ORIGINAL ARTICLE ASIAN JOURNAL OF MEDICAL SCIENCES

Comparison of hemodynamic effects of intravenous labetalol plus intravenous fentanyl and intravenous fentanyl alone for attenuating reflex responses to laryngoscopy and intubation: A prospective randomized controlled trial

Isha Jain[1], Satyendra Singh Yadav[2], Shakti Singhal[3], Jaykumar Kolewar[4], Preeti Goyal[5]

[1,4]Postgraduate Resident, [2]Associate Professor, [3]Assistant Professor, [5]Professor and Head, Department of Anaesthesiology, Gajra Raja Medical College, Gwalior, Madhya Pradesh, India

Submission: 21-02-2023 Revision: 02-05-2023 Publication: 01-06-2023

ABSTRACT

Background: Laryngoscopy is an essential part of endotracheal intubation. Direct laryngoscopy and tracheal intubation are a noxious stimulation that causes significant stress response for patient. It is this nociceptive response which leads to the changes in the physiologic parameters of the patient like hemodynamic changes. Therefore, combination of many drugs used with the primary anesthetic drug in an attempt to minimize the hemodynamic pressor response associated with intubation while limiting patient risk. **Aims and Objectives:** Direct laryngoscopy and tracheal intubation are the nociceptive response which leads to the changes in the hemodynamic parameters. Study aimed to compare the hemodynamic response of labetalol and fentanyl with only fentanyl during laryngoscopy and intubation, untoward adverse effects. **Materials and Methods:** One hundred and two of either sex, aged between 18 and 65 year of the American Society of Anesthesiology grade I/II under general anesthesia divided into two groups, Group LF and Group F with 51 patients in each. Group LF receives intravenous 0.25 mg/kg labetalol in 10 mL saline 5 min prior and fentanyl 2 μg/kg 3 min before intubation and Group F receives intravenous normal saline 10 mL 5 min before intubation and 2 μg/kg fentanyl 3 min before intubation. Changes in heart rate (HR), blood pressure, and saturation of oxygen in the blood documented in both the groups. **Results:** In the present study, HR, systolic blood pressure, diastolic blood pressure, and mean arterial blood pressure were noted down as before intubation, after intubation, at intubation, immediately after 1, 3, 5, 10, and 15 min for patients in both the groups. The results obtained from the analysis showed that there was an increase in parameters of Group F compared to Group LF as after intubation to 15 min due to stress response and statistically significant ($P<0.05$) in both the groups. **Conclusion:** Both labetalol and fentanyl can be used safely to attenuate the hemodynamic response, but labetalol and fentanyl combination prove to be more effective in attenuating hemodynamic response.

Key words: Fentanyl; Hemodynamic changes; Labetalol; Laryngoscopy

Access this article online

Website: http://nepjol.info/index.php/AJMS

DOI: 10.3126/ajms.v14i6.52489

E-ISSN: 2091-0576

P-ISSN: 2467-9100

INTRODUCTION

Direct laryngoscopy and tracheal intubation during general anesthesia lead to sympathetic stimulation and release of plasma catecholamines concentration which manifests clinically as tachycardia and hypertension along with raised intraocular and intracerebral pressure.[1]

An increase in heart rate (HR), together with elevation of systolic blood pressure (SBP), increases the rate pressure

Address for Correspondence:
Dr. Jaykumar Kolewar, Postgraduate Resident, Department of Anaesthesiology, Gajra Raja Medical College, Gwalior, Madhya Pradesh, India. **Mobile:** +91-9993083012. **E-mail:** drjaykumarkolewar@yahoo.com

product (RPP), thus compromising myocardial contractility and oxygen supply.[2] Variety of pretreatments ranging from topical anesthesia of larynx to administration of several classes of drugs such as nitroglycerine, B-blockers, and opioids have been made.

Each technique has its own disadvantages, so many times multimodal therapy rather than single intervention has been in practice to attenuate this response.

Labetalol is an antihypertensive alpha-1, beta-1, and beta-2 adrenergic antagonist agent. It lowers the blood pressure by decreasing systemic vascular resistance (alpha-1 blockade) whereas reflex tachycardia triggered by vasodilation is attenuated by simultaneous beta-blockade and cardiac output remains unchanged.[3] It has better safety profile and hemodynamic stability. Hence, labetalol may be the drug of choice to attenuate the adrenergic response to laryngoscopy and intubation.

Fentanyl commonly used in conjunction with a primary anesthetic because it is cost-effective and brings many other advantages. As a member of the opioid family, fentanyl is a μ-opioid receptor agonist that is characterized by high potency, rapid onset, and short duration of action and produces no histamine release – thus avoiding the negative cardiovascular effects caused by such a response.[4]

Aims and objectives

To compare the haemodynamic response of labetalol and fentanyl with only fentanyl during laryngoscopy and intubation under general anaesthesia,to evaluate whether labetalol and fentanyl combination is better than only fentanyl with regard to above criteria and to observe any side effects or complications.

Primary objectives

The primary objectives of this study were to compare the hemodynamic response of intravenous labetalol plus fentanyl with only fentanyl during laryngoscopy and intubation under general anesthesia.

Secondary objectives

The primary objectives of this study were as follows:

1. To evaluate whether labetalol and fentanyl combination is better than only fentanyl with regard to above criteria
2. To observe any side effect or complications.

MATERIALS AND METHODS

A prospective study with sample size of 102 patients of either sex, aged between 18 and 65 year, belonging to American Society of Anesthesiology (ASA) grade I and ASA grade II undergoing elective surgery under general anesthesia enrolled for the study in G.R. Medical college and J.A. Group of hospitals. Patient giving informed and written consent to participate in study, age between 18 and 65 years, patient of either sex, ASA grade I and ASA grade II are included in the study and patient's refusal, emergency surgeries, history of any significant pulmonary, cardiovascular, hepatorenal disease, hypertension, and patients on beta-blockers are excluded from the study.

All patients divided into two groups, Group LF and Group F with 51 patients in each group. Approval from the Institutional Ethics Committee taken and informed consent from the patient obtained.

All the patients were examined a day before surgery to do complete general, physical, and systemic examination. All the required routine and special investigations including complete blood count, random blood sugar, blood urea, serum creatinine, E.C.G. (above 30 years of age), and chest X-ray (above 30 year of age) as per hospital protocol were carried out.

The purpose and protocol of the study were explained to patients and informed written consent was obtained.

All patients were kept nil orally for at least 6 h before the procedure. On arrival of the patient in the operation theater, intravenous access with 18 G cannula was inserted into the patient's forearm. All routine monitors including pulse oximeter, B.P. cuff, and E.C.G were connected and observations were recorded by multipara monitor (Mindray Bene view T5 CM 23123727). Preloading was done with approximately 10 mL/kg of lactated ringer solution. All the baseline (B0) vitals parameters including pulse rate, non-invasive SBP, diastolic blood pressure (DBP), and mean arterial blood pressure (MAP) were recorded preoperatively. Saturation of oxygen in the blood (SPO_2) was also measured as minimum standard monitoring protocol but not included for our study purpose.

Selected 102 patients of ASA Grade I and II scheduled for surgeries under general anesthesia were randomly divided into two groups (n=51 each) by envelope method.

Group LF patient receives intravenous 0.25 mg/kg labetalol diluted in 10 mL saline 5 min prior and fentanyl 2 μg/kg 3 min before intubation.

Group F patient receives intravenous injection normal saline 10 mL 5 min before intubation and 2 μg/kg fentanyl 3 min before intubation.

Table 1: Heart rate wise distribution

Heart rate	Group F (n=51)	Group LF (n=51)	t-value	P-value
T1 (Before induction)	85.43±11.37	85.66±8.63	−0.118	0.908
T2 (After induction)	83.31±10.11	71.86±6.53	6.989	<0.0001
T3 (At intubation)	93.45±19.26	73.39±6.53	7.040	<0.0001
T4 (1 min)	92.78±18.20	72.88±6.43	7.362	<0.0001
T5 (3 min)	91.13±17.02	71.70±6.73	7.579	<0.0001
T6 (5 min)	88.27±14.39	71.21±6.79	7.652	<0.0001
T7 (10 min)	84.49±11.35	70.45±6.11	7.773	<0.0001
T8 (15 min)	82.80±9.80	70.33±5.94	7.770	<0.0001

Table 2: Systolic blood pressure wise distribution

SBP	Group F (n=51)	Group LF (n=51)	t-value	P-value
T1 (Before induction)	127.37±12.09	124.45±12.27	−1.214	0.2276
T2 (After induction)	119.86±13.79	109.86±8.93	4.345	<0.0001
T3 (At intubation)	129.56±10.09	111.94±8.99	9.311	<0.0001
T4 (1 min)	129.03±10.10	112.23±8.44	9.109	<0.0001
T5 (3 min)	127.74±9.72	111.47±9.24	8.664	<0.0001
T6 (5 min)	126.92±9.88	109.80±8.62	9.318	<0.0001
T7 (10 min)	125.74±9.23	108.60±7.87	10.059	<0.0001
T8 (15 min)	123.98±9.33	108.19±7.68	9.323	<0.0001

Table 3: Diastolic blood pressure wise distribution

DBP	Group F (n=51)	Group LF (n=51)	t-value	P-value
T1 (Before induction)	87.33±6.83	84.56±7.66	1.922	0.057
T2 (After induction)	79.88±6.97	71.23±6.60	6.427	<0.0001
T3 (At intubation)	85.31±5.79	74.03±6.87	8.956	<0.0001
T4 (1 min)	84.54±5.86	73.54±6.52	8.955	<0.0001
T5 (3 min)	83.43±6.08	72.66±6.11	8.910	<0.0001
T6 (5 min)	82.31±5.81	71.72±5.42	9.507	<0.0001
T7 (10 min)	80.58±4.59	70.54±5.48	10.022	<0.0001
T8 (15 min)	79.98±5.00	70.31±5.17	9.596	<0.0001

DBP: Diastolic blood pressure

For eligible patient, demographic information collected and a physical examination was performed. A standardized anesthesia regimen was followed. After preoxygenation Inj glycopyrrolate (0.004 mg/kg) will be given. Patients will get induce with thiopentone sodium (5 mg/kg) and atracurium (0.5 mg/kg). Intubation done with 8.5 mm and 7.5 mm size endotracheal tube for male and female patients, respectively, by the same experienced anesthetist. Anesthesia maintained on O2:N2O (50:50), 1% sevoflurane, and inj. atracurium. Any increase in HR and MAP >20% of B0 treated with increase of sevoflurane concentration and bolus dose of propofol.

Table 4: Mean arterial blood pressure wise distribution

MAP	Group F (n=51)	Group LF (n=51)	t-value	P-value
T1 (Before induction)	100.64±8.18	97.88±8.15	1.709	0.057
T2 (After induction)	93.23±8.74	84.68±6.97	5.965	<0.0001
T3 (At intubation)	100.01±6.64	86.68±6.92	9.889	<0.0001
T4 (1 min)	99.37±6.66	86.45±6.56	9.863	<0.0001
T5 (3 min)	98.25±6.65	85.60±6.28	9.866	<0.0001
T6 (5 min)	97.23±6.56	84.41±5.71	10.528	<0.0001
T7 (10 min)	95.58±5.61	83.21±5.38	11.352	<0.0001
T8 (15 min)	94.64±5.85	82.94±5.40	10.498	<0.0001

MAP: Mean arterial blood pressure

Table 5: SPO_2 wise distribution

SPO_2	Group F (n=51)	Group LF (n=51)	t-value	P-value
T1 (Before induction)	99.37±0.48	99.47±0.50	1.030	0.3053
T2 (After induction)	99.39±0.49	99.41±0.49	0.206	0.8371
T3 (At intubation)	99.37±0.48	99.47±0.50	1.030	0.3053
T4 (1 min)	99.41±0.49	99.49±0.50	0.816	0.4164
T5 (3 min)	99.37±0.48	99.45±0.50	0.824	0.4117
T6 (5 min)	99.35±0.48	99.47±0.50	1.030	0.3053
T7 (10 min)	99.45±0.50	99.47±0.50	0.000	1.0000
T8 (15 min)	99.33±0.47	99.47±0.50	1.249	0.2146

SPO_2: Saturation of oxygen in the blood

Table 6: Patient characteristics

Characteristics	Group LF	Group F	P-value
Age	45.90±9.65	44.03±9.20	0.3189
Sex (Male/Female)	37/14	32/19	0.2899
Weight	60.80±8.11	61.68±5.20	0.5157

Data are expressed in mean±SD, SD: Standard deviation

HR, SBP, DBP, and MAP recorded immediately after loading doses of labetalol and fentanyl, after induction, after intubation at 1, 3, 5, 10, and 15 min after induction.

At the end of surgery neuromuscular block will be reversed with injection neostigmine 0.05 mg/kg and injection glycopyrrolate 0.008 mg/kg. Incidence of hypotension or bradycardia will be recorded.

Statistical analysis

The statistical analysis of this study will be carried out by paired t-test. P>0.05 is statistically insignificant, P<0.05 is statistically significant, and P<0.01 is statistically highly significant.

The statistical analysis will be done using SPSS software (Version 20).

RESULTS

The results obtained from the analysis showed that there was an increase in HR of Group F compared to Group LF as after intubation to 15 min due to stress response and statistically significant (P<0.05) in both of them groups as shown in Table 1.

The results obtained from the analysis in Table 2 showed that there was an increase in SBP of Group F compared to Group LF as after intubation to 15 min due to stress response and statistically significant (P<0.05) in both of them groups.

The results obtained from the analysis in Table 3 showed that there was an increase in DBP of Group F compared to Group LF as after intubation to 15 min due to stress response and statistically significant (P<0.05) in both of them groups.

The results obtained from the analysis in Table 4 showed that there was an increase in MAP of Group F compared to Group LF as after intubation to 15 min due to stress response and statistically significant (P<0.05) in both of them groups.

The results obtained from the analysis in Table 5 showed that there was no any statistically significant between the two groups (P>0.05).

DISCUSSION

Laryngoscopy and tracheal intubation cause increase in reflex sympathoadrenal response.[5] These responses are transient and variable and may not be significant in otherwise normal individuals. However, in patients with cardiovascular compromise such as hypertension, ischemic heart disease, and cerebrovascular disease and in patients with intracranial aneurysms, even these transient changes in hemodynamic can result in potentially harmful effects such as left ventricular failure, pulmonary edema, myocardial ischemia, ventricular dysrhythmias, and cerebral hemorrhage.[6]

Because laryngoscopy and tracheal intubation can cause above-mentioned adverse events in patients with comorbid conditions, it is prudent to attenuate hemodynamic response associated with it.[7]

Beta-blockers are group of pharmacological agents employed for blunting hemodynamic response to laryngoscopy and intubation. However, studies have shown that they are efficient in attenuating HR response compared to blood pressure response.[8,9] Hence, a drug which can attenuate both the HR response and blood pressure response effectively to laryngoscopy and intubation without having any adverse effects such as respiratory depression, post-operative nausea and vomiting, and sedation would help in improving the patient outcome.

The use of agonist antagonist analgesics for both intraoperative and post-operative analgesia is an acceptable alternative.

In the present study, on comparing the age and weight distribution between the Group F and Group LF in Table 6, it was found that mean and standard deviation of age and weight were calculated as (45.90±9.65 years vs. 44.03±9.20 years) and (60.80±8.11 kg vs. 61.68±5.20 kg) for both the groups, respectively, which was statistically not significant (P>0.05). In addition, the gender status in both the group majority was male (62.74% vs. 72.54%) then females (37.25% vs. 27.45%).

HR, systolic pressure, diastolic pressure, and mean blood pressure were noted down as before intubation, after intubation, at intubation, immediately after 1, 3, 5, 10, and 15 min for patients in both the groups.

This study has demonstrated that the use of intraoperative infusion Labetalol+Fentanyl helps attenuate stress responses to different noxious stimuli during surgery and helps maintain hemodynamic stability when compared to fentanyl infusion.

Labetalol is an alpha-1, beta-1, and beta-2 adrenergic antagonist with antihypertensive properties. It lowers blood pressure by decreasing systemic vascular resistance (alpha-1 blockade), while reflex tachycardia caused by vasodilation which is suppressed by concurrent beta-blockade and cardiac output remains unchanged. It has a higher safety profile and greater hemodynamic stability. As a result, the main finding of this study was that intraoperative infusion of Labetalol + Fentanyl significantly reduces the pressor response to intubation, noxious stimuli, extubation, and recovery, as evidenced by significantly lower HR and mean arterial pressure in the LF group compared to the fentanyl group.

In the present study, before induction, mean HR (85.43±11.37 beats/min vs. 85.66±8.63 beats/min), mean systolic blood pressure (127.37±12.09 mmHg vs. 124.45±12.27 mmHg), mean DBP (87.33±6.83 mmHg vs. 84.56±7.66 mmHg), and MAP (100.64±8.18 mmHg vs. 97.88±8.15 mmHg) were found statistically insignificant between Group F to Group LF (P>0.05). While remaining parameters after intubation, at intubation, immediately after 1, 3, 5, 10, and

15 min for patients in both the groups were increasing in HR, SBP, DBP, and MAP of Group F compared to Group LF due to stress response with statistically significant (P<0.05).

Similar study by Patel et al.,[10] have found that immediately after intubation HR was 82.60±5.0/min in LF group and 97.64±4.71/min in Group F (P<0.01). MAP was higher in Group F than Group LF (106.84±3.89 mm of Hg, 83.02±3.75 mm of Hg, respectively P<0.001). Immediately after skull pin insertion rise in HR (Group LF 79.76±5.07/min and Group F 97.84±4.40/min, respectively, P<0.001) and MAP (Group LF 80.28±5.32 mm of Hg and Group F 103.17±7.66 mm of Hg, respectively, P<0.001) was at lesser extent in Group LF. It was defined that in Group F, HR and MAP were significantly raised but was within higher normal range suggesting that fentanyl also had attenuated pressure response, but, in labetalol group, it was better controlled.

In accordance to our study, Singh et al.,[11] studied that the effect of injections of labetalol (0.25 mg/kg) and fentanyl (2 μg/kg) on sympathomimetic response to laryngoscopy and intubation in vascular surgeries was found to cause a decrease in HR, blood pressure, and DBP in both groups before intubation. In comparison to Group C, the amount of fentanyl and labetalol that increased HR and MAP after intubation was minimal. At 7 min, they discovered that the HR and SBP had significantly dropped below the B0.

In consistent with our study, Meftahuzzaman et al.,[12] studied labetalol and fentanyl and found significantly less increase in HR, systolic, diastolic, mean arterial pressures, and RPP after intubation in Group L and Group F as compared to Group C. They found minimum increase in Group L and concluded that labetalol is better agent for attenuation of laryngoscopic and intubation reflex.

Limitations of the study

The safety profile of the drug combinations in patients with co-morbidities and critically ill patients were not studied. Depth of anaesthesia and adequacy of muscle relaxants which might affect haemodynamic changes were not monitored.

CONCLUSION

From the present study, it was concluded that, in Labetalol + Fentanyl group, patients received intravenous 0.25 mg/kg labetalol diluted in 10 mL saline 5 min prior and fentanyl 2 μg/kg 3 min before intubation throughout the surgery. It showed significant decrease in the HR, systolic blood pressure (SBP), DBP, and mean arterial pressure (MAP) throughout the study period.

In fentanyl group, patients received fentanyl at 2 μg/kg fentanyl 3 min before intubation throughout the surgery. However, the increase in HR, SBP, DBP, and MAP was recorded but reduction not more than those as recorded in LF group.

Hence, both Labetalol + Fentanyl and alone fentanyl in the above-mentioned dose can be used safely to attenuate the hemodynamic response without significant side effects, whereas Labetalol + Fentanyl proved to have better hemodynamic stability and more effective in attenuating hemodynamic response following intraoperative infusion when compared to Fentanyl.

ACKNOWLEDGMENT

We are grateful to our colleagues, teachers,guide, head of the department for their co operation and support during the research period.

REFERENCES

1. Bajwa SS, Kaur J, Singh A, Parmar SS, Singh G, Kulshrestha A, et al. Attenuation of pressor response and dose sparing of opioids and anaesthetics with pre-operative dexmedetomidine. Indian J Anaesth. 2012;56(2):123-128.
   https://doi.org/10.4103/0019-5049.96303
2. Maharaj RJ, Thompson M, Brock-Utne JG, Williamson R and Downing W. Treatment of hypertension following endotracheal intubation. S Afr Med J. 1983;63:691-694.
3. Goldberg ME, McNulty SE, Azad SS, Cantillo J, Torjman M, Marr AT, et al. A comparison of labetalol and nitroprusside for inducing hypotension during major surgery. Anesth Anal. 1990;70(5):537-542.
   https://doi.org/10.1213/00000539-199005000-00012
4. Bowdle TA. Adverse effects of opioid agonists and agonist-antagonists in anaesthesia. Drug Saf. 1998;19(3):173-189.
   https://doi.org/10.2165/00002018-199819030-00002
5. Derbyshire DR, Chmeilewski A, Fell D, Vater M, Achola K and Smith G. Plasma catecholamine responses to tracheal intubation. Br J Anaesth. 1983;55(9):855-860.
   https://doi.org/10.1093/bja/55.9.855
6. Fox EJ, Sklar GS, Hill CH, Villanue V and King BD. Complications related to the pressure response to endotracheal intubation. Anaesthesiology. 1977;47(6):524-525.
   https://doi.org/10.1097/00000542-197712000-00013
7. King BD, Harris L, Greifenstein F, Elder J Jr and Dripps RD. Reflex circulatory responses to direct laryngoscopy and intubation under general anaesthesia. Anaesthesiology. 1951;12(2):556-566.
   https://doi.org/10.1097/00000542-195109000-00002
8. Prys-Roberts C, Foex P, Biro GP and Roberts JG. Studies of anaesthesia in relation to hypertension versus adrenergic β receptor blockade. Br J Anaesth. 1973;45(7):671-680.

https://doi.org/10.1093/bja/45.7.671

9. McCammon RL, Hilgenberg JC and Stoelting RK. Effect of Propranolol on circulatory responses to induction of diazepam- nitrous oxide anesthesia and to endotracheal intubation. Anesth Analg. 1981;60(8):579-83.
10. Patel LP, Patel JC, Patel KP, Rathva CS and Tandel V. Comparison of effect of Labetalol and fentanyl with only fentanyl for attenuating pressure responses to intubation and skull pin insertion in neurosurgery. Indian J Clin Anaesth. 2018;5(2):199-204. https://doi.org/10.18231/2394-4994.2018.0037
11. Singh B, Saiyed A, Meena R, Verma I and Vyas CK. A comparative study of labetalol and fentanyl on the sympathomimetic response to laryngoscopy and intubation in vascular surgeries. Karnataka Anaesth J. 2015;1:64-68.
12. Meftahuzzaman SM, Islam MM, Ireen ST, Islam MR, Kabir H, Rashid H, et al. Comparison of efficacy of labetalol and fentanyl for attenuating reflex responses to laryngoscopy and intubation. Mymensingh Med J. 2014;23:242-8.

Authors' Contributions:
IJ- Literature survey, prepared first draft of manuscript, implementation of study protocol, data collection, data analysis, manuscript preparation and submission of article; **SSY-** Concept, design, clinical protocol, manuscript preparation, editing, manuscript revision and supervision; **SS-** Design of study, statistical analysis and interpretation; **JK-** Concept, coordination and preparation of manuscript; **PG-** Proofreading and revision of manuscript.

Work attributed to:
Gajra Raja Medical College and JA hospital, Gwalior, Madhya Pradesh, India.

Orcid ID:
Isha Jain - https://orcid.org/0009-0000-3156-0439
Satyendra Singh Yadav - https://orcid.org/0009-0006-1200-8757
Shakti Singhal - https://orcid.org/0000-0002-2331-9159
Jaykumar Kolewar - https://orcid.org/0009-0003-6882-3257
Preeti Goyal - https://orcid.org/0000-0002-6057-4781

Source of Support: Nil, **Conflicts of Interest:** None declared.