were recorded at

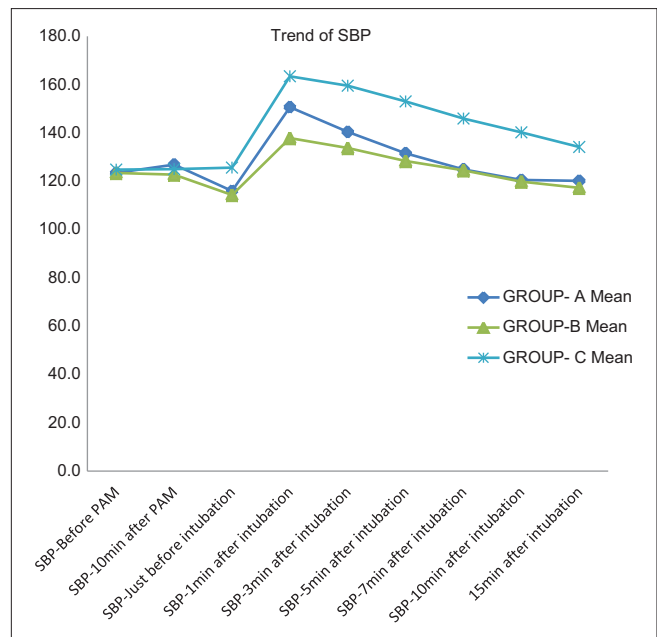


Figure 2: Comparison of SBP between the three groups

various time intervals. The RPP is an index of myocardial oxygen demand. In Group A, compared to the baseline value, there was a significant fall in RPP 15 min after intubation while in Group B, RPP decreased significantly 10 min after intubation and returned to the baseline at 7 min after intubation. Meanwhile, in Group C, RPP increased significantly all points. RPP after intubation was lower in the labetalol group than in the fentanyl group but the differences were significant only at 1 min and 15 min after intubation.

Figure 6 shows that in Group A, hypertension was in nine (32%) patients and tachycardia in five (18%) patients. In Group B, hypertension was in one (4%) patient and tachycardia in one (4%) of the cases intraoperatively. In Group C, hypertension was in 26 (93%) patients and tachycardia in 27 (96%) of the cases intraoperatively.

No respiratory depression and abnormal cardiac rhythm was noted in any of the three groups.

## DISCUSSION

The hemodynamic responses to laryngoscopy and intubation cause elevation in HR and BP. There may be life-threatening complications with these responses. Traditionally used drugs like lignocaine, clonidine, esmolol, etc., are either not fully effective or they are associated with considerable side effects at doses required to attenuate these responses. Therefore, it has become imperative to develop a novel technique/drug to prevent these potentially hazardous responses.

The drugs for controlling these hemodynamic responses aim to stabilize HR and BP during laryngoscopy and intubation in order to prevent any rise in myocardial workload and oxygen demand as well as to preserve the perfusion of vital organs.<sup>[8]</sup> It is desirable to use a drug with least, rapidly recognizable, and easily treatable adverse effects.

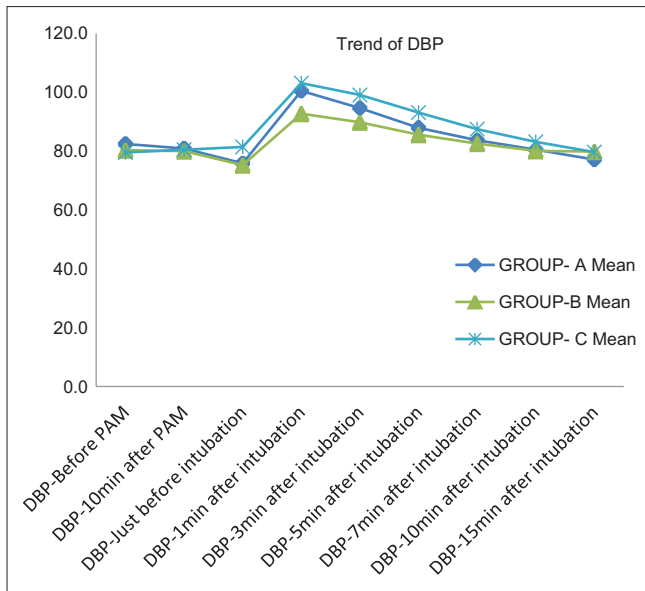


Figure 3: Comparison of DBP between the three groups

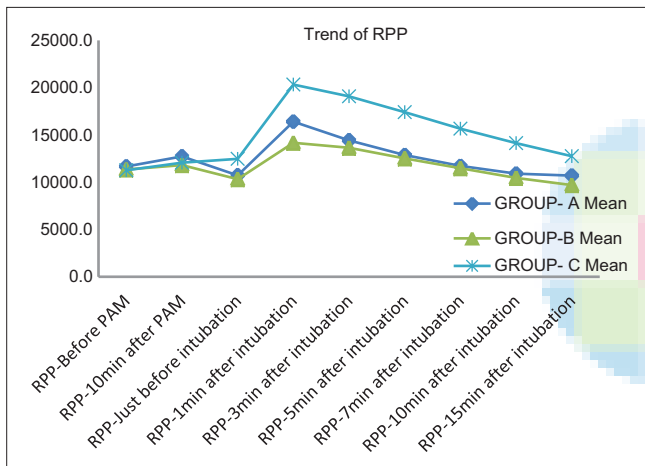


Figure 5: Comparison of RPP between the three groups

It is thought that fentanyl suppresses the hemodynamic response by increasing the depth of anesthesia and decreasing the sympathetic discharge.<sup>[9]</sup> Low doses of fentanyl were employed because a large dose leads to muscular rigidity, bradycardia, nausea, and vomiting. Large doses may also cause postoperative respiratory depression, especially in surgery with short duration (less than 1 h).<sup>[10]</sup>

Labetalol is an antihypertensive drug that decreases the pressure response of intubation by  $\alpha_1$  and  $\beta$ -adrenergic receptor blockade. Presynaptic  $\alpha_2$ -receptors are spared by labetalol so that the released norepinephrine can continue to inhibit further release of catecholamines via the negative feedback mechanism resulting from the stimulation of  $\alpha_2$ -receptors.

It has been used by many researchers like Singh *et al.*,<sup>[11]</sup> Inada *et al.*,<sup>[12]</sup> Ramanathan *et al.*,<sup>[13]</sup> and Maharaj *et al.*<sup>[14]</sup> for the attenuation of hemodynamic response to tracheal intubation as well as extubation in various doses, along with various

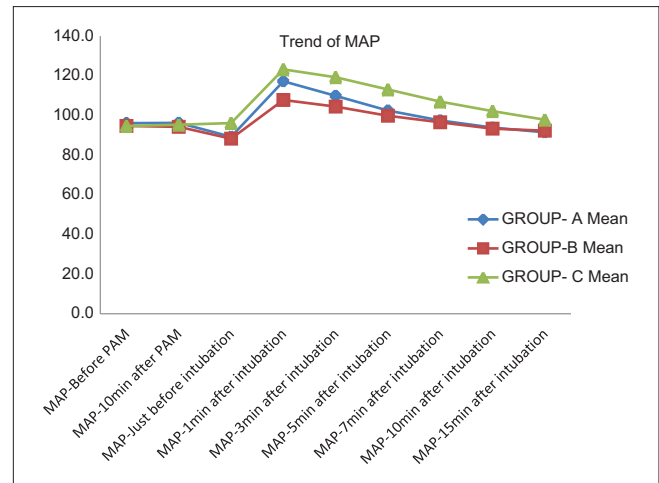


Figure 4: Comparison of MAP between the three groups

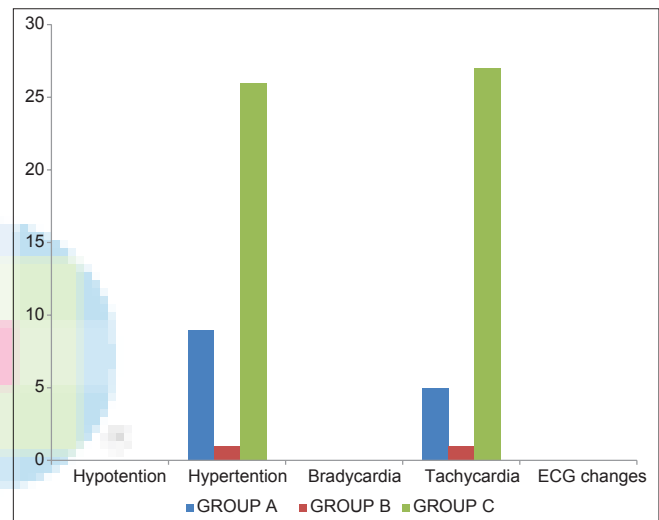


Figure 6: Side effects and complications

anesthetic regimens. They have been quite successful in their efforts and have found labetalol effective in attenuating the pressure responses to laryngoscopy and intubation but their findings need to be further substantiated and the effectiveness of labetalol in blunting the pressure response and its comparison to fentanyl needs to be evaluated in our scenario because these studies lack such information.

Gupta and Tank<sup>[9]</sup> noticed similar trends in PR, BP, and RPP before intubation and after intubation.

Chung *et al.*<sup>[15]</sup> also validate the findings; they had reported that a single dose of fentanyl of dosage 2 mcg/kg given preoperatively decreases the pressure response.

Channaiah *et al.*<sup>[16]</sup> also obtained the same result just before intubation and 1 min and 3 min after intubation using 2  $\mu$ /kg fentanyl at 5 min before intubation. They obtained the same result of RPP just before intubation but after intubation, there was an insignificant rise in RPP using 2  $\mu$ /kg fentanyl at 5 min before intubation; RPP after 5 min was significantly below the baseline.



Bostan *et al.*<sup>[17]</sup> also obtained the same result just before intubation at 1 min and 3 min after intubation using 1 µg/kg fentanyl at 3 min before intubation.

Ko *et al.*<sup>[18]</sup> in their study using fentanyl premedication 2 µg/kg and administration of 5 min before laryngoscopy found this smaller dose to be equally efficacious; only 14.9% increase in HR was noted.

Our results are a little different from the findings of Hassani *et al.*<sup>[19]</sup> who noted a significant fall in HR compared to the baseline immediately after intubation but the difference can be explained by the absence of glycopyrrolate injection in its anesthetic regimen.

Kim *et al.*<sup>[20]</sup> reported that a single dose of labetalol of dosage 0.25 mg/kg given preoperatively 5 min before intubation decreases HR significantly after intubation up to 10 min.

Roelofse *et al.*<sup>[21]</sup> found that labetalol of dosage 1 mg/kg given as an IV bolus 1 min before laryngoscopy was not effective in the attenuation of HR. This failure of the study can be explained by the different time of administration of the study drug because labetalol has peak effect after 5-10 min.<sup>[6]</sup> The incidence of hypotension, electrocardiogram (ECG) changes, and bradycardia were not much different between the three groups in our study.

Incidence of intraoperative hypertension was more in Group C compared to the study group. Singh *et al.*<sup>[11]</sup> observed only the side effect of labetalol in the form of bradycardia, intraoperatively. Seven (28%) patients developed bradycardia (PR < 50 bpm) after the study period of 10 min. The incidence of tachycardia and hypertension was significantly higher in the placebo group. These findings are similar to the findings in our study because bradycardia was noted after 10 min.

Gupta *et al.*<sup>[22]</sup> observed one case of bradycardia out of 32 (3.2%) during the study period of laparoscopic cholecystectomy in fentanyl compared to clonidine.

## CONCLUSION

We conclude that both fentanyl and labetalol effectively blunt the hemodynamic response to endotracheal intubation in patients undergoing vascular surgeries under general anesthesia and can be safely used. In lower doses, labetalol (0.25 mg/kg) is a better agent than fentanyl (2 µg/kg) in attenuating the sympathomimetic response to laryngoscopy and intubation.

## REFERENCES

1. Kayhan Z, Aldemir D, Mutlu H, Oğuş E. Which is responsible for the haemodynamic response due to laryngoscopy and endotracheal intubation? Catecholamines, vasopressin or angiotensin? *Eur J Anaesthesiol* 2005;22:780-5.
2. Prys-Roberts C, Foëx P, Biro GP, Roberts JG. Studies of anaesthesia in relation to hypertension. V. Adrenergic Beta-receptor blockade. *Br J Anaesth* 1973;45:671-81.
3. Martin DE, Rosenberg H, Aukburg SJ, Bartkowski RR, Edwards MW Jr, Greenhow DE, *et al.* Low-dose fentanyl blunts responses to tracheal intubation. *Anesth Analg* 1982;61:680-4.

4. Takahashi M, Sugiyama K, Hori M, Chiba S, Kusaka K. Naloxone reversal of opioid anesthesia revisited: Clinical evaluation and plasma concentration analysis of continuous naloxone infusion after anesthesia with high-dose fentanyl. *J Anesth* 2004;18:1-8.
5. Bowdle TA. Adverse effects of opioid agonists and agonist-antagonists in anaesthesia. *Drug Saf* 1998;19:173-89.
6. Kanto J, Allonen H, Kleimola T, Mäntylä R. Pharmacokinetics of labetalol in healthy volunteers. *Int J Clin Pharmacol Ther Toxicol* 1981;19:41-4.
7. Stoelting RK, Hillier SC. Pharmacology & physiology in anesthetic practice. In: *Handbook of Pharmacology and Physiology in Anesthetic Practice*. 2<sup>nd</sup> ed. Philadelphia, USA: Lippincott Williams & Wilkins; 2006. p. 87-342, 347.
8. Fox EJ, Sklar GS, Hill OH, Vilaneur R, King BD. Complications related to the pressor response to endotracheal intubation. *Anesthesiology* 1977;47:524-5.
9. Gupta S, Tank P. A comparative study of efficacy of esmolol and fentanyl for pressure attenuation during laryngoscopy and endotracheal intubation. *Saudi J Anaesth* 2011;5:2-8.
10. Leslie JB, Kalayjian RW, McLoughlin TM, Plachetka JR. Attenuation of the hemodynamic responses to endotracheal intubation with preinduction intravenous labetalol. *J Clin Anesth* 1989;1:194-200.
11. Singh SP, Quadir A, Malhotra P. Comparison of esmolol and labetalol, in low doses, for attenuation of sympathomimetic response to laryngoscopy and intubation. *Saudi J Anaesth* 2010;4:163-8.
12. Inada E, Cullen DJ, Nemeskal R, Teplick R. Effect of labetalol or lidocaine on the hemodynamic response to intubation: A controlled, randomized double-blind study. *J Clin Anesth* 1989;1:207-13.
13. Ramanathan J, Sibai BM, Mabie WC, Chauhan D, Ruiz AG. The use of labetalol for attenuation of hypertensive response to endotracheal intubation in preeclampsia. *AM J Obstet Gynecol* 1988;159:650-4.
14. Maharaj RJ, Thompson M, Brock-Utne JG, Williamson R, Downing JW. Treatment of hypertension following endotracheal intubation. A study comparing the efficacy of labetalol, practolol and placebo. *S Afr Med J* 1983;63:691-4.
15. Chung KS, Raymond S, Jonathan D. A comparison of fentanyl, esmolol and their combination for blunting the haemodynamic response. *Anaesth Analg* 1991;72:482-6.
16. Channaiah VB, Kurek NS, Moses R, Chandra SB. Attenuation of hemodynamic response to laryngoscopy and endotracheal intubation with pre induction IV fentanyl versus combination of IV fentanyl and sub lingual nitroglycerin spray. *Med Arch* 2014;68:339-44.
17. Bostan H, Ahmet Eroglu A. Comparison of the clinical efficacies of fentanyl, esmolol and lidocaine in preventing the hemodynamic responses to endotracheal intubation and extubation. *J Curr Surg* 2012;2:24-8.
18. Ko SH, Kim DC, Han YJ, Song HS. Small dose fentanyl: Optimal time of injection for blunting the circulatory response to tracheal intubation. *Anesth Analg* 1998;86:658-61.
19. Hassani V, Movassaghi G, Goodarzi V, Safari S. Comparison of fentanyl and fentanyl plus lidocaine on attenuation of hemodynamic responses to tracheal intubation in controlled hypertensive patients undergoing general anesthesia. *Anesth Pain Med* 2013;2:115-8.
20. Kim SS, Kim JY, Lee JR, Song HS. The effects of verapamil, labetalol, or fentanyl on hemodynamic responses to endotracheal intubation. *Korean J Anesthesiol* 1994;27:143-54.
21. Roelofse JA, Shipton EA, Joubert JJ, Grotepass FW. A comparison of labetalol, acebutolol, and lidocaine for controlling the cardiovascular responses to endotracheal intubation for oral surgical procedures. *J Oral Maxillofac Surg* 1987;45:835-41.
22. Gupta K, Lakhnopal M, Gupta PK, Krishan A, Rastogi B, Tiwari V. Premedication with clonidine versus fentanyl for intraoperative hemodynamic stability and recovery outcome during laparoscopic cholecystectomy under general anesthesia. *Anesth Essays Res* 2013;7:29-33.

**How to cite this article:** Babita, Singh B, Saiyed A, Meena R, Verma I, Vyas CK. A comparative study of labetalol and fentanyl on the sympathomimetic response to laryngoscopy and intubation in vascular surgeries. *Karnataka Anaesth J* 2015;1:64-8.

**Source of Support:** Nil. **Conflict of Interest:** None declared.