Section: Anesthesiology

Original Research Article

COMPARATIVE EVALUATION OF ESMOLOL, NITROGLYCERINE AND DILTIAZEM ON ATTENUATION OF THE CARDIOVASCULAR RESPONSES TO TRACHEAL EXTUBATION: A DOUBLE BLIND RANDOMIZED STUDY

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Abstract

Background: Emergence from anesthesia and tracheal extubation can be associated with hemodynamic circulatory responses characterized by tachycardia, hypertension. This sympatho-adrenal response results in increased cardiac workload, myocardial contractility leading to increased myocardial oxygen demand and may prove detrimental for patient with coronary artery disease. **Materials and Methods:** A randomized double blind study was conducted to examine the effects of single bolus dose of esmolol (1 mg/kg), NTG (1 µg/kg) and diltiazem (0.15 mg/kg) on hemodynamic changes during extubation in 120 ASA grade I and II patients undergoing major surgery under general anaesthesia. Anesthesia was induced with propofol 2 mg/kg and fentanyl 2 µg/kg, tracheal intubation was facilitated with vecuronium 0.1 mg/kg i.v. and maintained with 0.6% - 1% isoflurane and 60% N2O in O2. Muscle relaxation was achieved with vecuronium 0.1 mg/kg IV. The study medications were given 1 min after reversal and extubation performed 2 min later. **Results:** 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 0.15 mg/kg IV bolus showed similar response like NTG although it attenuated rise in arterial BP significantly at extubation failed to control rise in HR. No significant bradycardia, hypotension, arrhythmia occurred in any of the patients. Airway events like coughing, bucking, laryngospasm, excessive secretions were comparable in all the four groups. **Conclusion:** It was found that esmolol 1 mg/kg IV given 1 min after reversal was an effective method for controlling the hamodynamic response to extubation. However, caution should be taken for patients with poor left ventricular function, patients on chronic beta blocker and asthmatics. In these cases, NTG 1 µg/kg IV or diltiazem 0.15 mg/kg IV may be preferred.

INTRODUCTION

Tracheal intubation secures the airway in patients undergoing surgical procedures under general anaesthesia. At the end of the surgery, tracheal extubation is carried out which is frequently associated with cardiovascular stress response characterized by hypertension, tachycardia and increased serum concentration of catecholamines.[1,2] There is a correlation between the magnitude of the pressor response and increase in the concentration of catecholamines which usually lasts for few minutes1. This sympatho-adrenal response results in increased cardiac workload, heart rate and myocardial contractility which may culminate in increased myocardial oxygen demand and may prove fatal in

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patients suffering from coronary artery diseases.[3] Various factors also attributed to this haemodynamic response like pain of wound, emergence from anaesthesia or tracheal irritation.[4] Pharmacological agents such as lidocaine,[5] β-blockers,[6] fentanyl citrate,[3] calcium channel blockers,[4,7,8] inhalational agents,[9] have been evaluated to eliminate or blunt this stress response seen during extubation. The option of deepening the level of anesthesia to obtund the haemodynamic responses at intubation is not available at extubation.

In a study comparing the property of verapamil (0.05 mg/kg and 0.1 mg/kg) and diltiazem (0.2 mg/kg) to attenuate pressor responses during extubation by Mikawa et al8 during elective gynaecological surgery showed that the inhibitory effect was greatest with Verapamil 0.1 mg/kg while effect of veraparnil 0.05ng/kg was inferior to diltiazem(0.2mg/kg). Kovac AV et,[10] al in comparing the effectiveness of i.v. nicardipine versus i.v. esmolol in controlling heart rate and blood pressure response to emergence and extubation, showed that esmolol was more effective than nicardipine in attenuating the heart rate response to extubation, whereas the reverse was found true for blood pressure response. A study conducted by Gupta P, Panda B, Verma R,[11] regarding attenuation of hemodynamic responses to laryngoscopy and intubation following nitroglycerine and esmolol infusion observed that nitroglycerine 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. The present study was undertaken to evaluate the attenuating effects of esmolol, dittiazem and nitroglycerine belong to different pharmacological groups on haemodynamic changes with tracheal extubation.

MATERIALS AND METHODS

This prospective double blind randomized study was conducted in the department of anesthesiology and intensive care, B.B. Medical College and Hospital Balangir, Odisha after approval from Hospital ethics Committee. 120 adult patient of either gender between the age group 18 to 65 years belonging to ASA grade I & II and undergoing major surgeries under general anesthesia in supine position with intubation and controlled ventilation were divided into 30 patients each using closed envelope method.

Group A– received esmolol injection 1mg/kg iv as single bolus.

Group B –received nitroglycerine injection 1 microgram/kg iv as single bolus.

Group C- received diltiazem injection 0.15 mg/kg iv as single bolus.

Group D– control group received only saline iv.

Patients with coexisting systemic illness, any chronic medication, difficult airway, patients undergoing craniotomy or thoracotomy operations were excluded from the study. Anesthesia technique- In the operation theatre baseline parameters were noted (pulse rate, Blood Pressure, SpO2, ECG) and an iv access was secured. Anesthesia was induced with injection propofol 2mg/kg and injection fentanyl 2 µg/kg. Tracheal intubation was facilitated with injection vecuronium 0.1 mg/kg. Anasthesia was maintained with 0.6%-1.2% isofluorane and 60% N2O in oxygen. Intra operative monitoring included heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, SpO2, ECG (lead II) and ETCO2. The end tidal CO2 was maintained between 30-35 mm Hg. The BP and HR was maintained between 80% and 120% of the preoperative values by altering the concentration of isofluorane and giving additional doses of fentanyl until completion of surgery. Muscle relaxation was maintained by intermittent boluses of vecuronium 0.02 mg/kg. At the end of surgery isofluorane was switched off and patients were observed for return of spontaneous respiration. Residual muscle relaxation was reversed with injection neostigmine 0.05mg/kg and injection glycopyrrolate 0.01mg/kg on appearance of spontaneous ventilation. One minute after the reversal, the study medicines i.e. esmolol, nitroglycerine, diltiazem or saline was given. These medicines were prepared beforehand in a blinded manner and were unknown to the anaesthetist. A thorough oropharyngeal suctioning was done before extubation. Then trachea was extubated 2mins after the administration of study medications once following criteria were met.

1. Return of spontaneous respiration with adequate tidal volume.
2. Patient obeying verbal commands (eye opening).
3. Sustained hand grip.
4. End tidal concentration of isofluorane less than 0.1%.

Immediately after tracheal extubation patients were given 100% oxygen by a face mask for 5 minutes. Monitoring was done for base line values at the completion of surgery T0, at the appearance of spontaneous respiration T1, at the time of giving reversal T2, 1min after injecting study medication T3, at extubation T4, one minute after extubation T5, two minute after extubation T6, five minutes after extubation T7, ten minutes after extubation T8, thirty minutes after extubation T9. Patients were observed for any untoward events like Coughing, bucking, breath holding, excessive secretions, bronchospasm/laryngospasm, post-operative nausea and vomiting.

Statistical Evaluation

Assuming α-0.05 with power =80%, approximately-120 consecutive patients (ASA I & II) was randomized under 4 groups based on study medications ensuring at least 30 subjects was 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

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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.

RESULTS

The above table showed that age, weight, height, BMI, male female ratio and ASA grading were comparable between the groups [Table 1].

The type of surgeries was comparable in all the four groups [Table 2].

Data expressed as mean + SD, *p value < 0.05 (significant), **p value < 0.001 (highly significant) In the Esmolol group HR increased by 1%, SBP increased by 5%, (p value <0.001), DBP decreased by 2% and MAP increased by 1% at T4 i.e. at extubation. Then values came down to baseline by T9 [Table 3].

Data expressed as mean ± SD, *p value < 0.05 (significant), **p value < 0.001 (highly significant) in the NTG group, immediately after administration of the NTG (at T_3) HR increased by 56% (p value < 0.001) and at extubation (at T_4) HR increased by 49% (p value < 0.001) from baseline. HR values then gradually came down by T9. But SBP increased by only 10% (P value < 0.001), DBP increased by 4% (p value < 0.001) and MAP increased by 7% (p value < 0.001) at T_4 i.e. at extubation. Then arterial BP touched baseline by T9 [Table 4].

Data expressed as mean + SD, *p value < 0.05 (significant), **p value < 0.001 (highly significant). In Diltiazem group, immediately after its administration (T3), HR increased to 52% (p value<0.001) and at extubation (T4) HR increased to 48% (p value <0.001) from baseline. Whereas SBP increased by only 9% (P value<0.001), DBP increased by 1% and MAP increased by 5 % (p value < 0.05) from baseline at T4. All hemodynamic came down to baseline by T9 [Table 5].

Data expressed as mean + SD, *p value < 0.05 (significant), **p value < 0.001 (highly significant)

The above data revealed that all the haemodynamic variables (HR, SBP, DBP, MAP) showed highly significant rise (p value <0.001) from baseline T0 values at all the time points. The percentage increase was maximum at the time of extubation being 64% for HR (p value <0.001), 36% for SBP (p value <0.001), 30% for DBP (p value <0.001) and 33% for MAP (p value <0.001) as compared to baseline value (T0). Subsequently the values decreased but still remained significantly higher than the baseline values upto 10 min post extubation (T_8) [Table 6].

Data expressed as mean + SD, *p value < 0.05 (significant), **p value < 0.001 (highly significant) Baseline HR at T0 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 [Table 7].

Data expressed as mean + SD, *p value < 0.05 (significant), **p value < 0.001 (highly significant) Baseline (T0) 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 T7, NTG decreases SBP upto T5 and Diltiazem decreased SBP upto T6, T9 SBP values were comparable in four groups [Table 8].

Data expressed as mean + SD, *p value < 0.05 (significant), **p value < 0.001 (highly significant) Baseline DBP value at T0 was comparable in four groups. At T4, 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 T8. T9 value was comparable in all groups [Table 9].

Data expressed as mean + SD, *p value < 0.05 (significant), **p value < 0.001 (highly significant) Baseline (T0) MAP value was comparable in all four groups. Esmolol decreased MAP by 24% (p value < 0.001), NTG by 23% (p value < 0.001), Diltiazem by 22% (p value < 0.001) as compared to control group at extubation (T4). MAP values remained higher in all groups (more in control group) till T8. T9 value was comparable in 4 groups [Table 10].

This table shows that RPP was seen to be highest in control group at the time of extubation i.e. at T4 (20618 value > 20,000) followed by NTG (16092), diltiazem (15564) and esmolol (9918) [Table 11].

Data expressed as number, *p value < 0.05 (significant), The above table showed that all values in four groups were comparable to each other [Table 12].

Table 1: Distribution of children according to Demographic Profile

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
Weight. (Kg)	61.5+11.45	66.2+9.13	65.73+9.94	65.37+10.91	0.280
Height (Cm)	164.83+9.9	167.07+10.07	169.37+10.10	163.77+9.44	0.133
BMI (Kg/m2)	22.91+5.28	23.86+3.68	22.96+3.26	24.48+4.98	0.402
Male	14	15	16	16	0.948
Female	16	15	14	14	
ASA Grade-1	23	23	22	24	0.693
ASA Grade-2	7	7	8	6	

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Table 2: Type of surgery

Type of surgery	Group A (esmolol)	Group B (NTG)	Group C (diltiazem)	Group D (control)	P value
General Surg	6	7	5	7	0.704
Gynecological	7	7	4	4	
Orthopedics	7	5	7	8	
ENT	6	6	8	5	
Others	4	5	6	6	

Table 3: Hemodynamic variables in Group A (Esmolol)

	HR	SBP	DBP	MAP
T_0	71.83 ± 4.48	119.90 ± 7.96	77.70 ± 5.96	91.76 ± 4.72
T_1	83.97 ± 6.12**	135.83 ± 6.83**	83.47 ± 5.21**	100.09 ± 4.29**
T_2	103.47 ± 5.8**	153.43 ± 7.72**	88.40 ± 4.28**	110.09 ± 3.57**
T_3	92.03 ± 5.62**	140.30 ± 6.77**	88.93 ± 3.61**	102.05 ± 3.24**
T_4	72.63 ± 4.16	126.13 ± 5.04**	75.87 ± 3.068*	92.62 ± 2.63
T_5	80.30 ± 4.39**	128.47 ± 5.21**	78.03 ± 2.23	94.84 ± 2.22**
T_6	81.87 ± 4.05**	130.80 ± 4.70**	79.17 ± 4.09	96.37 ± 3.02**
T_7	82.04 ± 3.4**	131.87 ± 3.31**	81.00 ± 3.92*	97.95 ± 2.86**
T_8	82.37 ± 3.21**	129.50 ± 3.35**	77.23 ± 3.52	94.63 ± 2.78*
T_9	83.67 ± 4.11**	120.77 ± 5.25	74.57 ± 4.54*	90.96 ± 4.01

Table 4: Hemodynamic variables in Group B (NTG)

	HR	SBP	DBP	MAP
T_0	73.53 ± 9.92	117.53 ± 6.81	72.70 ± 5.29	87.64 ± 4.60
T_1	89.13 ± 9.95**	129.90 ± 6.29**	78.63 ± 4.34**	95.72 ± 3.67**
T_2	105.5 ± 7.86**	152.63 ± 7.16**	86.10 ± 3.77**	108.27 ± 3.37**
T_3	114.97 ± 9.15**	140.67 ± 5.18**	82.00 ± 3.12**	101.55 ± 2.90**
T_4	109.73 ± 9.15**	129.30 ± 4.19**	75.93 ± 3.29**	93.72 ± 2.32**
T_5	104.5 ± 8.02**	133.87 ± 4.09**	81.60 ± 3.93**	99.02 ± 2.65**
T_6	100.23 ± 8.44**	140.60 ± 7.40**	90.83 ± 9.44**	108.75 ± 3.28**
T_7	96.13 ± 6.94**	136.17 ± 5.21**	85.73 ± 3.61**	102.54 ± 2.33**
T_8	88.00 ± 5.29**	129.80 ± 7.77**	78.67 ± 3.80**	93.04 ± 3.19**
T_9	82.27 ± 4.79**	115.13 ± 5.58	74.70 ± 3.71	88.17 ± 2.73

Table 5: Hemodynamic variables in group C (Diltiazem)

	HR	SBP	DBP	MAP
T_0	73.18 ± 6.75	120.60 ± 7.23	75.63 ± 11.17	90.62 ± 8.19
T_1	87.50 ± 6.31**	130.37 ± 7.57 **	82.57 ± 8.36 *	98.50 ± 6.64 **
T_2	105.97 ± 6.08**	151.70 ± 8.45 **	89.30 ± 6.71 **	110.10 ± 5.05 **
T_3	111.07 ± 6.64**	142.30 ± 8.77**	84.30 ± 5.86**	103.03 ± 4.53**
T_4	108.03 ± 5.35**	131.97 ± 10.22**	76.40 ± 4.93	94.92 ± 4.43*
T_5	112.53 ± 5.34**	134.53 ± 8.63**	79.20 ± 4.91**	97.64 ± 4.04**
T_6	106.20 ± 5.31**	135.87 ± 7.69**	81.77 ± 4.77*	99.80 ± 3.89**
T_7	98.60 ± 4.86**	135.87 ± 7.43**	83.67 ± 4.06**	101.07 ± 3.63**
T_8	81.83 ± 5.42**	125.13 ± 8.86**	78.07 ± 4.20	92.08 ± 3.98
T_9	76.90 ± 4.95*	112.87 ± 7.83**	75.67 ± 4.50	88.06 ± 3.68

Table 6: Hemodynamic variables in group D (control)

	HR	SBP	DBP	MAP
T_0	75.23 ± 7.70	122.50 ± 11.01	75.70 ± 8.49	91.30 ± 6.41
T_1	90.70 ± 7.22**	133.10 ± 9.21**	82.27 ± 7.22**	91.31 ± 5.40
T_2	104.70 ± 11.06**	148.27 ± 8.81**	89.13 ± 5.71**	108.84 ± 4.42**
T_3	114.17 ± 10.85**	157.23 ± 7.69**	93.77 ± 5.69**	114.92 ± 4.18**
T_4	123.63 ± 9.51**	166.77 ± 6.86**	98.30 ± 5.22**	121.12 ± 3.85**
T_5	130.53 ± 8.86**	155.93 ± 8.82**	93.97 ± 4.39**	114.62 ± 4.36**
T_6	122.87 ± 8.41**	147.17 ± 8.18**	91.13 ± 4.80**	109.94 ± 4.03**
T_7	111.60 ± 5.96**	139.83 ± 8.18**	86.37 ± 4.52**	104.19 ± 3.74**
T_8	93.87 ± 8.81**	128.47 ± 7.95*	81.37 ± 4.49**	97.06 ± 3.06**
T_9	82.00 ± 6.91**	122.73 ± 7.30	78.13 ± 5.18	93.00 ± 4.02

Table 7: Comparison of Heart Rate in control group with study groups at different time points

	Group A (esmolol)	Group B (NTG)	Group C (diltiazem)	Group D (control)
T_0	71.83 ± 4.48	73.53 ± 9.92	73.18 ± 6.75	75.23 ± 7.70
T_1	83.97 ± 6.12*	89.13 ± 9.95	87.50 ± 6.31	90.70 ± 7.22
T_2	103.47 ± 5.8	105.5 ± 7.86	105.97 ± 6.08	104.70 ± 11.06
T_3	92.03 ± 5.62**	114.97 ± 9.15	111.07 ± 6.64	114.17 ± 10.85
T_4	72.63 ± 4.16**	109.73 ± 9.15**	108.03 ± 5.35**	123.63 ± 9.51
T_5	80.30 ± 4.39**	104.5 ± 8.02**	112.53 ± 5.34**	130.53 ± 8.86

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T_6	81.87 ± 4.05**	100.23 ± 8.44**	106.20 ± 5.31**	122.87 ± 8.41
T_7	82.04 ± 3.4**	96.13 ± 6.94**	98.60 ± 4.86**	111.60 ± 5.96
T_8	82.37 ± 3.21**	88.00 ± 5.29*	81.83 ± 5.42**	93.87 ± 8.81
T_9	83.67 ± 4.11	82.27 ± 4.79	76.90 ± 4.95*	82.00 ± 6.91

Table 8: Comparison of SBP in control group with study groups at different time points

	Group A (esmolol)	Group B (NTG)	Group C (diltiazem)	Group D (control)
T_0	119.90 ± 7.96	117.53 ± 6.81	120.60 ± 7.23	122.50 ± 11.01
T_1	135.83 ± 6.83	129.90 ± 6.29	130.37 ± 7.57	133.10 ± 9.21
T_2	153.43 ± 7.72	152.63 ± 7.16	151.70 ± 8.45	148.27 ± 8.81
T_3	140.30 ± 6.77**	140.67 ± 5.18**	142.30 ± 8.77**	157.23 ± 7.69
T_4	126.13 ± 5.04**	129.30 ± 4.19**	131.97 ± 10.22**	166.77 ± 6.86
T_5	128.47 ± 5.21**	133.87 ± 4.09**	134.53 ± 8.63**	155.93 ± 8.82
T_6	130.80 ± 4.70**	140.60 ± 7.40	135.87 ± 7.69*	147.17 ± 8.18
T_7	131.87 ± 3.31**	136.17 ± 5.21	135.87 ± 7.43	139.83 ± 8.18
T_8	129.50 ± 3.35	129.80 ± 7.77	125.13 ± 8.86	128.47 ± 7.95
T_9	120.77 ± 5.25	115.13 ± 5.58	112.87 ± 7.83	122.73 ± 7.30

Table 9: Comparison of DBP in control group with study groups at different time points

	Group A (esmolol)	Group B (NTG)	Group C (diltiazem)	Group D (control)
T_0	77.70 ± 5.96	72.70 ± 5.29	75.63 ± 11.17	75.70 ± 8.49
T_1	83.47 ± 5.21	78.63 ± 4.34	82.57 ± 8.36	82.27 ± 7.22
T_2	88.40 ± 4.28	86.10 ± 3.77	89.30 ± 6.71	89.13 ± 5.71
T_3	88.93 ± 3.61*	82.00 ± 3.12**	84.30 ± 5.86**	93.77 ± 5.69
T_4	75.87 ± 3.06**	75.93 ± 3.29**	76.40 ± 4.93**	98.30 ± 5.22
T_5	78.03 ± 2.23**	81.60 ± 3.93**	79.20 ± 4.91**	93.97 ± 4.39
T_6	79.17 ± 4.09**	90.83 ± 9.44	81.77 ± 4.77**	91.13 ± 4.80
T_7	81.00 ± 3.92**	85.73 ± 3.61	83.67 ± 4.06	86.37 ± 4.52
T_8	77.23 ± 3.52	78.67 ± 3.80	78.07 ± 4.20	81.37 ± 4.49
T_9	74.57 ± 4.54	74.70 ± 3.71	75.67 ± 4.50	78.13 ± 5.18

Table 10: Comparison of MAP in control group with study groups at different time points

	Group A (esmolol)	Group B (NTG)	Group C (diltiazem)	Group D (control)
T_0	91.76 ± 4.72	87.64 ± 4.60	90.62 ± 8.19	91.30 ± 6.41
T_1	100.09 ± 4.29	95.72 ± 3.67	98.50 ± 6.64	91.31 ± 5.40
T_2	110.09 ± 3.57	108.27 ± 3.37	110.10 ± 5.05	108.84 ± 4.42
T_3	102.05 ± 3.24**	101.55 ± 2.90**	103.03 ± 4.53**	114.92 ± 4.18
T_4	92.62 ± 2.63**	93.72 ± 2.32**	94.92 ± 4.43**	121.12 ± 3.85
T_5	94.84 ± 2.22**	99.02 ± 2.65**	97.64 ± 4.04**	114.62 ± 4.36
T_6	96.37 ± 3.02**	108.75 ± 3.28	99.80 ± 3.89**	109.94 ± 4.03
T_7	97.95 ± 2.86**	102.54 ± 2.33	101.07 ± 3.63*	104.19 ± 3.74
T_8	94.63 ± 2.78	93.04 ± 3.19	92.08 ± 3.98	97.06 ± 3.06
T_9	90.96 ± 4.01	88.17 ± 2.73	88.06 ± 3.68	93.00 ± 4.02

Table 11: Rate Pressure Product values in all the four groups at different time points

	Group A Esmolol	Group B NTG	Group C Diltiazem	Group D Control
T_0	8603.63±674.32	8643.37±1287.86	8816±939.06	9229.77±1356.28
T_1	11392.63±947.94	11392.03±947.94	11397.3±944.03	12105.4±1340.15
T_2	15883.9±1312.523	11571.9±1362.73	15992.2±1182.66	15503.33±1734.06
T_3	12917.03±1067.93	16155.7±1232.43	15791.03±1182.66	17938.93±1806.6
T_4	9918.37±654.37	16092.97±1310.03	15564.9±1238.58	20618.93±1788.83
T_5	10318.27±739.04	16155.7±1232.43	15130.5±1080.71	20356.07±1771.16
T_6	10707.53±651.471	14178.43±1155.65	14420.87±953.28	18078.5±1552.76
T_7	10865.07±509.35	13979.77±1024.80	13391.67±929.29	15614.07±1319.22
T_8	10662.43±406.98	14490.77±1381.2	9841.43±1100.37	12074.8±1503.8
T_9	10361.03±758.74	9455.73±814.24	8681.43±966.87	10058.23±966.87

Table 12: Comparison of untoward effects in four groups

Presence of symptoms	Group A (esmolol)	Group B (NTG)	Group C (diltiazem)	Group D (control)	P value
Cough					
Present	3	3	1	3	0.727
Absent	27	27	29	27	
Bucking					
Present	4	3	6	5	0.727
Absent	26	27	24	25	
Breath holding					
Present	4	5	3	3	0.840
Absent	26	25	27	27	

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Excess secretion					
Present	5	1	2	1	0.16
Absent	25	29	28	29	
Broncho spasm					
Present	2	2	3	4	0.777
Absent	28	28	27	26	
Laryngo spasm					
Present	2	1	3	2	0.784
Absent	28	29	27	28	
PONV					
Present	3	2	2	4	0.777
Absent	27	28	28	26	

DISCUSSION

Tracheal extubation often provokes increase in arterial blood pressure and heart rate.[1,12] 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.[13] It increases myocardial oxygen demand in patients with cardiovascular disease or those at risk of coronary artery disease8. Extubation is often performed in patients with lighter place of anesthesia. Extubation is also associated with mechanical irritation to airway causing coughing, bucking and straining.[5,14,15,16] Pain from surgery and emergence from general anesthesia may cause hemodynamic stress response.[4] Moreover it has been demonstrated that tracheal extubation increase plasma catecholamine levels which in turn cause tachycardia, increased myocardial contractility and increased SVR.[1,3] It has been shown that extubation increases heart rate and systolic BP by 20% in more than 70% of patients.[6]

Obtunding hemodynamic response to extubation may prove more challenging than that of intubation, where options such as deepening the level of anesthesia by higher concentration of inhalational agents, additional doses of induction agents and supplemental doses of analgesics are available. In contrast, at extubation techniques used to attenuate the hemodynamic responses must also ensure that safe extubation are not interfered with spontaneous eye opening, sustained head lift and adequate protective reflexes. Therefore cardiac and antihypertensive drugs may play a major role for attenuating response to extubation as compared to sedatives and narcotics. Here three drugs belonging to different groups i.e. esmolol (β blocker), nitroglycerine (vasodilator) and diltiazem (calcium channel blocker) were compared to assess their role in attenuating the cardiovascular response at extubation.

The demographic profile in the study with respect to age, sex, height, weight, BMI, ASA physical status and type of surgery were comparable in all the four groups. A significant extubation response was seen in the control group which did not receive any study medication. The rise in heart rate was significant throughout the entire period of study i.e. from T1 to T8. The rise in heart rate seen at T4 (i.e. at extubation) was 64% more from baseline with a 24% rise seen even at T8 i.e. 10 min post extubation. The SBP, DBP, MAP similarly showed a significant rise from baseline throughout the entire period with rise seen at T4 (i.e. at extubation) being 36% for SBP, 30% for DBP and 33% for MAP. Rate pressure product (SBP x HR) seen at T4 was 205,[12] in the control group. Levels of RPP > 20,000 are more commonly associated with angina and myocardial ischaemia.

In 1998, Fuji et al,[20] studied the inhibitory effects of calcium channel blockers, nicardipine (30 µg/kg) and diltiazem (0.2 mg/kg) on haemodynamic changes after tracheal extubation in 60 hypertensive patients (ASA grade II). They found that RPP after tracheal extubation was > 20,000 in control group, but these critical increases in RPP were avoided in nicardipine and diltiazem group.

In the esmolol group, the rise in HR was only 1% from baseline at T4 (at extubation). The blood pressure was also well controlled in this group as compared to control group. The SBP increased by 5%, DBP decreased by 2% while MAP increased by 1% from baseline at T4 (at extubation). All hemodynamic variables were seen to be lower than control group upto T8 i.e. 10min post extubation. RPP at T4 was found to be 9160. Esmolol with a rapid onset and extremely short duration of action (t½ - 9 min) appears to be an ideal drug for preventing acute rise in HR and BP. Andrew et al6 studied the effect of three different doses of esmolol i.e. 1mg/kg, 1.5mg/kg and 2 mg/kg given as bolus 2 min after reversal and found that though all doses were effective in alleviating increase in HR, 1mg/kg was insufficient to control the rise in SBP but the doses 1.5mg/kg and 2mg/kg though effective in controlling SBP in majority of cases, did produce hypotension of more than >20% in some of the patients.

In this study, no significant bradycardia or hypotension was observed throughout the time period of study and even at 30 min post extubation. Anthony et al,[10] compared nicardipine in a dose of 0.03 mg/kg with esmolol 1.5 mg/kg in attenuating the haemodynamic response to emergence and extubation and found that esmolol was more effective than nicardipine in attenuating the heart rate response to extubation and nicardipine was found more effective in controlling the blood pressure response.

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In the nitroglycerine group (NTG), the rise in heart rate was found to be 49% at T4 (i.e. at extubation) from baseline which became clinically significant though lower than control group. However, NTG effectively controlled arterial BP i.e. SBP increased by only 10%, DBP by 4% and MAP by 7% at T4 (at extubation). RPP was calculated to be 14188 at T4. In 1992, Mikawa et al9 studied two bolus doses of NTG i.e. 1.5 µg/kg and 2.5 µg/kg in 30 normotensive patients undergoing elective surgery and concluded that a single rapid IV dose of NTG is effective and safe method to attenuate the hypertensive response to laryngoscopy and tracheal intubation.

In 2010, Gupta et al,[11] studied the effect of NTG and esmolol infusion on attenuation of hemodynamic response to laryngoscopy and intubation. They found that the increase in MAP and RPP were significantly less in the nitroglycerine group compared to the control group. Esmolol effectively controlled the increase in SBP, DBP, MAP and HR. However, NTG although found to be effective in controlling rise in SBP and DBP, failed to attenuate increase in HR. This effect of NTG was found to be similar in our study. NTG in small IV bolus dose starts acting within 1 min and its duration is 1 to 5 minutes. In this group arterial BP (SBP, DBP, MAP) was found to be significantly lower as compared to control group from T3 to T5 i.e. from drug administration time to 1 min post extubation because of extremely short duration of action of NTG. NTG failed to control HR at T4, although it was significantly lower than control group due to its pharmacological effect of causing reflex tachycardia,[17]

Andrew et al,[18] studied the effect of intravenous (IV) NTG at dose 1µg/kg/min at the time of intubation in elective coronary artery bypass grafting (CABG). ECG and radionuclide angiography were performed prior to induction, tracheal intubation and at 1, 3, 5 and 6 min following intubation. A lower incidence of new regional wall motion abnormalities were found in patients receiving NTG as compared to control group suggesting myocardial protective role of NTG. In the diltiazem group, heart rate was not well controlled with a rise of 48% from baseline at T4 i.e. at extubation. Though this rise was less than the control group, it was clinically significant. HR values from T3 to T9 were found to be lower than control group, but they were more than 20% from baseline till T7 i.e. 5 min post extubation. This may be due to reflex sympathetic stimulation because of sudden hypotension12. Arterial BP on the other hand was well controlled with diltiazem group. The rise in SBP was seen by 9%, DBP by 1% and MAP by 5% at T4. The RPP at T4 was found to be 14256.

Nishina et al7 studied the effects of IV diltiazem (0.1 or 0.2 mg/kg) and lignocaine on hemodynamic changes during tracheal extubation in elective gynaecologic surgery and observed that a bolus dose of IV diltiazem 0.1 or 0.2 mg/kg attenuated the cardiovascular changes during tracheal extubation which was equal or superior to that of IV lignocaine 1 mg/kg. Yoshitaka et al19 studied 60 hypertensive patients undergoing elective orthopaedic surgery to compare 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 than each drug alone in preventing the cardiovascular response to extubation.

Coughing, bucking, breath holding, increased secretions and bronchospasm were found to be comparable in all the four groups.

CONCLUSION

A significant haemodynamic response was seen at extubation in the control group i.e. an increase in heart rate by 64% and rise in SBP, DBP, MAP by 36%, 30% and 33% respectively which were clinically significant. Esmolol in a dose of 1 mg/kg was found to be very effective in controlling this extubation response with rise in HR by 1%, rise in SBP, MAP by 5% and 1% and a fall in DBP by 2% resulting in RPP of 9160 at the time of extubation. Bradycardia or hypertension was not seen in patients. Nitroglycerine in a bolus dose of 1µg/Kg was found to effective in controlling arterial BP with a rise of SBP, DBP, MAP of 10%, 4% and 7% respectively, but was not effective in controlling tachycardia with 49% rise in HR at T4 and a maximum rise up to 56%. Diltiazem in a dose of 0.15 mg/Kg was found to be effective in controlling arterial BP with rise in SBP, DBP, MAP was seen to be 9%, 1% and 5% respectively while the rise in HR was 48% at extubation with a peak rise being 52%. Coughing, bucking, breath holding, increased secretions and bronchospasm were found to be comparable in all the four groups. No adverse cardiovascular events like severe bradycardia, hypotension or arrhythmia were seen in any of the patients.

To conclude, esmolol in a bolus dose of 1 mg/Kg given 1 min after reversal and 2 min prior to extubation s an effective method of controlling the hemodynamic extubation response as it controlled cardiovascular parameters like HR, SBP, DBP and MAP effectively without producing significant hypotension or bradycardia. However it may be used with caution in patients with left ventricular dysfunction or patients on chronic beta blockers where NTG or diltiazem may be preferred.

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