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Original Research Article

Attenuation of stress response to laryngoscopy and intubation: sublingual nitroglycerin spray vs intravenous fentanyl and sublingual nitroglycerin spray

Binod Pegu*, Suneeta Dutta, Deba Gopal Pathak, Kamal Chandra Deori

Department of Anaesthesiology, Silchar Medical College, Silchar, Assam, India

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***Correspondence to:**
Dr. Binod Pegu,
Email: binodpegu10@gmail.com

ABSTRACT

Background: Laryngoscopy and tracheal intubation is invariably associated with certain cardiovascular changes such as tachycardia, rise in blood pressure and a wide variety of cardiac arrhythmias. 1 Such complications are highly detrimental in patients with limited cardiovascular reserve specially in geriatric and elderly population. Various pharmacological agents have been used to attenuate these stress responses but none has yet been considered ideal. Therefore, purpose of this study is to investigate the efficacy of sublingual Nitroglycerine spray alone and sublingual Nitroglycerine spray with intravenous Fentanyl to attenuate the pressor response to laryngoscopy and intubation in normotensive patients.

Methods: A total of 120 ASA I and II patients of age group 18-60 years scheduled for elective surgical procedure under general anesthesia were randomly divided into 3 groups of 40 in each group. Group 1 control group, Group 2, received NTG sub-lingual spray (0.4mg/spray) two min. before induction, and Group 3 received inj. Fentanyl (2µg/kg) 5min before + NTG sub-lingual spray (0.4 mg/spray) 2min before induction. Vital parameters before and after induction and thereafter at specified time interval following laryngoscopy and intubation were recorded for comparison.

Results: Demographic characteristics and baseline vital parameters in both the groups were comparable. Significant differences in mean arterial pressure (MAP) and heart rate (HR) were observed in between the groups during postintubation period.

Conclusions: Combination of intravenous Fentanyl plus Nitroglycerin spray is more effective than NTG alone in attenuating the stress response following laryngoscopy and intubation.

Keywords: Endotracheal intubation, Fentanyl, Haemodynemic stabi, Nitroglycerine

INTRODUCTION

Laryngoscopy and tracheal intubation are mandatory for most patients undergoing operations under general anaesthesia, which invariably is associated with certain cardiovascular changes such as tachycardia, rise in blood pressure and a wide variety of cardiac arrhythmias.[1] The hemodynamic response to laryngoscopy and intubation was first described by Reid and Brace in 1940. A typical pressor response can leads to an average increase in blood pressure by 40-50% and heart rate by 20% and an elevation of both epinephrine and norepinephrine levels. These effects are generally well tolerated by overall healthy patients but can be lethal to patients with preexisting conditions such as coronary artery disease, recent myocardial infarction, hypertension, geriatric population pre-eclampsia, and cerebrovascular pathology such as tumours, aneurysms or increased intracranial pressure etc., and are at increased risk of morbidity and mortality.[2]

Geriatric and elderly patients which make up an increasingly large percentage of both the inpatient and outpatient hospital population, have an increased

incidence of coronary artery disease and cerebrovascular disease and elevated baseline blood pressure, making them especially susceptible to swings in blood pressure, and heart rate during laryngoscopy and endotracheal intubation, which is detrimental in patients with limited cardiovascular reserve with the resultant risk of Myocardial Infarction (MI), Stroke, Congestive heart failure or sudden death.[3-5]

The therapeutic armamentarium to counteract the cardiovascular responses to laryngoscopy and tracheal intubation includes a wide variety of drugs, techniques and routes of administration. A wide variety of pharmacological agents like Lignocaine, Fentanyl, Alfentanil, Remifentanil, Nifedipine, Beta-blockers, Gabapentin, Magnesium Sulfate,Verapamil, Nicardipine, Diltiazem etc. have been used to attenuate the hemodynamic responses to laryngoscopy and endotracheal intubation with varying results.[6-9]

Glyceryl Trinitrate (Nitroglycerin or NTG) which is a predominant veno-dilator has been recently introduced as lingual pump spray or pen spray, to attenuate the stress response to laryngoscopy and endotracheal intubation.[9]

Fentanyl citrate, an opioid is a phenylpiperidine of the 4-aminopiperidine series structurally related to pethidine and controls both heart rate and blood pressure responses.[10,11] However, Fentanyl can produce complex respiratory depression and truncal rigidity at higher doses. Administration of NTG alone during pre-intubation may not be sufficient to completely mediate hemodynamic response due to the tendency of Nitroglycerine to produce tachycardia.[12]

Despite the efficacy demonstrated in previous studies, in-depth analysis and ideal dose combination of Fentanyl and Nitroglycerine required to suppress the hemodynamic response to endotracheal intubation has not yet been determined.[13-16] Therefore, the purpose of this study is to investigate the efficacy of sublingual Nitroglycerine spray alone and sublingual Nitroglycerine spray with intravenous Fentanyl to attenuate the pressor response to laryngoscopy and intubation in normotensive patients.

METHODS

This was a prospective, randomized, controlled and parallel group clinical study and conducted in 120 patients aged 20-60 years of both sexes belonging to ASA grade I and II undergoing elective non cardiac surgery requiring endotracheal intubation for maintenance of anaesthesia. A written informed consent was taken from all the patients individually.

Sample size

Based on a pilot study a sample size of 40 per group with type I error of 0.05 and type II error of 0.20 for 25% difference in MAP between groups was calculated, hence a total of 120 patients were included. Patients belonging to ASA III and above, any emergency operation; patients with other co-morbid illness like diabetes, hypertension, respiratory disease, hepatic or renal derangements; patients on antipsychotic medication, history of allergy to the study drugs, anticipated difficult airway etc. were excluded from the study.

A detailed pre-anaesthetic evaluation including routine investigations was done on all patients and were explained about the anaesthesia technique. All patients were given Tablet Alprazolam 0.5 mg, orally on the night before the operation and preoperative fasting for 8 hours were ensured before administering the general anaesthesia. The patients were randomly allocated and divided into three groups of 40 each by closed envelope method. All patients received standard anaesthesia technique with injection Thiopentone sodium 5mg/kg and injection Vecuronium Bromide 0.1mg/kg as muscle relaxant and maintained with 66.66% N_2O in O_2 and Sevoflurane (0.2-1%) and Vecuronium top-up doses as necessary.

- Group-1: Control group- Normal saline infusion.
- Group-2: NTG group-NTG sub-lingual spray (0.4 mg/spray) two min. before induction.
- Group-3: NTG+ intravenous Fentanyl group- inj. Fentanyl (2µg/kg) 5min before + NTG sub-lingual spray (0.4 mg/spray) 2min before induction.

HR, SBP, DBP and MAP were recorded at T0: Baseline (before premedication), T: Just before intubation, T1: 1min after intubation, T3: 3 min after intubation, and T5: 5 min after intubation. Any incidence of hypotension (fall in SBP >20% from baseline), hypertension (rise in SBP >20% from baseline), bradycardia (fall in HR>20% from baseline), tachycardia (rise in HR >20% of baseline), arrhythmias, and ST-T changes etc. were noted and treated accordingly.

Statistical analysis

The data were recorded on predesigned and pretested proforma, and was tabulated and master chart was prepared in Microsoft Excel 2007. Demographic data, Heart Rate (HR), systolic BP, diastolic BP and Mean arterial pressure (MAP) were tabulated as Mean and Standard deviation.

Statistical significance was tested by ANNOVA test with Post hoc analysis, paired student t-test was used for analyses within the group and unpaired Student t-test was used for comparison between the groups and Chi square test with or without Yates' correction wherever applicable.

All analysis was done by using two tailed test, with P-value of less than 0.05 was considered significant and less than 0.001 as highly significant.

RESULTS

Demographic characteristics of patients were comparable. No significant difference was observed among the groups (p >0.05).

Table 1: Demographic profile.

Category	Group 1	Group 2	Group 3	P-Value
Age (yrs) Mean±SD	37.50±7.90	39.35±9.77	38.70±10.33	0.671
Male Female	24 (60%) 16(40%)	18(45%) 22(55%)	20(50%) 20(50%)	0.393
ASA I ASA II	26(65%) 14(35%)	24(60%) 16(40%)	25(62.5%) 15(37.5%)	0.899
Height (mtr) Mean±SD	1.51±0.05	1.51±0.04	1.52±0.04	0.588
Weight (kg) Mean±SD	62.33±5.56	63.18±4.16	62.53±4.60	0.715
BMI kg/m^2 Mean±SD	27.30±2.45	27.63±1.30	26.95±1.80	0.260

Heart rate changes

Baseline HR values of the patients in all the groups were comparable (p >0.05). Significant difference was observed in between group 1 and group 2, and in between group 2 and group 3, following induction.

Rise in heart rate during post-intubation periods were insignificant in between group 1 and group 2 but significant between group 2 and group 3 (Table 2).

Table 2: HR- beats/min (Mean±SD).

Time	Groups			P-Value		
	Group 1	Group 2	Group 3	Group 1 vs Group 2	Group 1 vs Group 3	Group 2 vs Group 3
T0	92.23±6.76	91.15±4.15	89.83±6.81	0.7036	0.1814	0.5922
T	90.38±10.92	95.93*±8.61	88.23±10.27	0.0378	0.6014	0.0022
T1	115.75±5.99** (25.5% rise)	117.68±8.81** (29.1%rise)	91.10±15.85	0.7143	<0.001	<0.001
T3	105.33±8.82**	107.25±5.18**	86.38±12.22	0.6204	<0.001	<0.001
T5	101.20±9.20**	104.53±8.40**	87.68±11.98	0.2983	<0.001	<0.001

*P <0.05, significant, **P <0.001, highly significant rise in HR as compared to baseline within the group

Table 3: MAP (mmhg)-(Mean±SD).

Time	Groups			P-Value		
	Group1	Group2	Group3	Group1 vs Group2	Group1 vs Group3	Group2 vs Group3
T0	90.80±10.8	92.4±8.37	88.48±9.38	0.7356	0.5257	0.1637
T	87.07±9.24	81.63±6.08 # (11.65% fall)	80.68±7.14 # (8.81% fall)	0.005	0.0008	0.8421
T1	113.72±4.80** (25.24% rise)	95.60±11.22	90.39±5.17	<0.001	<0.001	0.008
T3	109.32±3.37	93.84±9.04	88.002±6.52	<0.001	<0.001	0.005
T5	105.17±3.58	91.62±7.98	86.30±5.54	<0.001	<0.001	0.0003

*(P <0.05)- Significant, **(P <0.001)- highly Significant rise from baseline; # (P <0.05) Significant fall from baseline, MAP = Mean arterial pressure, SD = Standard deviation

Changes in MAP

Baseline values of MAP of all the groups were comparable (p >0.05). Significant differences were observed between group 1 and group and between group 2 and group 3 (p <0.001) (Table 3).

Adverse effects

Adverse effects like tachycardia, arrhythmia, hypertension was mostly seen in group 1 and group 2 in comparison to group 3. Patients in group 3 were observed to be haemodynemically more stable than the other two groups.

DISCUSSION

Intubation of the trachea alters respiratory and cardiovascular physiology both via reflex responses and by the physical presence of endotracheal tube. The usual circulatory responses to laryngeal and tracheal stimulation in anaesthetized subject are tachycardia and rise in arterial pressure.[3,6,7]

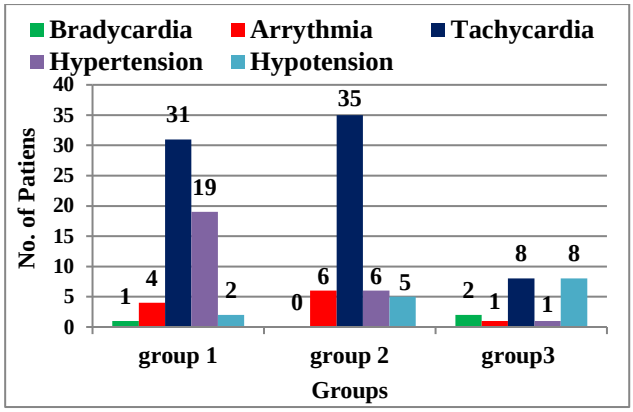

Figure 1: Adverse effects in the three groups.

Various studies have been performed on hemodynamic changes to laryngoscopy and intubation. Prys-Roberts et al, King et al etc., studied the reflex cardiovascular response such as hypertension and tachycardia to direct laryngoscopy and tracheal intubation during general anaesthesia.[1,4]

However these response usually does not present a problem for most the young and healthy patients but patients with cardiovascular or cerebrovascular disease, geriatric patients may be at increased risk of morbidity and mortality from the tachycardia and hypertension resulting from the stress.[3,4]

A varieties of pharmacological agents have been used to attenuate the hemodynamic response to laryngoscopy and intubation such as deep general anaesthesia, topical anaesthesia, Lignocaine, Fentanyl, Alfentanil, Remifentanil, Nifedipine, beta-blockers, Gabapentin, Magnesium sulfate, Verapamil, Nicardipine, Diltiazem with variable success rate.[5]

Nitroglycerin (Glyceryl trinitrate or NTG) relaxes vascular smooth muscles with venous dilation predominantly over arterial dilation. NTG had been administered in different doses and through different approaches like intranasal, topically or parenterally as a bolus or infusion to attenuate hemodynamic responses during laryngoscopy and intubation.[19] Kumari I et al used sublingual Nitroglycerin in two doses (0.4mg and 0.8mg) Kamra S et al used 2% topical Nitroglycerin ointment equivalent to 30 mg Nitroglycerin.[13,14] Fassoulaki A and Kaniaris P used Nitroglycerin intranasally in a dose of 60 mg.[15] Anant and Waghray used intranasal NTG spray for attenuation of pressor response to intubation.[16] All these studies cited above revealed conflicting results.

Fentanyl is an opioid commonly used as an adjunct to anaesthesia which increases the depth of anesthesia and decreases sympathetic discharge thereby causing suppression of hemodynamic response to laryngoscopy and intubation. Large dose of Fentanyl often leads to muscular rigidity, bradycardia, respiratory depression, post-operative nausea, and vomiting.[16]

In our study, we planned to compare the effect of Nitroglycerin sublingual spray alone in one group and the combination of Nitroglycerin sublingual spray plus intravenous Fentanyl in the other group in attenuation of intubation response. We administered Nitroglycerin sublingual spray (single spray) which delivered 400 microgram NTG, 2 minute before intubation in one group and intravenous Fentanyl 2µg/kg 5 minutes before followed by sublingual Nitroglycerin spray (1 spray) 2 minutes before intubation in the other group. 40 patients in each group of ASA grade 1 and 2 were chosen for the study.

The three groups of our study were comparable as regards of age and sex distributions (Table 1). The premedication technique, intubation and extubation techniques were similar in all the three groups. Hypoxia and hypercarbia were avoided. $EtCO_2$ was maintained between 30-40 mm Hg and saturation maintained above 97%. Continuous lead II ECG monitoring was done. The changes in haemodynamic parameters following laryngoscopy and intubation were measured and compared with pre-induction values, which were taken to be baseline. Both within the group and intergroup comparisons were done. The results and observations that were obtained in the present study are being compared in the light of other investigators.

Haemodynamic variables

The mean baseline HR SBP, DBP and MAP in the three groups were comparable.

In group 2 (NTG group), heart rate continued to rise till 1 minute after intubation and then gradually came down but it did not reach the baseline value. Rise of heart rate was maximum at 1 minute after intubation (29.1%) which was statistically highly significant (P <0.001). Significance difference was found in comparison to group-1 just before intubation (p <0.05). There was statistically no significant difference in between group 1 and group 2 at any point of time interval following intubation. Our finding was similar to the study conducted by. Vyas AB et al who conducted a study in 60 patients who received three different doses of intranasal Nitroglycerin (Group 1-400µg, Group 2-800µg and Group 3-1200µg, 20 patients in each group) five minutes before induction.[17] Kumari I et al also found similar observations in 90 adult ASA I and II patients using sublingual spray of NTG (1 spray and 2 spray one minute before intubation) in attenuation of pressor response to intubation.[13] Studies conducted by Mikawa K et al, Grover VK et al and Fassoulaki A and Kaniaris P have also documented that NTG does not attenuate the rise in heart rate following laryngoscopy and endotracheal intubation which can be attributed to reflex tachycardia produced by vasodilatation.[15,18,19]

When intravenous Fentanyl was used along with Nitroglycerin sublingual spray in group 3 (F+NTG), it

resulted in more optimal control of tachycardia produced by laryngoscopy and intubation. In the group 3, baseline heart rate came down just before intubation and then rose to maximum at 1 minute after intubation followed by gradual fall at 3rd and 5th minutes bellow the baseline value. Significant differences were observed in comparison to other two groups ($p < 0.001$) during each time interval following intubation. Our results coincide with a study conducted by Gupta and Tank et al, Parida S et al who used Fentanyl 2 µg/kg intravenously slowly 3 min before induction of anesthesia to attenuate the pressor response to laryngoscopy and intubation.[11,20] Withington PS et al found that the heart rate was consistently higher but not statistically significant after NTG infusion during Fentanyl, thiopentone, pancuronium anaesthesia in coronary artery bypass graft surgery.[21] Ebert JP et al reported Fentanyl intravenously decreased heart rate below baseline and maintained it there.[22]

Mean blood pressure

Maximum rise in mean blood pressure was seen at 1 minute post-intubation period in all the groups. Significant attenuation of mean blood pressure was observed in the both group 2 (NTG) and group 3 (F+NTG) during the post-intubation period in comparison to control group (group 1). However significant difference was found in between group 2 and group 3. A Stable haemodynamic with significant attenuation of SBP, DBP, MBP and heart rate was found in the group 3 following endotracheal intubation in comparison to group 1 and group 2. In studies conducted by Vyas AB et al, Kumari I et al, Kamra S et al, Grover VK et al, Mahajan RP et al etc. also found similar results coinciding our study.[13,14,17,19,23]

Fusciardi J et al concluded that addition of Nitroglycerin by infusion to low-dose Fentanyl anesthesia produced no significant change in MPB, heart rate, cardiac index, or PCWP and is an attractive method for induction as well as decreasing the incidence of myocardial ischemia associated with laryngoscopy and intubation in patients with stable angina undergoing short-duration noncardiac surgery.[12]

Adverse effects

Adverse effects are shown in Figure 1. Bradycardia was treated with Inj. Atropine and hypotension with mephentermine. Out of 120 patients 11 (9.16%) patients (4 in Group 1, 6 in Group 2, and 1 in Group 3) had rhythm changes in the form of ventricular bigeminy, atrial ectopics or ventricular premature beats following intubation. Ko SH et al reported 11% incidence of rhythm disturbance during laryngoscopy and intubation in their study.[24] No ST-changes were observed. None of the cases had any bronchospasm or chest wall rigidity.

Limitations

Present study was done in a small group of 40 patients each in the groups. All patients were belonging to ASA I and II. Patients with comorbid conditions like coronary artery disease, hypertension and diabetes, etc. were excluded from the study. Another major limitation of our study is that stress mediators were not measured during the study period which would have given the measurement of effect of study drugs on stress response to laryngoscopy and tracheal intubation. In addition, influence of age of patient on pressor response to laryngoscopy and intubation or role of preoperative antihypertensive medications were not evaluated in our study. Hence further research can be done to study the effects of age and antihypertensive medications on laryngoscopy and endotracheal intubation can be planned.

CONCLUSION

Combination of intravenous Fentanyl plus Nitroglycerin spray is more effective than NTG alone in attenuating the haemodynamic response following laryngoscopy and intubation without any major side effects in otherwise healthy patients undergoing elective surgeries under general anaesthesia. However, more studies with larger population is required to come to a final conclusion.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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