

Attenuation of pressor response following intubation: Efficacy of nitro-glycerine lingual spray

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Abstract

Background and Aims: The role of nitro-glycerine (NTG) lingual spray for attenuation of the hemodynamic response associated with intubation is not much investigated. We conducted this study to evaluate the efficacy of NTG lingual pump or pen spray in attenuation of intubation induced hemodynamic responses and to elucidate the optimum dose.

Material and Methods: In a prospective randomized controlled trial, 90 adult patients of ASA I, II, 18-60 year posted for elective general surgery under general anesthesia with intubation were randomly allocated to three groups as Group C (control) – receiving no NTG spray, Group N1 – receiving 1 NTG spray and Group N2 – receiving 2 NTG spray one minute before intubation. Systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate were recorded at baseline, just before intubation (i.e., 60 s just after induction and NTG spray), immediately after intubation, at 1, 2, 5 and 10 min after intubation.

Results: Incidence of hypertension was significantly higher in Group C (60%, $n = 18$) as compared to Group N1 and N2 (10%, $n = 3$ each), $P < 0.01$. Mean value of SBP, DBP and MAP showed a significant rise as compared to baseline, following intubation in control group (15.31% in SBP, 12.12% in DBP, 17.77% in MAP) that persisted till 5 min, while no significant rise was observed in Group N1 and N2. There was a trend toward fall in blood pressure in Group N2 (4.95% fall in SBP, 4.72% fall in MAP) 1-min following spray, which was clinically insignificant. Mean value of SBP, DBP and MAP was significantly higher in Group C than in Group N1, which was in turn greater than Group N2 (Group C > N1 > N2), $P < 0.05$. However, incidence of tachycardia was comparable in three groups (70% in group C, 63.33% in Group N1 and 67.77% in Group N2, $P > 0.05$).

Conclusions: We concluded that the NTG lingual spray in dose of 0.4 mg (1 spray) or 0.8 mg (2 sprays) was effective in attenuation of intubation induced hemodynamic response, in terms of preventing significant rise in SBP, DBP and MAP compared to control group.

Key words: General anesthesia, hemodynamic responses, nitro-glycerin, nitro-glycerin lingual spray

Introduction

In 1940, Reid and Brace first described a hemodynamic response to laryngoscopy and intubation.^[1] It leads to an average increase in blood pressure by 40-50% and 20% increase in

heart rate (HR).^[2] The increase in blood pressure and HR is usually transient and variable but can be unpredictable and life-threatening if left unaddressed. This response is undesirable in susceptible patients, especially in patients with systemic hypertension, coronary artery disease and intracranial aneurysm and may result in potentially deleterious effects like left ventricular failure, arrhythmias, myocardial infarction, cerebral hemorrhage and rupture of cerebral aneurysm.^[3]

A wide variety of pharmacological agents were used to attenuate the hemodynamic responses to laryngoscopy and endotracheal intubation like lignocaine,^[4] fentanyl,^[5] alfentanil,^[6] remifentanyl,^[6] nifedipine,^[7] beta-blockers,^[8] gabapentin,^[9] magnesium sulfate,^[10] verapamil, nicardipine, diltiazem^[11] with varying results.

Glyceryl trinitrate (nitro-glycerin or NTG) relaxes vascular smooth muscles with venous dilation predominantly over arterial

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dilation.^[12] NTG had been administered intranasally,^[13] or parenterally as a bolus^[14] or infusion^[15] to attenuate hemodynamic responses during laryngoscopy and intubation but preparation, standardization and stabilization of such solution is not without problem and cost effectiveness has been questioned.^[9,16,17]

Recently NTG lingual pump spray or pen spray has been introduced, for spraying onto or under the tongue. Use of NTG spray for attenuating pressor response of laryngoscopy and endotracheal intubation has been sparsely evaluated; hence, the present study was conducted to test the hypothesis whether use of NTG spray before intubation is effective for attenuation of hemodynamic response to endotracheal intubation. The optimum dose of NTG spray was also investigated.

Material and Methods

After institutional ethical committee approval, a prospective randomized controlled study was conducted 90 ASA physical status I and II patients of both sexes, aged 18-60 years scheduled for elective general surgery under general anesthesia. All the patients under study were subjected to a detailed preanesthetic evaluation to rule out any anatomical or systemic disorders. After taking informed consent from each patient, history of past prolonged illness and drug therapy was elicited. Routine and relevant special investigations were carried out. Exclusion criteria were patients with known allergy to anesthetic or any other drug, atrio-ventricular conduction block, congestive heart failure, cardiac arrhythmias, hypertension or other cardiovascular disease and receiving anti hypertensives, sympathomimetics, vagomimetics, antidepressant drugs and phosphodiesterase inhibitors, anticipated difficulty in intubation, severe obesity (body mass index $>35 \text{ kg/m}^2$).

Based on a pilot study, we found that the systolic blood pressure (SBP) increased in 70% of patients in the control group as compared to 25% of patients who received a single dose of NTG spray. Taking into account an alpha error of <0.05 and a power of 0.8 we calculated that a total of 76 patients in three groups were required to detect a significant difference. Compensating for dropouts, it was decided to include 30 patients in each group.

Ninety patients were randomly divided into three groups (30 patients in each group) using a sealed envelope technique. Group allocation was done as per the administration of NTG spray as 1 spray (Group N1), 2 sprays (Group N2) and no spray (Group C - Control).

All patients in the study received a standard general anesthesia technique followed by endotracheal intubation. On the night

before surgery tablet alprazolam 0.5 mg was given. On arrival in operation room pulse-oximeter, noninvasive blood pressure, electrocardiogram were applied and the patient's HR, SBP, DBP, MAP and peripheral oxygen saturation (SpO_2) were recorded as baseline data.

After securing a peripheral intravenous line, infusion of Ringer lactate was started. Patients were premedicated with glycopyrrolate (0.2 mg), ondansetron (4 mg) and nalbuphine (10 mg) intravenously. Ringer lactate 8 ml/kg was given before induction. Patients were preoxygenated for 3 min, and anesthesia was induced with propofol (2 mg/kg) and rocuronium (0.9 mg/kg) over a 15 s period.

Immediately after induction NTG lingual spray was administered as one metered spray (400 mcg) in group N1 and two metered sprays (800 mcg) in group N2. Patients in Group C did not receive NTG spray. We used Nitrocin spray pen (Samarth Pharmacy Pvt. Ltd., Mumbai).

Laryngoscopy was attempted 60 s after induction of anesthesia and NTG spray. NTG spray and intubation was done in all cases by an experienced anesthesiologist. If intubation took more than 30 s or more than 1 attempt case was excluded from the study. After confirmation of endotracheal tube position, anesthesia was maintained using 60% N_2O in 40% O_2 .

HR, SBP, DBP and MAP were recorded at T1: Baseline (before premedication), T2: Just before intubation (60 s after induction and NTG spray), T3: Just after intubation, T4: 1 min after intubation, T5: 2 min after intubation, T6: 5 min after intubation, T7: 10 min after intubation.

During the study period of 10 min, the occurrence 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 $>20\%$ from baseline), arrhythmias, and ST-T changes were noted and treated. Ephedrine 6 mg was given when SBP $<90 \text{ mmHg}$.

Statistical analysis

Data were entered and analyzed using MS Excel and Epi Info 6 system. Qualitative or categorical data were presented as number (proportion) and compared using Chi-square test. Quantitative or continuous variables were presented as mean \pm standard deviation and compared using Student's *t*-test and analysis of variance. $P < 0.05$ was considered as statistically significant.

Results

Patient's age, weight, sex, ASA grade and type of surgery were statistically comparable in three groups, $P > 0.05$

[Table 1]. All patients in the study were intubated within 30 s in a single attempt. Changes in HR, SBP, DBP and MAP are shown in Tables 2-5, Figure 1.

Hypotension (i.e., fall in SBP > 20% of baseline) in 3 (10%) in group N1 and 4 (13.3%) patients in group N2 after induction and NTG spray. However, SBP didn't decrease below 90 mmHg in any of these patients, and ephedrine was not required as per study protocol.

Two (6.66%) patients in group C had ventricular premature beats immediately after intubation which responded to intravenous lignocaine (xylocard) 3 ml.

Discussion

Laryngoscopy and intubation cause sympathetic stimulation leading to pressor response characterized by approximately 20% rise in HR and 40-50% rise in blood pressure,^[2] which

Table 1: Baseline characteristics

Variables	Group C (n = 30) (%)	Group N1 (n = 30) (%)	Group N2 (n = 30) (%)	Total (%)	Intergroup P
Age (years)	38.80±11.51	43.10±11.51	43.0±12.57	41.63±11.91	0.075
Weight (kg)	56.07±7.73	56.47±7.73	52.63±7.97	55.06±7.91	0.12
Sex					
Male	14 (46.7)	10 (33.3)	12 (40)	36 (40)	0.63
Female	16 (53.3)	20 (66.7)	18 (60)	54 (60)	0.078
ASA grade					
I	17 (56.7)	21 (70)	21 (70)	59 (65.6)	0.134
II	13 (43.3)	9 (30)	9 (30)	31 (34.4)	0.23
Type of surgery					
Cholecystectomy	7 (23.3)	6 (20)	8 (26.7)	21 (23.3)	0.45
Exploratory laparotomy	7 (23.3)	9 (30)	8 (26.7)	24 (26.7)	0.124
Modified radical mastectomy	5 (16.7)	6 (20)	2 (6.7)	13 (14.4)	0.245
Pyelolithotomy	10 (33.3)	8 (26.7)	12 (40)	30 (33.3)	0.45
Others	1 (3.3)	1 (3.3)	0 (0)	2 (2.2)	0.52
Duration of laryngoscopy (s)	23.83±2.33	22.17±2.47	23.50±2.57	23.17±2.54	0.065

Data are comparable in three groups ($P > 0.05$), ASA = American Society of Anesthesiologists

Table 2: Comparison of HR

Time	HR (mean±SD) beats/min			P		
	Group C (n = 30)	Group N1 (n = 30)	Group N2 (n = 30)	C/N1	C/N2	N1/N2
T ₁	93.77±16.29	91.63±13.41	89.33±8.69	0.582	0.194	0.434
T ₂	97.94±20.77*	97.50±13.84*	95.03±9.49*	0.186	0.143	0.412
T ₃	109.47±16.35*	102.90±13.90*	104.24±8.24*	0.099	0.122	0.494
T ₄	112.17±15.54* (19.62% rise)	104.77±14.94*	104.53±14.85*	0.065	0.055	0.940
T ₅	105.37±15.42*	108.80±15.93* (18.73% rise)	105.67±7.84* (19.03% rise)	0.296	0.925	0.298
T ₆	100.90±14.59	107.93±12.95*	106.33±8.63*	0.053	0.085	0.576
T ₇	101.83±15.77	108.43±12.48*	104.07±11.51*	0.078	0.534	0.164

* $P < 0.05$, significant rise in HR as compared to baseline within the group, HR = Heart rate, SD = Standard deviation

Table 3: Comparison of SBP

Time	SBP (mean±SD)			P		
	Group C (n = 30)	Group N1 (n = 30)	Group N2 (n = 30)	C/N1	C/N2	N1/N2
T ₁	128±10.1	131.20±7.70	127.80±9.57	0.173	0.938	0.135
T ₂	125.30±16.17	129.1±11.25	123.13±17.38	0.295	0.619	0.120
T ₃	138.83±20.98*	130.03±8.75	124.03±12.84	0.038	0.002	0.039
T ₄	147.6±18.09* (15.31% rise)	129.70±8.93	121.47±11.16* (4.95% fall)	0.000	0.000	0.003
T ₅	138.03±16.90*	129.27±10.02	122.63±11.19	0.018	0.000	0.019
T ₆	134.27±12.81*	130.60±9.36	124.83±10.81	0.817	0.014	0.038
T ₇	129.87±14.51	132.03±9.40	126.40±11.09	0.445	0.133	0.051

*Significant ($P < 0.05$) rise in SBP from baseline, *Significant ($P < 0.05$) fall in SBP from baseline, SBP = Systolic blood pressure, SD = Standard deviation

Table 4: Comparison of DBP

Time	DBP (mean±SD)			P		
	Group C (n = 30)	Group N1 (n = 30)	Group N2 (n = 30)	C/N1	C/N2	N1/N2
T ₁	83.27±6.87	85.33±5.90	83.27±5.36	0.217	1.00	0.161
T ₂	81.77±12.67	81.93±8.92	80.80±8.70	0.953	0.732	0.620
T ₃	96.30±18.37*	82.73±8.96	81.57±6.38	0.001	0.000	0.564
T ₄	99.37±14.15* (12.12% rise)	86.30±6.15	80.17±9.19	0.000	0.000	0.004
T ₅	91.03±14.17*	85.80±8.79	81.20±7.14	0.091	0.001	0.030
T ₆	93.00±12.55*	86.67±8.65	83.47±6.92	0.081	0.065	0.119
T ₇	86.07±13.12	85.40±16.44	84.50±8.15	0.849	0.120	0.789

*Significant (P < 0.05) rise in DBP from baseline, DBP = Diastolic blood pressure, SD = Standard deviation

Table 5: Comparison of MAP

Time	MAP (mean±SD)			P		
	Group C (n = 30)	Group N1 (n = 30)	Group N2 (n = 30)	C/N1	C/N2	N1/N2
T ₁	97.73±9.15	98.40±5.43	96.77±7.07	0.175	0.649	0.291
T ₂	97.57±9.07	96.17±14.72	92.20±10.01# (4.72% fall)	0.659	0.034	0.227
T ₃	110.23±19.15*	98.73±8.57	93.40±7.043	0.004	0.000	0.013
T ₄	115.10±15.69* (maximum 17.77% rise)	100.57±6.25	93.17±8.38	0.000	0.000	0.000
T ₅	105.50±15.32*	99.83±8.34	93.67±10.04	0.080	0.001	0.012
T ₆	105.17±10.78*	101.33±7.61	95±7.79	0.668	0.000	0.024
T ₇	100.03±14.66	102.4±7.52	98.13±7.80	0.254	0.542	0.212

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

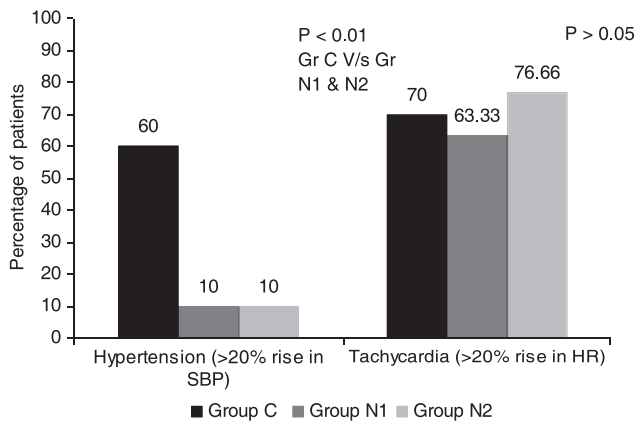


Figure 1: Comparison of incidence of hypertension and tachycardia following intubation in three groups

can be tolerated well by normal patients but may cause deleterious effects in patients with hypertension or ischemic heart disease (IHD).^[3] The magnitude of pressor response can be assessed by observing the rise in HR (demand), SBP (afterload), DBP (preload), and MAP. We observed that NTG spray does not attenuate the rise in HR.

Previous studies^[11,17-20] have also documented that NTG does not attenuate the rise in HR after intubation which can be attributed to reflex tachycardia produced by vasodilation.

Other studies have reported effective attenuation of

pressor response by NTG used intranasally,^[14,21] as ointment,^[14] intravenously as bolus injection,^[11,15,16,22] and IV infusion.^[23,24] We have documented a blunting of pressor response by the lingual spray of NTG in doses of 400 and 800 mcg. There was a trend toward fall in blood pressure in group N2; but it was clinically insignificant. Hussain and Zaeem^[21] also described that among NTG treated patients post-intubation hypotension occurred in 80%.

The principal advantage of using NTG is that, while a desirable and transient hypotension is achieved, cardiac output is not likely to decrease. Preload reduction and accompanying decrease in ventricular end-diastolic pressure^[17] reduces myocardial oxygen demand and increases endocardial perfusion by dilating the coronary vessels, NTG may increase the coronary blood flow and oxygen delivery to the myocardium. Because of its predominantly venodilatory action, it seems to be the best choice in patients with low cardiac output and moderately elevated resistance.^[12]

Myocardial oxygen consumption or demand (as measured by the pressure-rate product, tension-time index, and stroke-work index) is decreased by both the arterial and venous effects of NTG resulting in a more favorable supply-demand ratio.^[17]

There were some limitations of the study. Firstly, the study

was carried out in patients who were normotensive, not having associated CVS or CNS disease. Our finding cannot be extrapolated in patients with hypertension, IHD or difficult airway. Secondly, no invasive methods of recording blood pressure or pulmonary artery pressure were used, so beat to beat fluctuation of BP cannot be measured.

Conclusions

We conclude that NTG spray in dose of 1 spray (400 mcg) or 2 spray (800 mcg) given 1 min before intubation is effective in attenuating the pressor response to laryngoscopy and intubation in normotensive ASA I-II patients. NTG is not able to attenuate the rise in HR.

We suggest the future studies should focus on evaluation of attenuation of pressor response by NTG spray in hypertensive patients.

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