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Original Research Article

# Comparative Evaluation of Esmolol, Nitroglycerine and Diltiazem on Attenuation of the Cardiovascular Responses to Tracheal Extubation: A Prospective Randomized Study

**Dr Narayan Acharya[1], Dr Daityari Routray[2]**
[1]Assoc Prof, [2]Prof, Department of Anaesthesiology, MKCG Medical College, Berhampur, Odisha

***Corresponding author**
Dr Narayan Acharya
Email: drnarayan2017@gmail.com

**Abstract:** Increase in blood pressure and heart rate most commonly occurs from reflex sympathetic discharge in response to laryngotracheal stimulation during intubation and extubation. Hypertensive response to extubation might be enhanced and can be dangerous to hypertensive subjects. Various agents have been used to attenuate hypertensive response but none is ideal. 120 patients of ASA grade I/II were included in study. The patients were randomly assigned to four groups of thirty each through a computer generated number. Group A = received 1mg/ kg of esmolol intravenously (n=30), Group B = received 1µg/kg of nitroglycerine intravenously (n=30), Group C = received 0.2mg/ kg of diltiazem intravenously (n=30) and group D received normal saline (placebo). These agents were administered one minute after reversal. HR, SBP, DBP and MAP were monitored and analyzed. The HR, SBP, SBP, MAP increased significantly during tracheal extubation in the control group ($p<0.001$). Esmolol 1 mg/kg IV bolus effectively controlled HR and mean arterial BP during extubation. NTG 1 µg/kg IV bolus effectively controlled arterial BP but not effective in controlling HR. Diltiazem 0.2 mg/kg IV bolus showed similar response like NTG. Although it attenuated rise in arterial BP significantly at extubation, it failed to control rise in HR. No significant bradycardia, hypotension, arrhythmia occurred in any of the patients. We concluded that esmolol in dose of 1 mg/kg intravenously prevented the rise in both heart rate and blood pressure effectively. Esmolol was more effective in attenuating rise in systolic blood pressure, diastolic blood pressure and mean blood pressure when compared to nitroglycerine and diltiazem.
**Keywords:** diltiazem, esmolol, nitroglycerine, extubation

## INTRODUCTION

Tracheal intubation secures the airway in patients who are undergoing surgical procedures under general anaesthesia. At the end of the surgery, tracheal extubation is carried out i.e. the removal of endotracheal tube from the trachea. Tracheal intubation is frequently associated with cardiovascular stress response characterized by hypertension, tachycardia and increased serum concentration of catecholamines and similar phenomenon is also seen during extubation [1, 2]. There is a correlation between the magnitude of the pressor response and increase in the concentration of catecholamines [3]. The changes in catecholamine levels occur very rapidly and last for few minutes [4, 5]. This sympatho-adrenal response results in increased cardiac workload, heart rate and myocardial contractility which may culminate in increased myocardial oxygen demand and could prove fatal particularly in patients suffering from coronary artery diseases [6, 7]. Various factors have been attributed to this hemodynamic response, like pain of wound, emergence from anaesthesia or tracheal irritation [8].

Different pharmacological agents such as lidocaine [9], β-blockers [10], fentanyl citrate [11], calcium channel blockers [12], inhalational agents [13] have been evaluated to eliminate or blunt this stress response seen during extubation. However the pharmacological mechanisms for the control of hemodynamic changes during tracheal extubation are different for different group of drugs and most of the studies in past have compared the efficacy of different doses of same drug or the two different drugs belonging to same pharmacological group. The present study was undertaken to evaluate the attenuating effects of esmolol, diltiazem and nitroglycerine that belong to different pharmacological groups on haemodynamic changes occurring during tracheal extubation.

## METHODS

This prospective randomized study was conducted in a tertiary health care centre, Odisha after approval from Hospital Ethics Committee. 120 patient of either gender between the age group 18 to 60 belonging to ASA grade I & II and undergoing major surgeries under general anesthesia in supine position with intubation and controlled ventilation were taken up. They were randomly divided in four groups of 30 patients each using closed envelope method .Group A – received esmolol injection 1 mg/kg iv as single bolus**.** Group B - received nitroglycerine injection 1 micro gram/kg iv as single bolus, Group C - received diltiazem injection 0.2mg/kg iv as single bolus, Group D – control group received only saline. Patients with coexisting systemic illness, any chronic medication, and difficult airway, patients undergoing craniotomy or thoracotomy operation were excluded from this study. Thorough pre-anesthetic checkup was done as per the protocol of our department. All patients were pre medicated with tablet alprazolam 0.25mg in the night before the day of surgery. In the operation theatre baseline parameters (PR, BP, SpO2, and ECG) were noted, and an iv access was secured.

Anaesthesia was induced with injection propofol 2mg /kg iv, inj midazolam 0.05mg/kg iv and injection fentanyl 2μg/kg iv and tracheal intubation was facilitated with injection vecuronium 0.1mg/kg i.v. Anaesthesia was maintained with 0.6%-1.2% isoflurane and 60% N2O in oxygen. Intra –operative monitoring included HR, SBP, DBP, MAP, SpO2, ECG and ETCO2. The end tidal partial CO2 was maintained between 30-35 mm Hg. The BP was recorded immediately before the induction of anaesthesia and every five minutes during anaesthesia using automated noninvasive BP monitor. The BP and HR were maintained between 80% and 120% of the preoperative values by altering the concentration of isoflurane and giving additional doses of fentanyl until completion of surgery. Muscle relaxation was maintained by intermittent boluses of vecuronium 0.02mg/kg i.v.

30 min before surgery iv paracetamol 1 gm was injected iv. Residual muscle relaxation was reversed with injection neostigmine 0.05mg/kg iv and injection glycopyrrolate 0.01mg/kg i.v. on appearance of spontaneous ventilation. 1 minute after the reversal given, either of the study medicines i.e. esmolol, nitroglycerine, diltiazem or saline was administered i.v. These medicines were prepared beforehand by an assistant and their identity was unknown to the anaesthetist. The total volume of study medicines was made to 2 ml in all the groups. Thorough oropharyngeal suction was done before extubation. Then trachea was extubated once criteria for extubation were met. Return of spontaneous respiration with adequate tidal volume, obeying verbal commands (eye opening), good hand grip were the criteria for extubation. Immediately after tracheal extubation patient was given 100% oxygen by a facemask for 5 minutes.

Parameters like HR, Systolic BP, Diastolic BP, Mean arterial BP at the completion of surgery – $T_0$,At the appearance of spontaneous respiration-$T_1$,At the time of giving reversal –$T_2$,1 min after injecting study medication –$T_3$, At extubation-$T_4$,One minute after extubation-$T_5$,Two minute after extubation-$T_6$, Five minutes after extubation-$T_7$,Ten minutes after extubation-$T_8$, Thirty minutes after extubation-$T_9$ were monitored. Events like coughing, bucking and breath holding were monitored. Excessive secretions, bronchospasm/laryngospasm, post-operative nausea and vomiting and any other untoward events were monitored.

## STATISTICAL EVALUATION

Assuming α-0.05 with power =80%, approximately 120 patients were randomized under 4 groups based on study medications ensuring at least 30 subjects were available under each group. The data of continuous variables was presented as Mean ± SEM (Standard Error of Mean). Statistical significance was carried out using a two way (time & group) analyses of variance/ non-parametric Friedmann two way ANOVA test. For comparing between two groups students't' test / non-parametric Mann-Whitney test was applied.The categorical data was analyzed by Chi-square test / Fisher exact test and P< 0.05 was taken as level of statistical significance.

## RESULT

Table 1 shows demographic parameters like age, weight, height and BMI which were comparable in all the four groups.

Baseline HR at $T_0$ was comparable in four groups. At extubation (T4), esmolol decreased HR by 41% (p value <0.001), NTG decreased by 28% (p value <0.001) and diltiazem decreased by 22% (p value <0.001) as compared to control group. T9 values were comparable in all the four groups. Heart rate was more controlled in esmolol group in comparison to nitroglycerin and diltiazem.

**Table-1:Comaprision of demographic parameters in all groups**

| Parameters | Group A (esmolol) | Group B (NTG) | Group C (diltiazem) | Group D (control) | P value |
|---|---|---|---|---|---|
| Age (yrs) | 37.13 + 11.99 | 37.27 + 12.63 | 40.20 + 11.47 | 38.87 + 12.55 | 0.733 |
| M/F | 14/16 | 15/15 | 16/14 | 16/14 | 0.948 |
| Wt. (Kg) | 61.5 + 11.45 | 66.2 + 9.13 | 65.73 + 9.94 | 65.37 + 10.91 | 0.280 |
| Ht (Cm) | 164.83 + 9.9 | 167.07+10.07 | 169.37+10.10 | 163.77 + 9.44 | 0.133 |
| BMI (Kg/$m^2$) | 22.91 + 5.28 | 23.86 + 3.68 | 22.96 + 3.26 | 24.48 + 4.98 | 0.402 |

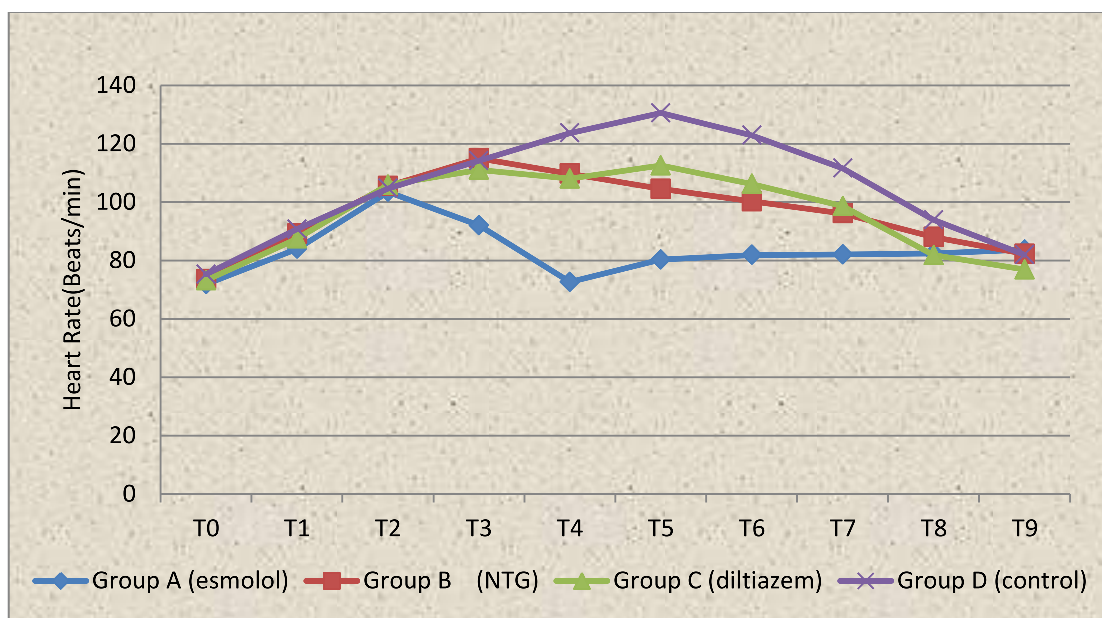


**Fig 1: Comparison of HR in Control Group with Study Groups at Different Time Points**

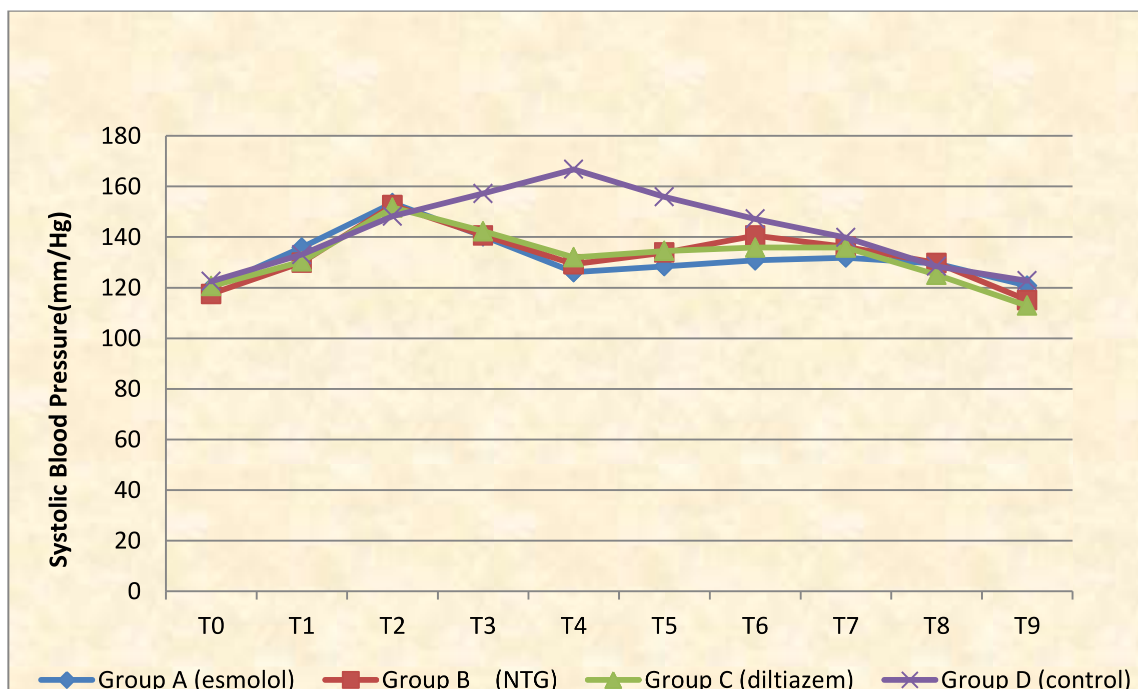


**Fig 2: Comparison of SBP in control group with study groups at different time points**

Baseline ($T_0$) SBP values were comparable in all four groups. When we compared SBP in four groups at T4, i.e. at extubation, esmolol decreased SBP by 24% (p value <0.001), NTG decreased by 22% (p value <0.001) and diltiazem decreased by 21% (p value <0.001) with respect to control group. Esmolol decreased SBP upto $T_7$, NTG decreases SBP upto T5 and Diltiazem decreased SBP upto $T_6$, and T9 SBP values were comparable in four groups.

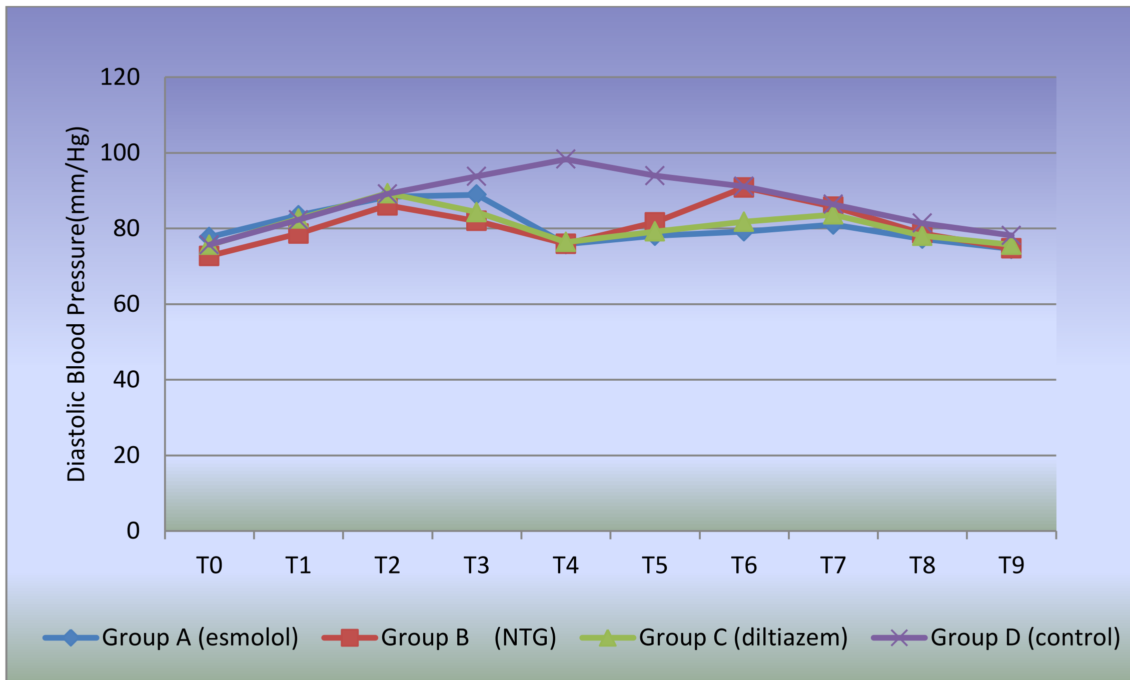


**Fig 3: Comparison of DBP in control group with study groups**

Baseline DBP value at $T_0$ was comparable in four groups. At $T_4$, as compared to control group, esmolol decreased DBP by 23% (p value <0.001), NTG by 23% (p value <0.001) and diltiazem by 22% (p value <0.001). Then DBP values gradually increased in 4 groups (but values remained lower than control group in three study groups) upto $T_8$. $T_9$ value was comparable in all groups.

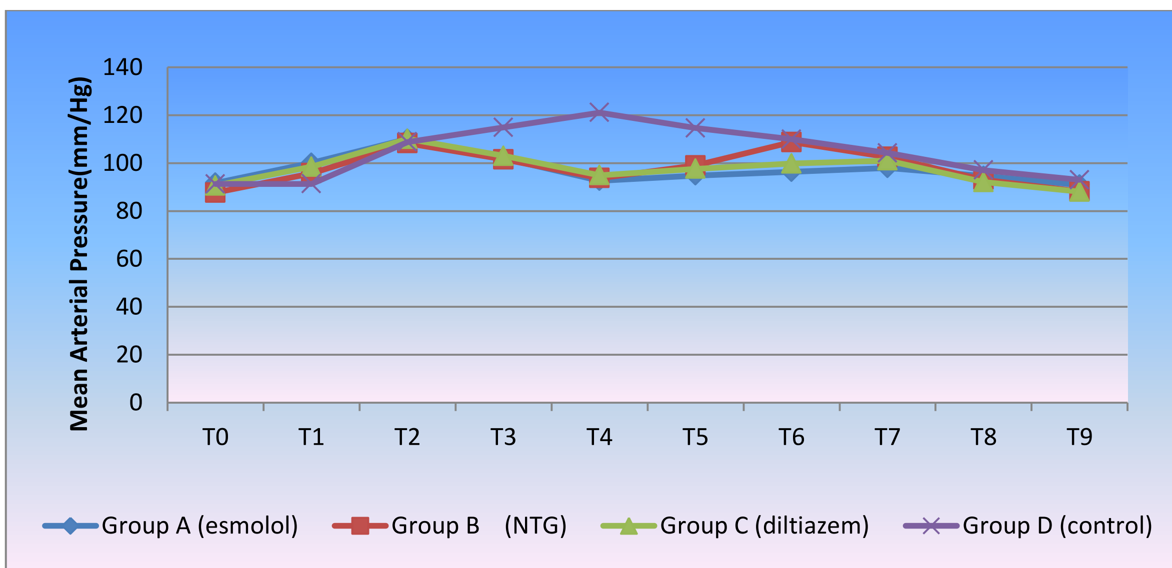


**Fig 4: Comparison of MAP in Control Group with Study Groups at Different Time Points**

Baseline ($T_0$) MAP value was comparable in all four groups. Esmolol decreased MAP by 24% (p value < 0.001), NTG by 23% (p value < 0.001), and Diltiazem by 22% (p value < 0.001) as compared to control group at extubation ($T_4$). MAP values remained higher in all groups (more in control group) till T8. $T_9$ value was comparable in 4 groups.

## DISCUSSION

Tracheal extubation like intubation often provokes increase in arterial blood pressure and heart rate [14, 15]. These hemodynamic changes during extubation, although of little consequence to healthy patients may be severe and prove dangerous in patients with hypertension and coronary artery disease [16]. They cause dangerous increase in myocardial oxygen demand in patients with cardiovascular disease or those at risk of coronary artery disease [17]. Many factors are responsible for these hemodynamic changes at extubation. Firstly, extubation is often performed with patients in lighter plane of anaesthesia. Extubation is also associated with mechanical irritation to airway causing coughing, bucking and straining. Other factors involved are pain from surgery and emergence from general anaesthesia [18]. Moreover it has been demonstrated that tracheal extubation increase plasma catecholamine levels which in turn cause tachycardia, increased myocardial contractility and increased systemic vascular resistance [19]. Miyazaki has shown that extubation increases both heart rate and systolic BP by 20% in more than 70% of patients [20].

Obtunding this hemodynamic response to extubation may prove more challenging than that of intubation, because there are no options of deepening the anaesthesia [21, 22]. In 1992, Mikawa *et al.;* studied two bolus doses of NTG i.e. 1.5 µg/kg and 2.5 µg/kg in 30 normotensive patients undergoing elective surgery. They concluded that a single rapid IV dose of NTG is effective and safe method to attenuate the hypertensive response to laryngoscopy and tracheal intubation [23]. Andrew *et al.;* studied the beneficial effect of intravenous (IV) NTG at dose 1µg/kg/min at the time of intubation in 20 patients scheduled for elective coronary artery bypass grafting (CABG). ECG and radionuclide angiography were performed prior to induction, prior to tracheal intubation and at 1, 3, 5 and 6 min following intubation. They found a lower incidence of new regional wall motion abnormalities in the patients receiving NTG as compared to control group suggestive of myocardial protective role of NTG [24].

Nishina *et al.;* studied the effects of IV diltiazem (0.1 or 0.2 mg/kg) on hemodynamic changes during tracheal extubation and observed that a bolus dose of IV diltiazem 0.1 or 0.2 mg/kg attenuated the cardiovascular changes during tracheal extubation. This effect of diltiazem was equal or superior to that of IV lignocaine 1 mg/kg [25]. Yoshitaka *et al.;* studied 60 hypertensive patients (ASA physical status II) undergoing elective orthopedic surgery and compared the efficacy of combined diltiazem (0.2 mg/kg) and lignocaine (0.1 mg/kg) with each drug alone in attenuating the hemodynamic responses to extubation. They concluded that diltiazem and lignocaine combination is more effective prophylaxis than each drug alone in preventing the cardiovascular response to extubation and emergence in hypertensive patients [26].

Gupta *et al.;* conducted a study regarding attenuation of haemodynamic responses to laryngoscopy and intubation following NTG and esmolol infusion .It was observed that NTG prevented a rise in DBP and SBP but failed to attenuate increase in HR, while esmolol effectively controlled the increase in SBP, DBP, MAP, HR following intubation. So esmolol infusion is more effective in attenuating haemodynamic responses to intubation as compared to NTG infusion [27]. Subhada *et al.;* conducted a study to examine the effects of i.v. diltiazem (0.1mg /kg), i.v. esmolol 1mg/kg on 150 ASA grade I patients undergoing elective general surgery and they concluded that a bolus dose of intravenous diltiazem 0.1mg/kg or esmolol 1mg/kg given at 2 min before extubation was of value in attenuating the cardiovascular changes occurring in association with tracheal extubation. Esmolol was more effective than diltiazem in attenuating the heart rate changes. Diltiazem is more effective than esmolol in attenuating the systolic blood pressure changes [28].

We conducted a randomized double blind study to examine the effects of single bolus dose of esmolol (1 mg/kg), NTG (1 µg/kg) and diltiazem (0.2 mg/kg) on hemodynamic changes during extubation. The HR, SBP, SBP, MAP increased significantly during tracheal extubation in the control group (p<0.001). Esmolol 1 mg/kg IV bolus effectively controlled HR and arterial BP during extubation. NTG 1 µg/kg IV bolus effectively controlled arterial BP but not effective in controlling HR. Diltiazem 0.2mg/kg IV bolus showed similar response like NTG. Although it attenuated rise in arterial BP significantly at extubation but failed to control rise in HR. No significant bradycardia, hypotension and arrhythmia occurred in any of the patients. Airway events like coughing, bucking, laryngospasm and excessive secretions were comparable in all the four groups.

## CONCLUSION

Esmolol 1 mg/kg IV given 2 min after reversal is an effective method for controlling the hemodynamic response to extubation. However caution should be

taken for patients with poor left ventricular function, patients on chronic beta blocker and asthma. In these cases, NTG 1 μg/kg IV or diltiazem 0.2 mg/kg IV may be preferred.

## REFERENCES


1. Yörüko D, Göktug A, Alano Z, Tulunay M. Comparison of intravenous metoprolol, verapamil and diltiazem on the attenuation of haemodynamic changes associated with tracheal extubation. European journal of anaesthesiology. 1999 Jul 1; 16(07):462-7.
2. Dyson A, Isaac PA, Pennant JH, Giesecke AH, Lipton JM. Esmolol attenuates cardiovascular responses to extubation. Anesthesia & Analgesia. 1990 Dec 1; 71(6):675-8.
3. Nishina K, Mikawa K, Maekawa N, Obara H. Fentanyl attenuates cardiovascular responses to tracheal extubation. Acta anaesthesiologica scandinavica. 1995 Jan 1; 39(1):85-9.
4. Mikawa K, Nishina K, Maekawa N, Obara H. Attenuation of cardiovascular responses to tracheal extubation: verapamil versus diltiazem. Anesthesia & Analgesia. 1996 Jun 1;82(6):1205-10.
5. Mikawa K, Nishina K, Takao Y, Shiga M, Maekawa N, Obara H. Attenuation of cardiovascular responses to tracheal extubation: comparison of verapamil, lidocaine, and verapamil-lidocaine combination. Anesthesia & Analgesia. 1997 Nov 1; 85(5):1005-10.
6. Fuhrman TM, Ewell CL, Pippin WD, Weaver JM. Comparison of the efficacy of esmolol and alfentanil to attenuate the hemodynamic responses to emergence and extubation. Journal of clinical anesthesia. 1992 Dec 31; 4(6):444-7.
7. O'DWYER JP, Yorukoglu D, Harris MN. The use of esmolol to attenuate the haemodynamic response when extubating patients following cardiac surgery—a double-blind controlled study. European heart journal. 1993 May 1; 14(5):701-4.
8. Nishina K, Mikawa K, Shiga M, Maekawa N, Obara H. Prostaglandin E1 attenuates the hypertensive response to tracheal extubation. Canadian journal of anaesthesia. 1996 Jul 1; 43(7):678-83.
9. Fujii Y, Kihara SI, Takahashi S, Tanaka H, Toyooka H. Calcium Channel Blockers Attenuate Cardiovascular Responses to Tracheal Extubation in Hypertensive Patients. Survey of Anesthesiology. 1999 Jun 1; 43(3):141.
10. Fujii Y, Saitoh Y, Takahashi S, Toyooka H. RETRACTED ARTICLE: Combined diltiazem and lidocaine reduces cardiovascular responses to tracheal extubation and anesthesia emergence in hypertensive patients. Canadian Journal of Anesthesia/Journal canadien d'anesthésie. 1999 Oct 1; 46(10):952.
11. Zalunardo MP, Zollinger A, Spahn DR, Seifert B, Pasch T. Preoperative clonidine attenuates stress response during emergence from anesthesia. Journal of clinical anesthesia. 2000 Aug 31; 12(5):343-9.
12. Kovac AL, McKinley C, Tebbe CJ, Williams C. Comparison of nicardipine versus placebo to control hemodynamic responses during emergence and extubation. Journal of cardiothoracic and vascular anesthesia. 2001 Dec 31; 15(6):704-9.
13. Tsutsui T. Combined administration of diltiazem and nicardipine attenuates hypertensive responses to emergence and extubation. Journal of neurosurgical anesthesiology. 2002 Apr 1; 14(2):89-95.
14. Wang YQ, Guo QL, Xie D. Effects of different doses of esmolol on cardiovascular responses to tracheal extubation. Hunan yi ke da xue xue bao= Hunan yike daxue xuebao= Bulletin of Hunan Medical University. 2003 Jun; 28(3):259-62.
15. Jee D, Park SY. Lidocaine sprayed down the endotracheal tube attenuates the airway-circulatory reflexes by local anesthesia during emergence and extubation. Anesthesia & Analgesia. 2003 Jan 1; 96(1):293-7.
16. Guler G, Akin A, Tosun Z, Eskitascoglu E, Mizrak A, Boyaci A. Single-dose dexmedetomidine attenuates airway and circulatory reflexes during extubation. Acta anaesthesiologica scandinavica. 2005 Sep 1; 49(8):1088-91.
17. Kovac AL, Masiongale A. Comparison of nicardipine versus esmolol in attenuating the hemodynamic responses to anesthesia emergence and extubation. Journal of cardiothoracic and vascular anesthesia. 2007 Feb 28; 21(1):45-50.
18. Shirasaka T, Iwasaki T, Hosokawa N, Komatsu M, Kasaba T, Takasaki M. Effects of landiolol on the cardiovascular response during tracheal extubation. Journal of anesthesia. 2008 Aug 1; 22(3):322-5.
19. Turan G, Ozgultekin A, Turan C, Dincer E, Yuksel G. Advantageous effects of dexmedetomidine on haemodynamic and recovery responses during extubation for intracranial surgery. European journal of anaesthesiology. 2008 Oct 1; 25(10):816-20.
20. Miyazaki M, Kadoi Y, Saito S. Effects of landiolol, a short-acting beta-1 blocker, on hemodynamic variables during emergence from anesthesia and tracheal extubation in elderly patients with and without hypertension. Journal of anesthesia. 2009 Nov 1;23(4):483.
21. Heartley m, Vaughan RS. Problem associated with tracheal extubation. Br J Anaesth 1993:71:561-68.

22. Bostan H, Eroglu A. Comparison of the clinical efficacies of fentanyl, esmolol and lidocaine in preventing the hemodynamic responses to endotracheal intubation and extubation. Journal of current surgery. 2012; 2(1):24-8.
23. Mikiwa K, Hasegawa M, Suzuki T, Maekawa N. Attenuation of hypertensive response to tracheal intubation with nitroglycerine. J Clin Anesth 1992 Sept-Oct: 4(5):367-371.
24. Andrew P, Enrico M, Timothy L. The effect of nitroglycerine on response to tracheal intubation. Assessment by radionuclide angiography. Anesthesiol Analgesia 1989 Jun: 68(6):718-723.
25. Nishina K, Mikawa K, Maekawa N, Obara H. Fentanyl attenuates cardiovascular responses to tracheal extubation. Acta anaesthesiologica scandinavica. 1995 Jan 1; 39(1):85-9.
26. Fujii Y, Saitoh Y, Tanaka H, Toyooka H. RETRACTED ARTICLE: Cardiovascular responses to tracheal extubation or LMA removal in children. Canadian Journal of Anesthesia/Journal canadien d'anesthésie. 1998 Feb 1; 45(2):178-81.
27. Min JH, Chai HS, Kim YH, Chae YK, Choi SS, Lee A, Choi YS. Attenuation of hemodynamic responses to laryngoscopy and tracheal intubation during rapid sequence induction: remifentanil vs. lidocaine with esmolol. Minerva anestesiologica. 2010 Mar; 76(3):188-92.
28. Shubhada Aphale, Arshdeep Singh, Jyotsna Bhosale,. Comprison of diltiazem and esmolol in attenuating the cardiovascular responses to tracheal extubation.. Innovative Journal of Medical and Health Science.2015; 5(1):1-5.