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Comparison of Esmolol and Diltiazem in Attenuating the Hemodynamic Response at Extubation.

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Abstract

Background and Aims: Emergence from anesthesia and tracheal extubation can be associated with hemodynamic circulatory responses characterized by tachycardia and hypertension. This sympatho-adrenal response results in increased cardiac workload and myocardial contractility leading to increased myocardial oxygen demand and may prove detrimental for patients with coronary artery disease.

Methods: We conducted a randomized double-blind study to examine the effects of single bolus dose of esmolol (1 mg/kg) and diltiazem (0.15 mg/kg) on hemodynamic changes during extubation in 60 ASA grade I and II patients undergoing major surgery under general anesthesia. Anesthesia was induced with propofol 2 mg/kg and fentanyl 2 µg/kg and tracheal intubation was facilitated with vecuronium 0.1 mg/kg i.v. Anesthesia was maintained with 0.6% - 1% isoflurane and 60% N2O in O_2. The patients were randomly assigned to one of the two groups (n=30 for each group). Group E received esmolol 1 mg/kg IV and Group D received diltiazem 0.15 mg/kg IV. These medications were given 1 min after reversal and extubation performed 2 min later. Changes in HR, MAP and RPP was measured during and after tracheal extubation. Incidence of adverse events was also noted.

Results: Esmolol 1 mg/kg IV bolus effectively controlled HR, MAP and RPP during extubation. Diltiazem 0.15 mg/kg IV bolus effectively controlled MAP but was not effective in controlling HR or RPP. No significant bradycardia, hypotension, arrhythmia occurred in any of the patients. Airway events like coughing, bucking, laryngospasm, excessive secretions were comparable in both the groups.

Conclusion: Esmolol 1mg/kg was more effective in controlling the hemodynamic response to extubation than Diltiazem 0.15 mg/kg in patients undergoing surgery under general anesthesia with tracheal intubation.

Keywords: Esmolol, Diltiazem, Anesthesia, Extubation, Hemodynamic response, Intubation.

Introduction

Securing airway during general anesthesia is most commonly done by endotracheal intubation, followed by extubation at the end of the procedure. Both intubation and extubation are associated with stress responses due to sympathetic stimulation. The major concerns during the recovery period are due to post extubation oxygenation failure and cardiovascular responses in high risk patients. There is increased oxygen consumption [1] and increased catecholamine release during the recovery period [2,3] causing hemodynamic responses like tachycardia and hypertension [4]. Such response may adversely affect the balance between myocardial oxygen supply and demand causing myocardial ischemia & increase morbidity in high risk patients, especially those with cardiovascular disease [5,6]. Suppression of this postoperative sympathetic response by any technique may be beneficial. Various clinical studies have shown that the perioperative use of sympatholytic drugs [7] decreases sympathetic activity, tachycardia and hypertension during emergence from general anesthesia. Different pharmacological medications like lidocaine, esmolol, nitroglycerin, alfentanil, and fentanyl [8-12] have been used to control these hemodynamic responses to tracheal extubation [5].

The aim of this study was to evaluate the efficacy of esmolol and diltiazem in attenuating the cardiovascular responses to tracheal extubation.

Material & Methods

This prospective double-blind randomized study was conducted in the Department of Anesthesiology and Critical care, VIMSAR, Burla, Odisha after approval from the Institutional Ethics Committee. After obtaining informed consent, 60 adult patients of either gender between the age of 18 to 65 belonging to ASA grade I & II and undergoing surgeries under general anesthesia with endotracheal intubation were included in the study. Patients with coexisting systemic illness, patients on any chronic medication, patients with difficult airway Patients undergoing craniotomy or thoracotomy procedures were excluded from study. The patients were randomly allocated into two groups of 30 patients each using closed envelope method.

Group E - received Esmolol injection 1 mg/kg i.v. as single bolus

Group D - received Diltiazem injection 0.15mg/kg i.v. as single bolus

Thorough pre-anesthetic check-up was done. All patients were pre-medicated with tablet Alprazolam 0.25mg orally on the night before surgery. On arrival to the operation theatre, monitors were attached to the patient and baseline recordings of heart rate, blood pressure, oxygen saturation and ECG were noted. Patients were premedicated with inj. Midazolam and injection fentanyl 2µg/kg iv. General anesthesia was induced with injection Propofol 2mg /kg iv and tracheal intubation was facilitated with injection vecuronium 0.1mg/kg i.v. It was maintained with 0.6%-1.2% isoflurane and 60% N2O in oxygen. The BP was recorded immediately before the induction of anesthesia and every five minutes during anesthesia using automated noninvasive BP monitor. The BP and HR were maintained between 80% and 120% of the pre-operative baseline values by altering the concentration of isoflurane and giving additional doses of fentanyl until completion of surgery. Muscle relaxation was maintained by intermittent bolus doses of vecuronium 0.02mg/kg i.v. At the end of surgery isoflurane was discontinued and muscle relaxation was reversed with inj. Neostigmine 0.05mg/kg iv and injection glycopyrrolate 0.01mg/kg i.v.

After 1 minute of the reversal administration, the study medications i.e. esmolol or diltiazem were given according to the schedule decided. A thorough oro-pharyngeal suction was done before extubation. Then

patient was extubated 2 mins after the study medications once following criteria are met.

1. Return of spontaneous respiration with adequate tidal volume.
2. Obeying verbal commands (eye opening)
3. Sustained hand grip, head lift and leg lift for 5 secs.
4. End tidal concentration of isoflurane less than 0.1%

Immediately after tracheal extubation patient was given 100% oxygen by a facemask for 5 minutes.

Heart rate, MAP and Rate pressure product (RPP) were noted down at the time of giving reversal, 1 min after injecting study medication, at extubation, 1 minute, 2 minute, 5 minutes, 10 minutes, 30 minutes after extubation and denoted by T_0, T_1, T_2, T_3, T_4, T_5, T_6, and T_7, respectively.

Occurrence of events such as coughing, bucking, breath holding, excessive secretions, bronchospasm or laryngospasm, post-operative nausea and vomiting, any other untoward events were observed.

Based on previous studies [13], and assuming α-0.05 with power of the study 80%, 6 patients in each group were required to show a 20 % difference in RPP between the two groups at the time of extubation. Considering dropouts and for better weightage of results, 30 patients were enrolled in each group. Sample size was calculated using http://hedwig.mgh.harvard.edu/sample_size/size.html.

Results

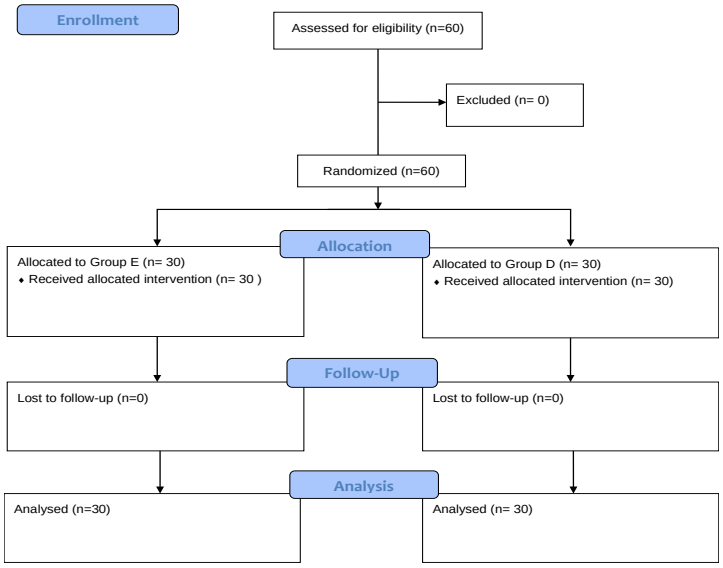


Fig 1. Consort Diagram

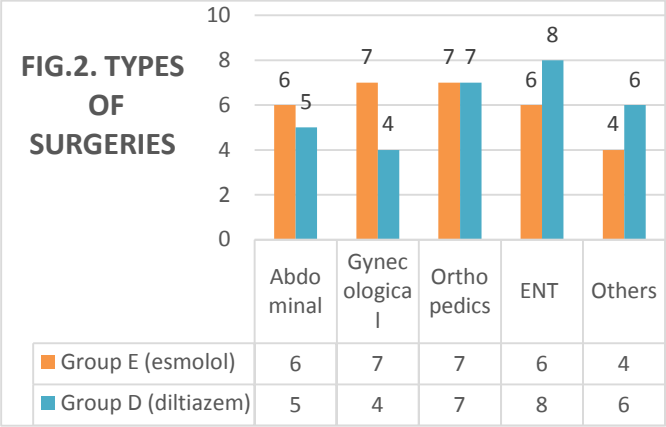
Table 1. shows the comparison of demographic characteristics and ASA grades of all patients in both groups. Both groups were similar statistically with no significant difference. Table 2 and Fig.2 show the distribution of different types of surgeries in both groups. There was no statistical difference between both groups.

Table 1. Demographic Profile

Group	Age in years (SD)	Sex (M/F)	Weight in kg (SD)	Height in m (SD)	BMI (SD)	ASA Grade (I/II)
E	37.13 (11.99)	14/16	61.5 (11.45)	1.64 (0.09)	22.92 (5.28)	23/7
D	40.20 (11.47)	16/14	66.7 (10.23)	1.69 (0.10)	23.38 (3.92)	23/7
P value	0.75	0.6	0.26	0.52	0.15	1.0

Table 2. Type of surgery

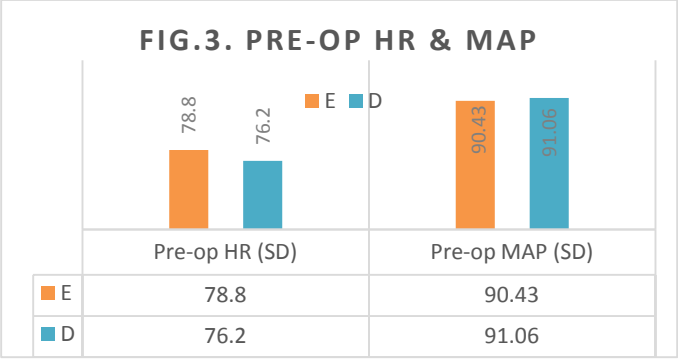
Type of surgery	Group E (esmolol)	Group D (diltiazem)	P value
Abdominal	6	5	0.810
Gynecological	7	4	
Orthopedics	7	7	
ENT	6	8	
Others	4	6	



The preoperative heart rate, MAP and RPP were also similar in both groups as shown in Table 3 and Fig.3 & 4., with no statistically significant difference between the two groups.

Table 3. Pre-operative parameters

Group	Pre-op HR (SD)	Pre-op MAP (SD)	Pre-op RPP (SD)
E	78.8 (10.13)	90.43 (5.80)	9369.06 (1635.96
D	76.2 (11.24)	91.06 (7.36)	8887.03 (2165.01)
P value	0.35	0.71	0.335



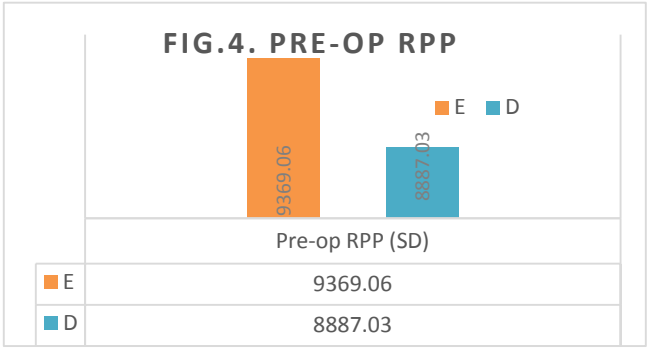
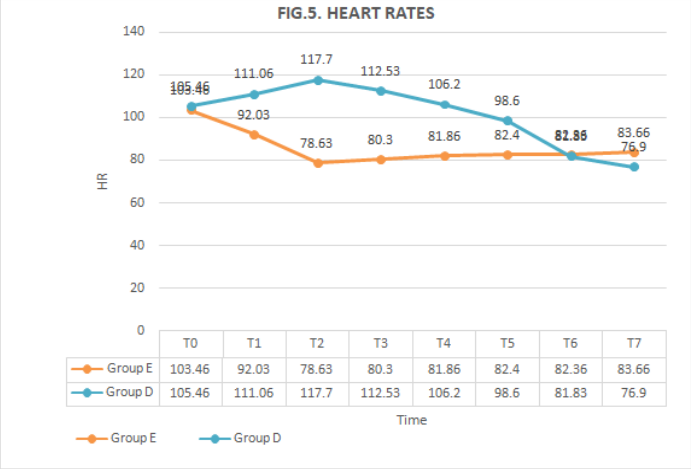


Table 4 shows the heart rates at various times in both groups. There was no statistically significant difference in the heart rates between both groups at the time of administration of reversal (T_0). In group E, the heart rates were significantly lower at all times when compared to that at reversal administration. In group D, the heart rates were significantly higher than that at the time of reversal administration at 1 minute after injection of study drug, at extubation and at 1 minute after extubation. There was no significant difference in heart rates in group D at 2 minutes after extubation, when compared with that at administration of reversal. The heart rates at 5 minutes, 10 minutes and 30 minutes after extubation in group D were significantly lower than that at the time of reversal administration. When both groups were compared with each other, the heart rate was significantly lower at all times in group E than group D till 5 minutes after extubation. There was no statistically significant difference at 10 minutes after extubation in both groups. At 30 minutes after extubation, heart rate was significantly lower in group D than in group E.

Table 4. Comparison of Heart Rates

Time	Mean Heart Rate (SD)				p Value E-D
	Group E	P Value intragroup	Group D	P Value intragroup	
T0	103.46 (5.81)	-	105.46 (6.08)	-	0.19
T1	92.03 (5.62)	<0.001	111.06 (6.64)	<0.001	<0.001
T2	78.63 (4.16)	<0.001	117.7 (5.40)	<0.001	<0.001

T3	80.3 (4.39)	<0.001	112.53 (5.34)	<0.001	<0.001
T4	81.86 (4.05)	<0.001	106.2 (5.13)	0.086	<0.001
T5	82.4 (3.40)	<0.001	98.6 (4.86)	<0.001	<0.001
T6	82.36 (3.21)	<0.001	81.83 (5.42)	<0.001	0.64
T7	83.66 (4.11)	<0.001	76.9 (4.95)	<0.001	<0.001



The comparison of MAP of both groups has been shown in Table 5. The MAP in both group E and group D was significantly lesser than at the time of reversal administration at all times, with all p values being <0.001. The difference MAP in group E and group D at the time of reversal administration and one minute after reversal administration was not significant. At all other times, the MAP in group E was significantly lower than group D.

Table 5. Comparison of MAP

Time	MAP (SD)				p Value E-D
	Group E	p Value intergroup	Group D	p Value intergroup	
T0	110.16 (3.54)		110.2 (5.05)		0.97
T1	102.06 (3.32)	<0.001	103.63 (4.54)	<0.001	0.13
T2	92.63 (2.68)	<0.001	94.93 (4.36)	<0.001	0.017
T3	94.86 (2.27)	<0.001	97.60 (3.95)	<0.001	0.002
T4	96.36 (3.02)	<0.001	99.83 (3.91)	<0.001	<0.001
T5	97.93 (2.87)	<0.001	101.03 (3.71)	<0.001	0.001
T6	94.66 (2.79)	<0.001	92.10 (3.93)	<0.001	0.005
T7	90.93 (4.05)	<0.001	88.10 (3.63)	<0.001	0.006

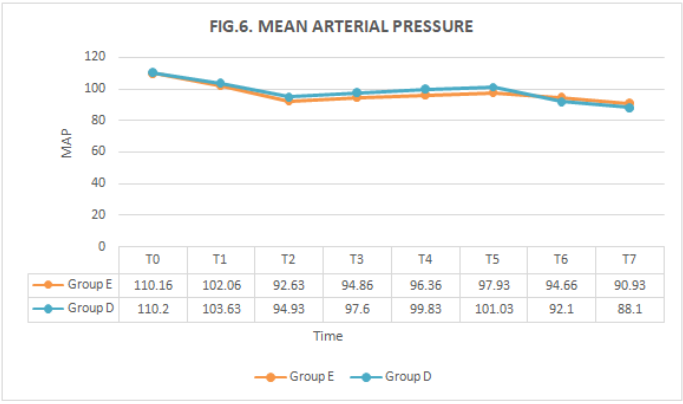


Table 6 compares the RPP between the two groups at different times. The RPP for group E at the time of reversal administration was 15883.9±1312.52 while that for group D was 15992.2±1182.66 and the difference between the two was not statistically significant. The RPP of both groups was significantly lesser than at the time of reversal administration at all times. The RPP for group E at the time of extubation was 9918.36±654.37 and that for group D was 15564.9±1238.58. The difference between the two groups was highly significant with a p value of <0.001. The RPP in group E was significantly lower than group D at all times.

Table 6. Comparison of RPP

Time	RPP (SD)				p Value E-D
	Group E	p Value	Group D	p Value	
T0	15883.9 (1312.52)		15992.2 (1182.66)		0.73
T1	12917.03 (1067.93)	<0.001	15457.7 (2068.15)	0.15	<0.001
T2	9918.36 (654.37)	<0.001	15564.9 (1238.58)	0.035	<0.001
T3	10051.6 (1723.01)	<0.001	15130.73 (1080.67)	<0.001	<0.001
T4	10707.53 (651.47)	<0.001	14420.86 (953.28)	<0.001	<0.001

T5	10865.06 (509.35)	<0.001	13391.66 (929.29)	<0.001	<0.001
T6	10662.43 (406.98)	<0.001	9841.43 (1100.37)	<0.001	<0.001
T7	10361.03 (758.74)	<0.001	8681.70 (820.00)	<0.001	<0.001

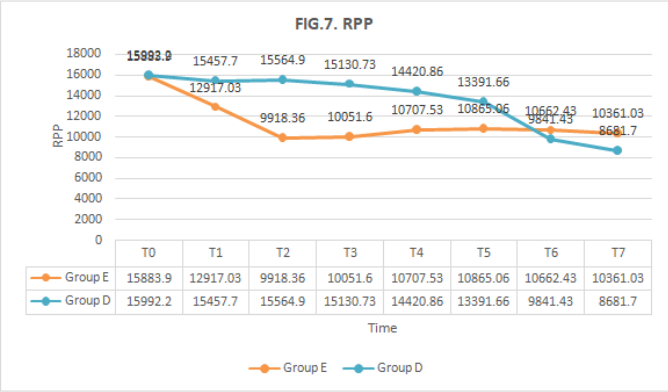
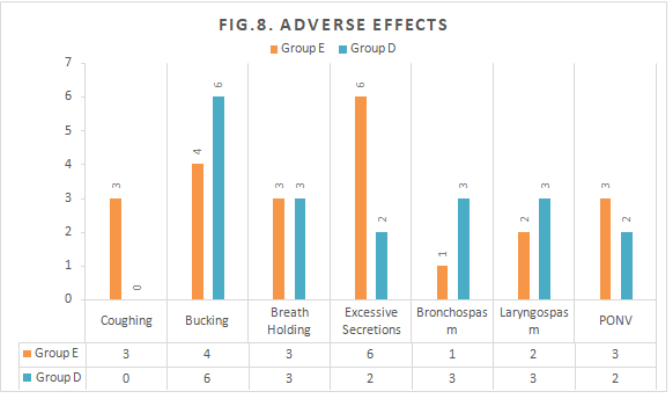


Table 7 shows the incidence of adverse effects in both groups. There was no statistically significant difference in the incidence of adverse effects between both groups.

Table 7. Incidence of Adverse Events

Adverse event	Incidence		p value
	Group E (%)	Group D (%)	
Coughing	3 (10%)	0 (0%)	0.08
Bucking	4 (13.3%)	6 (20%)	0.49
Breath Holding	3 (10%)	3 (10%)	1
Excessive Secretions	6 (20%)	2 (6.6%)	0.12
Bronchospasm	1 (3.3%)	3 (10%)	0.3
Laryngospasm	2 (6.6%)	3 (10%)	0.64
PONV	3 (10%)	2 (6.6%)	0.64



DISCUSSION

The 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 [14]. They cause increase in myocardial oxygen demand in patients with cardiovascular disease or those at risk of coronary artery disease [15]. Many factors are responsible for these hemodynamic changes at extubation. Extubation is often performed with patients in lighter place of anesthesia and is associated with mechanical irritation to the airway, causing coughing, bucking and straining [1,8,16,17]. Other factors involved are pain from surgery and emergence from general anesthesia [18]. It has been demonstrated that tracheal extubation causes an increase in plasma catecholamine levels, which in turn cause tachycardia, increased myocardial contractility and increased systemic vascular resistance [10,19]. Extubation increases both heart rate and systolic BP by 20% in more than 70% of patients [5].

Obtunding this 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 can be conveniently used. In contrast, at extubation, techniques used to attenuate the hemodynamic responses must also ensure that criteria for safe extubation are not interfered with i.e. spontaneous eye opening, sustained head lift and adequate protective reflexes.

We compared two drugs belonging to different groups i.e. esmolol (β blocker) and diltiazem (calcium channel blocker) to assess their role for attenuating the cardiovascular response at extubation in 60 ASA grade I and II patients.

In our study we found that esmolol was more effective in controlling the heart rate during extubation than diltiazem. The difference was maximum at the time of extubation. 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. We found an increase in heart rate in the diltiazem group after administration of the drug and at the time of extubation. This may be due to reflex sympathetic stimulation because of sudden hypotension. This was similar to the findings of Agarwal [20], Kumar [21], Sarkar [22] and Gupta [13]. In our study, we found mean arterial pressures to be similar in both groups at all times. The difference, even though being statistically significant, was not significant clinically, and between acceptable limits.

Rate pressure product is calculated by multiplying heart rate with systolic blood pressure and is a good estimate of myocardial oxygen requirement. The rate pressure product (RPP) levels close to 20,000 are normally associated with angina and myocardial ischemia [23]. In the present study, the rate pressure product (RPP) following extubation was not more than 20,000 in any study group, suggesting that critical increases in rate pressure product (RPP) can be avoided by using esmolol or diltiazem prior to extubation. These findings confirmed their cardio-protective effect. The RPP in the esmolol group was lower at all times than diltiazem. This corresponds to the findings of Parvez [24], Mohan [25] and Gupta [13]. In our study, no significant bradycardia or hypotension was observed throughout the time period of study and even at 30 min post extubation.

Airway events like coughing, bucking, breath holding, increased secretions and bronchospasm were found to be comparable in both the groups. The limitations of our study were that we have used non-invasive blood pressure for monitoring. Invasive blood pressure measurement would have given us a beat to beat variation and better results. We also have based the administration of reversal drugs and study drugs on clinical criteria rather than neuromuscular and depth of anesthesia monitoring. Using those modalities would have provided us with better guides for drug administration.

Conclusion

Esmolol 1 mg/kg iv given 1 min after reversal is a more effective method for controlling the hemodynamic response to extubation than Diltiazem 0.15 mg/kg iv.

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