

A Comparative Study of Effects of Intravenous Nitroglycerine and Esmolol on Hemodynamic Response Following Tracheal Extubation

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Abstract: ***Introduction:** One of the main concerns for the anesthesiologist is to prevent hypertension, tachycardia and arrhythmias during extubation, and to ensure an awake patient with fully airway control and stable hemodynamics. Our aim was to compare the effects of intravenous Nitroglycerine and intravenous Esmolol on hemodynamic response following tracheal extubation in patients posted for major surgical procedure and to study its safety and side effects if any associated with it. **Materials & Methods:** The patients were randomly divided into two groups and would receive the drugs blindly. **GROUP A (Esmolol group) (n=50):** received intravenous Esmolol (1mg/kg body wt). **GROUP B (NTG group) (n=50):** received intravenous Nitroglycerin (1mcg/kg body weight). **Observations:** Administration of intravenous nitroglycerin and intravenous esmolol prior to extubation in ASA grade I patients are effective, practical, easy and relatively safe method of protecting patient from the hypertension and complications related with hypertension without much affecting heart rate during extubation. **Conclusion:** Intravenous Esmolol has as much haemodynamic stability as intravenous Nitroglycerine during extubation period and both attenuates extubation response without any adverse effect and complications.*

Keywords: Extubation, Esmolol, Hypertension, Nitroglycerine

1. Introduction

Tracheal extubation is an equally important part of general anaesthesia as intubation and is commonly carried out after surgery and anaesthesia when effects of muscle relaxant are fully reversed and the patient is maintaining an acceptable respiratory rate and depth and hemodynamic parameters. But tracheal extubation has always received less emphasis than intubation¹. Extubation is associated with awakening, pain, anxiety and airway irritation which may lead to haemodynamic responses similar to intubation, resulting in hypertension, tachycardia and arrhythmias². It is more hazardous in a patient with hypertension, myocardial insufficiency or cerebral vascular disease and is associated to increased incidence of cerebral haemorrhage, myocardial ischemia and pulmonary oedema. Therefore, attenuation of this hemodynamic responses to tracheal extubation is of paramount importance to anaesthesiologist. Several strategies have been evolved to blunt the hemodynamic response to tracheal extubation.

Pharmacological agents are more popular and an ideal agent has to be non anaesthetic, non sedative, short acting with no respiratory depressant action. Various drugs like lignocaine², esmolol¹², clonidine¹³, diltiazem¹⁴, fentanyl¹⁵, dexmedetomidine^{16,17} and nitroglycerine¹⁸ have been studied for preventing extubation response. Though some benefits have been observed with those, most of these approaches have not been proved entirely satisfactory but intravenous NTG and Esmolol are most commonly used drugs because of their immediate action, short half life and lack of sedative properties. Nitroglycerine

generate NO (Nitric oxide) in vascular smooth muscle which produce vasodilatation leading to decrease in blood pressure. Esmolol is an ultra short-acting cardioselective beta adrenoceptor antagonist whose rapid onset, short duration of action (t_f = 9 min) and rapid elimination due to conversion to an inactive free acid metabolite by plasma esterases makes this an ideal agent for suppressing acute increases in systolic blood pressure and heart rate associated with periods of heightened catecholamine output. We plan to do a randomised control double blind study to compare tracheal extubation response comparing iv Nitroglycerine and iv Esmolol in ASA 1 patients undergoing elective surgical procedure. Our aim was to compare the effects of intravenous Nitroglycerine and intravenous Esmolol on hemodynamic response following tracheal extubation in patients posted for elective surgical procedure and to study its safety and side effects if any associated with it.

2. Materials and Methods

Study design: Hospital based Double blind Randomized Comparative and Interventional study. Prior approval from ethical committee was taken. 100 patients were included in the study.

Inclusion criteria

SA 1 Patients
Age 20 – 60 yrs
Patient undergoing major surgical procedure under general anaesthesia with tracheal intubation

Exclusion criteria

Unwilling to participate in the study
 ASA grade 2,3,4 and 5 Patients
 Emergency surgical procedure
 Known hypertensive on regular antihypertensive treatment and at least 2 readings of blood pressure exceeding 140/90 mm of Hg during preoperative hospitalization period
 Pre existing hemodynamic instability and major hemodynamic changes during intra operative period
 Diabetes Mellitus
 Having bleeding disorders
 History of sleep apnea
 Patient requiring post operative ventilator support

Randomization and Grouping: The patients were randomly divided into two groups and would receive the drugs blindly.

GROUP A (Esmolol group) (n=50): received intravenous Esmolol (1mg/kg body wt) as a single bolus in 10 ml NS

GROUP B (NTG group) (n=50): received intravenous Nitroglycerin (1mcg/kg body weight) as a single bolus in 10 ml NS

The randomization list was generated by a random number function using the Microsoft Excel 2003 spreadsheet, resulting in a list of 100 patients assigned to participants receiving the drugs.

Blinding: Identical looking coded syringes were prepared by an anaesthesiologist not involving in the study. The drug administrator and the person making the observation were blind to the study.

Premedication: All patients were pre medicated with inj midazolam, inj glycopyrolate i.v. Patients were connected to pulse oximeter, electrocardiograph monitor and automated non invasive blood pressure. I.V. access was obtained.

Baseline parameters blood pressure & pulse recorded.

Induction: After pre oxygenation 100% oxygen for 3min, anesthesia was induced with intravenous Inj. Thiopentone 5mg / kg body weight and Inj. Fentanyl 2µg/kg body weight. Tracheal intubation was facilitated with neuromuscular blocker intravenous Inj. Succinylcholine 2mg / kg body weight. Under direct laryngoscopic vision intubation was performed, tube will be secured and confirmed with ETCO2 monitoring .

Maintenance: Anesthesia was maintained with O2, N2O, atracurium and with 0.8% to 1.5% Isoflurane. Hemodynamic parameters heart rate, systolic blood pressure, distolic blood pressure, mean arterial blood pressure and oxygen saturation was monitored throughout surgery and recorded every 5minutes. Isoflurane was stopped 5 minutes before last surgical stimulus.

Extubation: When spontaneous respiratory attempts were present, oropharyngeal suction was done. Residual neuromuscular blockade was reversed with Inj.Glycopyrolate 0.008 mg / kg and Inj. Neostigmine 0.05 mg / kg. One minute after reversal study drug (Inj. NTG iv

1µg/kg or Inj.Esmolol 1mg/kg in 10ml of NS) was given over 60sec. Extubation was done when patient meets extubation criteria. Immediately after tracheal extubation 100% O2 will be given via face mask for 5minutes. Haemodynamic parameters will be noted every 1 minute till extubation from stoppage of Isoflurane.

Post operative: After extubation heart rate, systolic blood pressure, diastolic blood pressure & O2 saturation was noted every 2 minutes for 10 minutes [0, 2, 4, 6, 8, 10] , then every 5 minutes for 30 mins.

Incidences of any arrhythmias, ischemia or any other side effects or complications were noted.

Statistical analysis:

- All data was calculated as mean, standard deviation, proportions and percentage
- Unpaired T test was used to test significance of means (age and weight)
- Chi square test was used to test significance of proportions (sex)
- Analysis of variance (ANOVO) was used for comparing intragroup and intergroup heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure
- T test was used for comparing Rate Pressure Product.
- p value less than 0.05 was considered statistical significant

3. Observation and Results

The observations made out of this study are as follows.

	NTG		Esmolol		P value
	Mean	SD	Mean	SD	
SBP	128.54	10.72	125.30	11.07	0.140
DBP	83.20	8.27	82.08	8.74	0.511
HR	89.90	13.40	88.68	12.20	0.635

Data is expressed as mean ± S.D. P<0.05 is significant.

This table shows that mean SBP, mean DBP and mean HR was slightly higher in NTG group as compared to Esmolol group but the difference was not statistically significant. So the baseline clinical variables were comparable in both the groups.

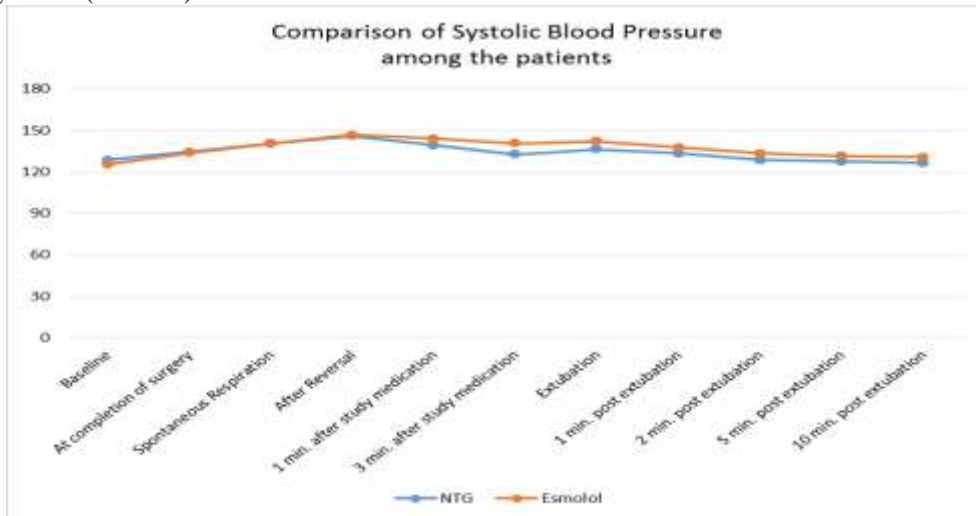
SBP; Changes in SBP among the patients

	NTG		Esmolol		P value
	Mean	SD	Mean	SD	
Baseline-	128.54	10.72	125.30	11.07	0.140
At completion of surgery-T0	134.36	12.52	133.76	9.40	0.786
Spontaneous Respiration-T1	140.66	12.88	140.44	10.83	0.926
After Reversal-T2	145.84	15.92	146.80	10.55	0.723
1 min. after study medication-T3	139.14	13.72	144.08	8.99	0.035
3 min. after study medication-T4	132.60	12.59	140.64	9.79	0.002
Extubation-T5	136.28	12.04	142.08	10.06	0.010
1 min. post extubation-T6	133.26	12.15	137.60	9.21	0.046
2 min. post extubation-T7	128.64	11.21	133.3	10.03	0.030
5 min. post extubation-T8	127.44	10.64	131.6	9.87	0.045
10 min. post extubation-T9	126.40	9.31	130.66	10.63	0.035

Data expressed as mean ± S.D. P<0.05 is significant.

Baseline values were comparable in both groups. The increase in SBP at the end of surgery(T0) was comparable in both the groups(P=0.786).At T1 also the SBP was comparable in both the groups(P=0.926).At T2 mean SBP was slightly higher in Esmolol group but the difference was statistically insignificant(P=0.723).SBP fell down from T3

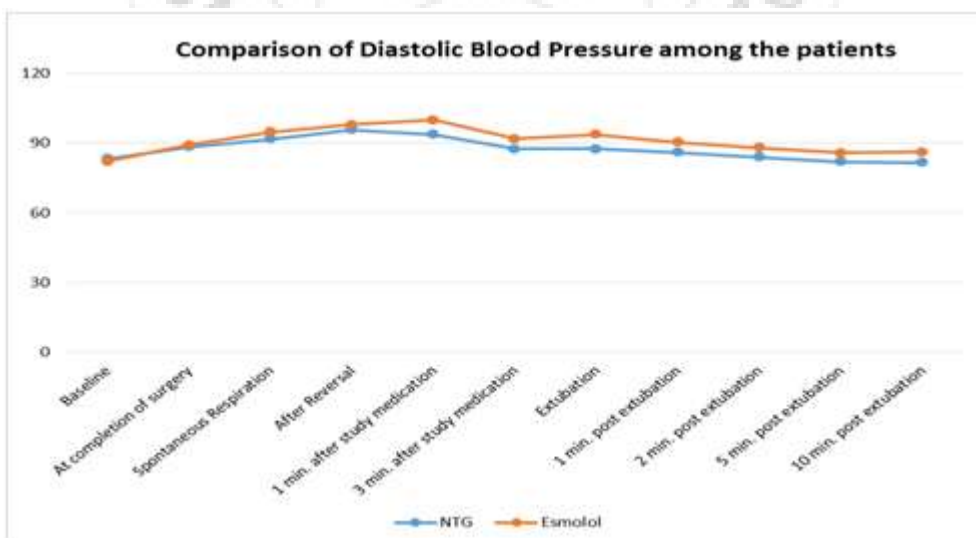
to T9 in both groups i.e. after administration of study medication. At all the time points from T3 to T9 ,the SBP was higher in Esmolol group as compared to NTG group and the difference was statistically significant(P<0.05).



DBP; Changes in DBP among the patients

	NTG		Esmolol		P value
	Mean	SD	Mean	SD	
Baseline	83.20	8.27	82.08	8.74	0.511
At completion of surgery-T0	88.30	8.81	89.04	8.63	0.672
Spontaneous Respiration-T1	91.62	9.59	94.58	10.79	0.150
After Reversal-T2	95.62	11.47	97.88	10.44	0.305
1 min. after study medication-T3	93.64	14.97	99.8	12.83	0.029
3 min. after study medication-T4	87.40	8.84	91.78	10.31	0.049
Extubation-T5	87.36	14.34	93.68	10.13	0.012
1 min. post extubation-T6	86.00	9.81	90.32	9.04	0.024
2 min. post extubation-T7	83.90	9.57	87.96	8.31	0.025
5 min. post extubation-T8	81.96	8.38	85.78	9.43	0.034
10 min. post extubation-T9	81.64	8.33	86.08	8.92	0.011

Data expressed as mean±S.D. P<0.05 significant. Baseline DBP is comparable in both groups. Rise in DBP was seen at T0,T1 and T2 in both the groups. It was slightly higher in Esmolol group as compared to NTG group, but the difference was statistically insignificant.



Fall in DBP was seen in both groups after study drug administration i.e. from T3 to T9.At all the time points from T3 to T9,DBP was lower in NTG group as compared to Esmolol group and the difference was statistically significant(P<0.05).

HR; Changes in HR among the patients

	NTG		Esmolol		P value
	Mean	SD	Mean	SD	
Baseline	89.90	13.40	88.68	12.20	0.635
At completion of surgery-T0	93.72	15.24	90.80	14.86	0.334
Spontaneous Respiration-T1	100.04	14.99	99.28	18.70	0.823
After Reversal-T2	106.02	15.05	101.38	16.73	0.147
1 min. after study medication-T3	103.02	19.70	94.48	13.63	0.013
3 min. after study medication-T4	105.73	15.77	90.44	12.60	0.000015
Extubation-T5	104.62	15.53	92.04	13.13	0.000031
1 min. post extubation-T6	102.02	15.03	89.74	11.34	0.000012
2 min. post extubation-T7	99.70	13.64	87.86	12.33	0.000015
5 min. post extubation-T8	97.46	12.76	85.84	12.91	0.000017
10 min. post extubation-T9	95.70	11.03	83.86	12.95	0.0000035

Data expressed as mean ± S.D.

P<0.05 significant. Baseline HR was comparable in both the groups(P>0.05).HR raised from T0 to T2 in both the groups, it was slightly higher in NTG group but the difference was statistically insignificant(P>0.05).After administration of study medication i.e from T3 to T9 ,fall in HR was seen in Esmolol group, but there was not much change seen in NTG group.HR was higher in NTG group from T3 to T9 as compared to Esmolol group and the difference was statistically significant (P<0.05).

4. Summary of Observation and Results

- 1) There was no significant difference in demographic parameters of patients in the two groups.
- 2) There was no significant difference in duration of surgery and duration of anaesthesia in the two groups.
- 3) The baseline hemodynamic parameters (mean heart rate, mean systolic blood pressure, mean diastolic pressure and mean arterial pressure) were comparable in the two groups.
- 4) There was a significant increase in heart rate, systolic, diastolic blood pressure and mean arterial pressure noted after reversal in two groups.
- 5) Increase in heart rate in NTG group was not statistically significant when compared to Esmolol group.
- 6) Increase in heart rate in Esmolol group was significantly lower from administration of study drug till 15minutes after extubation when compared to NTG group.
- 7) After NTG, systolic blood pressure, diastolic blood pressure and mean arterial blood pressure were under control within one minutes, remaining close to baseline during extubation and came to baseline after two minutes of extubation.
- 8) After Esmolol, systolic blood pressure, diastolic blood pressure and mean arterial blood pressure were under control within one minutes, remaining close to baseline during extubation and came to baseline after two minutes of extubation.
- 9) One minutes, remaining close to baseline during extubation and came to baseline after two minutes of extubation.
- 10) Systolic blood pressure, diastolic blood pressure and mean arterial blood pressure was significantly lower in NTG group
- 11) Compared to Esmolol group just before extubation till two minutes of extubation.

5. Discussion

The present study was a prospective, randomized, controlled and double blind study.

6. Comparison of heart rate

Nitroglycerine: In our study we noted that, as compared to baseline, there was a significant increase in heart rate after termination of anaesthesia in all the patients. During extubation, though heart rate was found to be increased in NTG group, it was not statistically significant when compared with esmolol group during extubation (p>0.05). There is minimal data about nitroglycerine for extubation response but has been effectively used as a rescue drug for controlling hypertension during extubation while studying other drugs. The drug has also been used by several authors during tracheal intubation with favourable hemodynamic effect. **Firoozbaksh et al24 (2008)** in his study to evaluate the effect of intravenous nitroglycerine on blood pressure during intubation found similar response of heart rate. **Anant S et al25** found significant attenuation of hypertensive response to laryngoscopy and intubation following intranasal NTG spray. The increase in heart rate was comparable with the control patients.

S. Kamra et al28 examined the effects of 2% nitroglycerin ointment rubbed on the forehead prior to intubation and found that increase in pulse rate was not significant.

In our study the increase in heart rate following the administration of NTG was significant.

In addition, in the present study injection neostigmine and injection glycopyrrolate were given intravenously simultaneously and as both the drugs affect the heart rate, the change produced by NTG was masked and the combine effect was noted. The principal advantage of the drug is that while a desirable and transient reduction in blood pressure is achieved, cardiac output is unlikely to decrease due to increase in heart rate. Besides, by dilating the coronary vessels NTG increases the coronary blood flow and oxygen delivery to myocardium and is primarily indicated to treat the acute myocardial ischemia. Thus tachycardia is not a major concern in these patients.

Esmolol: In our study we found Esmolol attenuated the tachycardiac response to extubation more effectively than NTG group. We found significant control of heart rate within 1 minute of intravenous administration and persisted till 10 minutes after extubation. Similar results were found by **Dyson et al12** when they injected esmolol 1.5mg/kg two to five minutes before extubation. This dose was sufficient to produce attenuation of increase in heart rate.

Similarly **Dutta et al 18** observed increase in heart rate just before extubation which returned to baseline in three minutes after extubation. However, in this study esmolol infusion was started at the rate of 100 mg/kg/min four minutes before extubation and continued upto five minutes after extubation. Our study is contrary to that of **Dutta et al18** due to methodological difference between two studies.

Nitroglycerine vs Esmolol: In our study we found Esmolol attenuated the tachycardiac response to extubation more effectively than Nitroglycerine group. We found has significant control of heart rate within 1 minute of intravenous administration and persisted upto 10 minutes after extubation. Several studies have shown that there is increased incidence of Myocardial infarction when intra operative heart rate are >110 /min⁴⁷. In our study none of the patients in group - B showed heart rate >110 /min heart rate remained near the baseline value throughout the extubation period. In our study we found Esmolol has better control over heart rate as compared to NTG,

Comparison of blood pressure

In the present study the baseline value of mean systolic blood pressure, diastolic blood pressure, mean arterial blood pressure were comparable between the two groups and the difference was not significant. Mean systolic blood pressure, diastolic blood pressure, mean arterial blood pressure were found to be significantly lower in NTG groups when compared with Esmolol during extubation.

Nitroglycerine

In our study we found that after NTG, systolic blood pressure, diastolic blood pressure, mean arterial blood pressure was under control within minute of medication and remained close to baseline during extubation. Though there is minimal data about nitroglycerine for extubation response, it has also been effectively used as a rescue drug for controlling hypertension during extubation while studying other drugs. The drug has also been used by several authors during tracheal intubation with favourable haemodynamic effects. **Firoozbaksh et al²⁴** found that following tracheal intubation mean arterial pressure and systolic blood pressure increased to a significantly lesser extent in patients receiving intravenous nitroglycerine.

S. Kamra et al²⁸ examined the effects of 2% nitroglycerin ointment rubbed on the forehead prior to intubation and found that the rise in systolic arterial pressure was significantly lower as compared to the control group ($p<0.001$).

J.Dich-Niels²² et al found similar effects with intranasally administered nitroglycerin (NTG) on the cardiovascular response to laryngoscopy and intubation. Results of the present study also confirm similar hemodynamic changes with nitroglycerine used during tracheal extubation in all patients.

Esmolol:

In Esmolol group systolic blood pressure, diastolic blood pressure, mean arterial blood pressure were under control within minute of medication and remained close to baseline during extubation. Similar result was found by **Dyson et al¹²** in his study doses of 1.5 and 2 mg/kg controlled both systolic blood pressure and heart rate, but the larger dose produced significant decreases in systolic blood pressure.

Keskin and colleagues⁴¹ administered esmolol 500 μ g/kg IV bolus before extubation and infused 200 μ g/ kg esmolol in 4 minutes after extubation and they concluded that it was effective in controlling the BP and HR during extubation.

Nitroglycerine vs Esmolol:

In our study we found that at time of extubation blood pressure was significantly lower in NTG group as compared to Esmolol group. It was insignificant immediately after 2 minutes of extubation when compared to NTG group. Systolic blood pressure, diastolic blood pressure and mean arterial blood pressure were decreased than baseline in Esmolol group but higher when compared to NTG group. Similarly **Ersin and colleagues⁴²** reported that IV Esmolol after dose of 1 mg/kg was effective in preventing the hemodynamic response when administered 3 minutes before extubation. In other studies by **Turlapaty P³⁸** shows that Esmolol is a short-acting intravenous beta blocker for acute critical care settings found esmolol to decrease the DAP less than SAP and this resulted in a better control of the systemic blood pressure and HR.

Complications

In the present study, SBP >180 mm Hg was considered dangerous and injection esmolol hydrochloride was used as a rescue drug to control hypertension and none patient required inj. esmolol. Results of the present study also confirm similar hemodynamic changes with Nitroglycerine and Esmolol used during tracheal extubation in patients.

7. Conclusion

We conclude from this study that, administration of intravenous nitroglycerin in a dose of 1 μ g/kg and intravenous esmolol in a dose of 1 mg/kg prior to extubation in ASA grade I patients are effective, practical, easy and relatively safe method of protecting patient from the hypertension and complications related with hypertension without much affecting heart rate during extubation. After surgery they stabilizes hemodynamics, allows easy extubation, provides a more comfortable recovery.

Rise in systolic blood pressure, diastolic blood pressure and mean arterial pressure is significantly controlled by intravenous Nitroglycerin while rise in heart rate is significantly controlled by intravenous Esmolol during extubation period. Hence we conclude intravenous Esmolol has as much haemodynamic stability as intravenous Nitroglycerine during extubation period and both attenuates extubation response without any adverse effect and complications.

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