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Effect of 1 puff of sublingual nitroglycerin spray versus 1 puff of normal saline spray in attenuating pressor response to extubation

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Abstract
Ideal agent to attenuate hemodynamic response to extubation should be readily available, easy to administer, cost effective with fast onset of action and peak with minimal side effects.
Nitroglycerin is one of the most widely used drug to control intra-operative rise in blood pressure. Nitroglycerin is potent vasodilator, predominantly acting on venules than arterioles by generating nitric oxide (NO) in vascular smooth muscle. A thorough pre-anaesthetic evaluation was done on day before surgery. Detailed medical history was elicited and detailed physical examination was carried out. Patients were kept nil per orally for 8 hours prior to surgery. Preoperatively investigations like CBC, RBS and Sr. Creatinine were done. ECG and CXR were done if patient was more than 40 years of age. In our study patient received 1 puff (0.4mg) which resulted in a small although insignificant increase in BP till 3 minutes. It may be possible to attenuate this small increase in BP by using higher dose of NTG spray instead of 0.4mg and requires further evaluation. It was observed that there was tachycardia as Injection Glycopyrrolate was given just before intervention since, both the groups received the same drug it will not act as bias.

Keywords: sublingual nitroglycerin spray, normal saline spray, extubation

Introduction
Extubation is one of the most crucial part of general anaesthesia as there are marked hemodynamic changes to extubation [1] such as increase in heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure to mention few. These changes even though transient may be troublesome in some individuals like people who are hypertensive, with past history of cerebrovascular accident, myocardial ischemia sometimes leading to arrhythmia and cardiac arrest.
The exact mechanism of extubation response [2] is not known but it is believed to involve both sympathetic and parasympathetic systems. The sympathetic response involves polysynaptic pathway with Glossopharyngeal and Vagus nerve forming afferent arc to the sympathetic nervous system via brain stem and spinal cord. This causes firing of adrenergic mediators such as norepinephrine and epinephrine which leads to increase in HR and blood pressure. Parasympathetic reflex is monosynaptic and is more common in children.
This hemodynamic response to extubation can be attenuated by number of non-pharmacological methods such as extubation in deeper planes of anaesthesia or by using laryngeal mask airway(3) and pharmacological methods such as topical anaesthesia using lignocaine or pre-treatment with beta blockers, fentanyl dexmedetomidine, remifentanyl, prostaglandins magnesium sulphate or nitroglycerin [3, 4].
Ideal agent to attenuate hemodynamic response to extubation should be readily available, easy to administer, cost effective with fast onset of action and peak with minimal side effects.
Nitroglycerin is one of the most widely used drug to control intra-operative rise in blood pressure. Nitroglycerin is potent vasodilator, predominantly acting on venules than arterioles by generating nitric oxide [5, 6]. (NO) in vascular smooth muscle.
Sublingual Nitroglycerin spray is used to treat acute hypertensive crisis and acute anginal attack which is simple and easy to use.
There are many studies showing the effect of sublingual Nitroglycerin spray to attenuate hemodynamic changes to intubation however very few have studied its effect during

extubation.
Hence in our study we have observed the effect of sublingual NTG spray and compared it with normal saline spray to attenuate hemodynamic response to extubation.

Methodology
Approval from ethical committee and written informed consent was obtained. A total of 60 patients undergoing surgery under general anaesthesia with endotracheal intubation were included in the study.
After having met inclusion and exclusion criteria and having obtained informed consent, patients were randomized based on computer generated randomization table into one of the two groups.

Group A: where patients received 1 puff of sublingual nitroglycerin spray 1 minute after administration of reversal.

Group B: where patients received 1 puff of sublingual normal saline spray 1 minute after administration of reversal.
A thorough pre-anaesthetic evaluation was done on day before surgery. Detailed medical history was elicited and detailed physical examination was carried out. Patients were kept nil per orally for 8 hours prior to surgery. Preoperatively investigations like CBC, RBS and Sr. Creatinine were done. ECG and CXR were done if patient was more than 40 years of age.
On the day of surgery 18G intravenous line was secured in the pre-operative recovery room and IV fluids were started. Once patient was shifted to operation theatre standard monitors (i.e. Pulse oxymeter, ECG, NIBP) were attached.
Patients were preoxygenated with 100% Oxygen for three minutes. Patients were premedicated with Inj. Glycopyrrolate 0.005mg/kg and Inj. Midazolam 0.05mg/kg and Inj. Fentanyl 2mcg/kg.
Patient was induced with Inj. Thiopentone 5 mg/kg followed by Inj. Succinylcholine 2mg/kg. With the onset of neuromuscular blockade laryngoscopy was done and endotracheal intubation was done with appropriate size endotracheal tube.
Intraoperatively patients were maintained with Oxygen, Nitrous oxide and Isoflurane. Inj. Vecuronium in a dose of 0.1 mg/kg and maintenance with 1/4th of loading dose was given for neuromuscular blockade.
At the end of the procedure patients were reversed with Inj. Glycopyrolate 0.01mg/kg and Inj Neostigmine 0.05mg/kg.
One minute after administration of reversal drug, Group A patient received one puff of NTG spray (GTN spray, Medley pharmaceuticals, India, 1 puff= 0.4mg) sublingually and group B patient received one puff of Normal Saline spray sublingually. Blinding was achieved by using identical spray bottles. The anaesthesiologist administering the spray and recording the various parameters was blinded to the drug. Heart rate, Systolic blood pressure, Diastolic blood pressure, Mean blood pressure and SpO2 were recorded at the time of administration of reversal (TR), at the time of administration of spray (T0) and subsequently every minute till 10 minutes. Patients were extubated when spontaneous respiratory attempts were adequate, patient obeyed to verbal commands and criteria for extubation were met. Time of extubation was also noted.
Incidences such as arrhythmia, hypotension or tachycardia or any other side effects were noted. Patients were kept in PACU for 2 hours after extubation and were followed up for side effects or adverse events if any. Patients were removed from the study if there were extensive hemodynamic alteration intraoperatively and if patients required post - op ventilation.

Statistical Analysis
The data was tabulated and master chart was prepared. Microsoft Excel was used to tabulate data and SPSS 22.0 and R environment version 3.2.2 was used to analyse data. The categorical data was tabulated as ratios and percentages and continuous data was presented mean $\pm$ standard deviation. Student t test was used to find significance of study parameters on continuous data between two groups. A p value of < 0.05 was considered statistically significant. The data was represented in tables and appropriate charts.

Results
The minimum age group was 19 years and maximum was 55 years in Group A. In Group B minimum age group was 19 years and maximum was 58 years. The mean age in Group A was 39.2 years and yielded a standard deviation of 11.74, in Group B the mean age was 35.9 years and yielded a standard deviation of 11.26. The p value was 0.266 which made age distribution in two groups comparable.

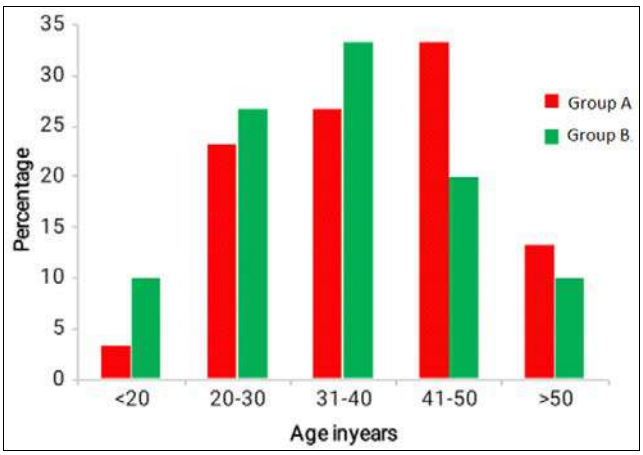

Fig: which made age distribution in two groups comparable

Table 1: Systolic blood pressure

FOR SBP						
	Group A		Group B			
	Mean	S.D.	Mean	S.D.	P Value	Inference
TR	122.00	8.67	122.03	3.55	0.9845	NS
T0	124.00	8.67	124.03	3.55	0.9845	NS
T1	124.00	5.41	132.00	3.66	< 0.0001	HS
T2	126.03	6.70	140.00	3.79	< 0.0001	HS
T3	128.20	6.29	148.03	3.04	< 0.0001	HS
T4	122.02	4.87	158.27	2.38	< 0.0001	HS
T5	120.03	4.73	154.13	3.64	< 0.0001	HS
T6	118.03	4.67	152.00	4.18	< 0.0001	HS
T7	115.00	4.35	149.97	3.60	< 0.0001	HS
T8	108.07	4.50	142.00	4.07	< 0.0001	HS
T9	104.07	4.04	138.00	4.25	< 0.0001	HS
T10	102.07	3.91	132.03	4.45	< 0.0001	HS

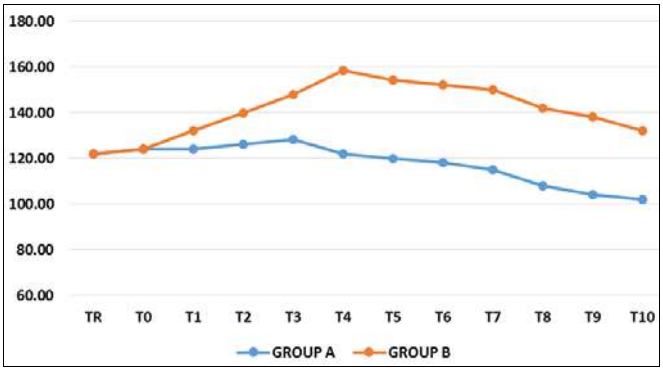

Fig 1: Mean SBP

In Group A

Mean SBP at the time of reversal (TR) was 122.00 ± 8.67 and at the time of administration of NTG spray (T0) was 124.00±8.67. The SBP increased till 3 minutes when the maximum mean BP was 128.20±6.29. This SBP subsequently reduced gradually till 10 minutes (T10) which was 102.07±3.91.

Group B

Mean SBP at the time of reversal (TR) was 122.03± 3.55 and at the time of administration of NTG spray (T0) was 124.03±3.55. The SBP increased till 4 minutes (T4) when the maximum mean BP was 158.27±2.38. This SBP remained high till 10 minutes. This increase in SBP when compared with that of group A was statistically highly significant.

Table 2: Diastolic blood pressure

	Group A		Group B			
	Mean	**S.D.**	**Mean**	**S.D.**	**p Value**	**Inference**
TR	81.8	5.86	82.13	4.81	0.8106	NS
T0	82.40	8.14	85.13	4.81	0.1189	NS
T1	84.43	5.60	88.00	4.85	0.0107	S
T2	84.99	5.19	93.07	4.09	< 0.0001	HS
T3	84.83	6.64	98.07	3.47	< 0.0001	HS
T4	83.03	7.24	102.33	3.41	< 0.0001	HS
T5	82.07	5.81	100.03	4.49	< 0.0001	HS
T6	81.00	5.86	98.03	4.81	< 0.0001	HS
T7	80.00	6.31	95.80	4.21	< 0.0001	HS
T8	78.00	5.29	94.97	3.61	< 0.0001	HS
T9	76.03	3.41	94.00	3.05	< 0.0001	HS
T10	76.17	3.59	90.00	3.73	< 0.0001	HS

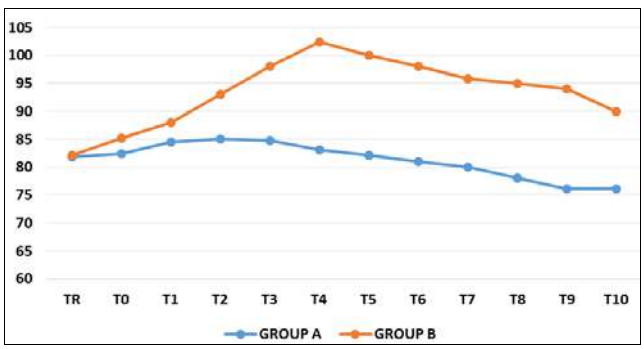

Fig 2: Mean DBP

In Group A

Mean DBP at the time of reversal (TR) was 81.80±5.86 and at the time of administration of NTG spray (T0) was 82.40±8.14. The DBP increased till 3 minutes when the maximum mean BP was 84.83±6.64. This DBP subsequently reduced gradually till 10 minutes (T10) with the mean being 76.17±3.59.

In Group B

Mean DBP at the time of reversal (TR) was 82.13 ±4.81 and at the time of administration of saline spray (T0) was 85.13 ±4.81. The DBP increased till 4 minutes (T4) when the maximum mean BP was 102.33±3.41.When compared this increase in DBP was statistically highly significant, p value being< 0.0001. This DBP remained high till 10minutes.

Discussion

Nitroglycerin is known to produce reflex tachycardia due to sympathetic stimulation however in our study none of the patient showed any significant tachycardia. In the study done by Deepak Singh *et al.* named "Effect of Nitroglycerin spray to blunt the hemodynamic response to endotracheal extubation in lumbar disc surgery [7], concluded that tachycardia was insignificant in NTG group. Similarly study by "Anant S *et al.* and Dich-Niels *et al.*" [8] found that following intranasal NTG spray there was attenuated pressor response to laryngoscopy and intubation without significant increase in heart rate. "Firoozbaksh *et al.*" [9] also found that there was no significant increase in heart rate following use of intravenous nitroglycerin during intubation. Our study also confirms similar hemodynamic changes, there was tachycardia in Group A but it was not statistically significant.

In our study, there was a small insignificant increase in SBP, DBP and MAP in the NTG group till 3 minutes. Subsequently SBP, DBP and MAP reduced till 10 minutes remaining lower than baseline (TR).

In NS group SBP, DBP and MAP markedly increased with maximum values seen at 4 minutes. SBP, DBP and MAP remained high till 10 minutes. This shows that NTG spray is considerably effective in attenuating pressor response to extubation. The results were similar to a study undertaken by Ameya a Tagalpallewar *et al.* and as well Deepak Singh *et al.* Nitroglycerin is most commonly used rescue antihypertensive in anesthesia practice. A study undertaken by Sunil Tuljapure, Vaishali Kotambkar *et al.* in their study titled "A randomized controlled study of tracheal extubation response following nitroglycerine (NTG) sublingual spray in normotensive and hypertensive patients" [10] concluded that NTG is effective to attenuate pressor response to extubation, the effect of which started after 3 minute of sublingual NTG spray, our study also showed similar result. It is noted that onset of action of sublingual NTG is 2-3 minute hence a time gap of 3 minute was required for its action. In our study we found that "systolic blood pressure, diastolic blood pressure and mean arterial pressure" were under control within four minutes and remained to baseline during extubation in Group A where as in Group B it remained constantly high during extubation and returning to baseline thereafter 8-10 minutes post extubation. Intravenous NTG is also used during tracheal intubation to study its effect on attenuation of pressor response by Firoozbaksh *et al.* [9] also showed similar result so as also S Kumara *et al.* in their study on effect of 2% NTG ointment which was rubbed on the forehead of patients before intubation found that increase in blood pressure was significantly low when compared with control group. Similar result was found in study done by Ameya *et al.* in

their study on efficacy of sublingual nitroglycerin spray in attenuation of hemodynamics to tracheal extubation.

The present study was aimed at determining efficacy of 1 puff of sub lingual NTG (0.4 mg) spray versus 1 puff of normal saline spray in attenuating the pressor response during extubation. We have successfully established that 1 puff of sublingual Nitroglycerin spray is effective, practical, easy to administer and safe in attenuating pressor response to tracheal extubation.

Our study was undertaken in patients belonging to ASA I and II, these results may not be applicable in hypertensive patients who may still show pressor response to extubation. Hence further evaluation of the effectiveness of NTG spray in controlled as well as uncontrolled hypertensive patients is required.

In our study patient received 1 puff (0.4mg) which resulted in a small although insignificant increase in BP till 3 minutes. It may be possible to attenuate this small increase in BP by using higher dose of NTG spray instead of 0.4mg and requires further evaluation. It was observed that there was tachycardia as Injection Glycopyrrolate was given just before intervention since, both the groups received the same drug it will not act as bias.

Conclusion

We observed that SBP and DBP increased till 3rd minute in Group A and thereafter had better hemodynamic control of pressor response to extubation compared to baseline and returning to baseline after 9 minutes. Whereas in Group B, SBP and DBP increased progressively till 10 minutes. This increase in hemodynamic response was statistically significant.

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