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Original Article

Attenuation of Hemodynamic Responses to Endotracheal Extubation with Different Doses of Diltiazem with Lignocaine: A Placebo-Controlled Study

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Abstract

Introduction: Endotracheal extubation causes transient hemodynamic stimulation leading to increase in blood pressure and heart rate (HR) due to increase in sympathoadrenergic activity caused by epipharyngeal and laryngopharyngeal stimulation. Lignocaine, a sodium channel blocker, attenuates the hemodynamic response to tracheal extubation by inhibiting sodium channels in the neuronal cell membrane, decreasing the sensitivity of the heart muscles to electric impulses. Diltiazem, a calcium channel blocker, attenuates hemodynamic response by blocking voltage-sensitive L type channels and inhibiting calcium entry-mediated action potential in smooth and cardiac muscle. **Aims and Objectives:** The aims and objectives of this are to study and to compare the efficacy of combination of intravenous (i.v.) diltiazem 0.1 mg/kg and i.v. lidocaine 1.0 mg/kg, diltiazem 0.2 mg/kg and lidocaine 1.0 mg/kg, lignocaine 1.0 mg/kg with normal saline given to attenuate exaggerated hemodynamic extubation responses and airway reflexes during extubation. **Materials and Methods:** This study was undertaken with 105 patients belonging to the age group 20–65 years with physical status ASA Classes I and II of either sex. Group A received injection diltiazem 0.1 mg/kg and preservative-free lignocaine 1 mg/kg. Group B received injection diltiazem 0.2 mg/kg and lignocaine 1 mg/kg. Group C received injection lignocaine 1 mg/kg with normal saline. In this study group, the drug dosage was fixed based on the previous studies. **Results:** At postextubation, significant difference in HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) were observed from 1 to 10 min between three groups. The difference in HR, SBP, DBP, and MAP were statistically significant between Group C in comparison with Group A and Group B from 1 min postextubation to 10 min. **Conclusion:** Combined diltiazem and lidocaine are more effective prophylaxis than lidocaine alone for attenuating the cardiovascular responses to tracheal extubation.

Keywords: Airway extubation, diltiazem, hemodynamics, lignocaine

Introduction

Problems associated with extubation, recovery, and emergence are equally common as the problems at intubation.[1] Endotracheal extubation causes transient hemodynamic stimulation leading to increase in blood pressure and heart rate (HR) due to increase in sympathoadrenergic activity caused by epipharyngeal and laryngopharyngeal stimulation.

Most patients tolerate hypertension and tachycardia without any significant consequences, but some show an exaggerated response which is poorly tolerated and may lead to myocardial ischemia, cardiac decompensation, pulmonary edema, and cerebral hemorrhage.[2] Respiratory complications are cough, sore throat, laryngospasm, and bronchospasm which leads to hypoxemia. Laryngospasm is the most common cause for postextubation upper airway obstruction.

Extubation under deep anesthesia decreases cardiovascular stimulation and reduces the incidence of coughing and straining on the tube. However, the incidence of respiratory complications is found to be greater after extubation under deep anesthesia, irrespective of the type of surgery.[3]

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Bucking occurring during extubation can mimic Valsalva maneuver physiologically. It can cause negative pressure pulmonary edema if lung volumes are less than vital capacity. It can also cause abrupt increase in intracavitary pressures (intraocular, intrathoracic, intra-abdominal, and intracranial) which could put patient at high risk.[4,5]

Various attempts have been made to attenuate the pressor response by the use of drugs such as deep anesthesia induced by inhalational anesthetics, sympathetic blockers (beta-blockers), α_2 agonists, calcium channel blockers (verapamil, diltiazem, nicardipine), intratracheal local anaesthetic instillation, intracuff lidocaine, intravenous (i.v.) lignocaine, short-acting opioids such as fentanyl, alfentanyl remifentanil, and prostaglandin-E1. Lidocaine, a sodium channel blocker, attenuates the hemodynamic response to tracheal extubation by inhibiting sodium channels in the neuronal cell membrane, decreasing the sensitivity of the heart muscles to electric impulses. It is also a direct cardiac depressant and peripheral vasodilator. It also suppresses airway reflexes. It has analgesic as well as anti-arrhythmic properties.

Diltiazem, a calcium channel blocker, attenuates hemodynamic response by blocking voltage-sensitive L type channels and inhibiting calcium entry-mediated action potential in smooth and cardiac muscle. It also has peripheral vasodilatation property. As studies with 0.1 mg/kg, diltiazem and lidocaine 1 mg/kg were found to be less in our literature search; we planned this study.[6,7]

Aims and objectives

The aims and objectives of this study are to study and to compare the efficacy of the combination of i.v. diltiazem 0.1 mg/kg and i.v. lidocaine 1.0 mg/kg, diltiazem 0.2 mg/kg and lidocaine 1.0 mg/kg, and lignocaine 1.0 mg/kg with normal saline given 2 min before extubation on exaggerated hemodynamic responses regarding,

a. Changes in vital parameters such as HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure
b. Airway reflexes-cough, laryngospasm, and bronchospasm
c. Complications such as hypotension, bradycardia associated with the drug.

Materials and Methods

Source of data

A total of 105 patients admitted for elective surgeries posted under general anesthesia at during February 2015 to August 2016.

Method of collection of data

Inclusion criteria

All elective patients belonging to the age group 20–65 years with patients' physical status ASA Classes I and II undergoing operative procedure under general anesthesia were included in this study.

Exclusion criteria

Patients refusal, patients suffering from cardiac (ischemic heart disease, arrhythmias, angina, previous myocardial infarction, and hypertension), and pulmonary diseases, any contraindication to study drugs lidocaine and diltiazem administration, pregnant, and lactating women, patients posted for emergency surgeries, and patients with psychiatric and neurovascular disorders were excluded from the study.

Sampling procedure

This was a double-blinded randomized control, prospective study.

After obtaining informed written consent, patients randomly divided into three groups of 35 each. Randomization was done by computer-generated table.

Group A: Received injection diltiazem 0.1 mg/kg and preservative free lidocaine mg/kg
Group B: Received injection diltiazem 0.2 mg/kg and lidocaine 1 mg/kg
Group C: Received injection lidocaine 1 mg/kg with normal saline.

Ethical committee approval was taken for the study. An informed consent was taken from the patients. The following investigations were done preoperatively: complete hemogram, bleeding time, clotting time, random blood sugar, blood urea and serum creatinine, serum electrolytes, urine analysis for sugar, albumin, and microscopy, electrocardiogram, and chest X-ray.

All patients were examined a day before surgery and a detailed history of the patient was taken. A thorough clinical examination was conducted and necessary investigations sent and reviewed before surgery. Lignocaine (0.1 ml subcutaneous) test dose was given to all patients to test for allergic reaction. Airway assessment was done using Mallampati score. Patient kept nil per oral after 10.00 pm and patient's received tablet ranitidine 150 mg orally and tablet alprazolam 0.25 mg orally as premedication at night before surgery and at 6.00 am on the day of surgery with sips of H_2O.

In operation theater, patients were connected to monitors – electrocardiography, pulse oximetry and noninvasive blood pressure. An i.v. line was secured and patients were given i.v. Ringer Lactate. Patient premedicated with injection glycopyrrolate 0.2 mg i.v. + injection fentanyl 2 μg/kg. Preoxygenation with bag and mask for 3 min was done. Induction with injection thiopentone 5 mg/kg, muscle relaxant injection suxamethonium 2 mg/kg for muscle relaxation before intubation and intubation was done.

General anesthesia maintained with 60% N_2O, 40% O_2, and isoflurane (0.8–1 MAC) followed by vecuronium bromide, a neuromuscular blocking agent 0.1 mg/kg as loading dose, and 0.02 mg/kg as maintenance dose. After surgery, isoflurane and nitrous oxide was discontinued. Baseline values of HR, SBP, DBP, and mean arterial pressure (MAP) were noted. Reversal injection neostigmine 0.05 mg/kg + injection glycopyrrolate

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0.01 mg/kg i.v. were given. Appropriate study drug given over 1, 2 min before extubation.

Values of HR, SBP, DBP, and MAP noted immediately after extubation at 1, 2, 3, 5, and 10 min after tracheal extubation.

Statistical analysis

The sample size calculated by the previous literature based on the mean reduction in HR and MAP with diltiazem + lidocaine from immediate and after 10 min the estimated sample size for mean difference in HR is 20 and for MAP is 13 since we are comparing the effect of drug diltiazem + lidocaine with two different dosages of diltiazem. The sample size is taken as 35 per group (total = 105)

Sample Size

$$n = \frac{2\sigma^2(2_{\alpha/2} + 2\beta)^2}{d^2}$$

2α = 95% confidence level = 1.96

2β = power at 80% =0.842

d = mean difference (values at baseline-values at 10 min)

Statistical evaluation of data or parameters will be done using-mean, average, standard deviation, and ANOVA for comparison of results.

Data were entered into Microsoft excel data sheet and were analyzed using SPSS 22 Statistics Desktop-IBM. USA.

- Categorical data were represented in the form of frequencies and proportions
- Chi-square analysis of variance was the test of significance to identify the mean difference between more than two groups.

$P < 0.05$ was considered as statistically significant in the above tests.

Results

In our study, mean age was slightly higher in Group A, followed by Group C, and lowest mean age was seen in Group B. There was no significant difference in mean age between three groups as shown in Table 1.

In our study, mean weight of individuals in Group A was 63.4 ± 8.7 kg, Group B was 61.1 ± 10.3 kg, and in Group C was 63.3 ± 7 kg. There was no significant difference in mean weight between three groups as shown in Table 2.

Mean HR in three groups is shown in Table 3. At prereversal, no difference in HR was observed between three groups Whereas postextubation significant difference in HR was observed from 1 to 10 min between three groups. *Post hoc* Bonferroni analysis showed that the difference in mean HR was statistically significant between Group C in comparison with Group A and Group B from 1 min postextubation to 10 min. There was no significant difference in HR between Group A and Group B at all the intervals.

Table 1: Age distribution of individuals between three groups

	Group (mean±SD)			*P*
	Group A	Group B	Group C	
Age	36.3±9.0	31.5±12.3	33.8±11.0	0.185

SD=Standard deviation

Table 2: Weight distribution of individuals between three groups

	Group (mean±SD)			*P*
	Group A	Group B	Group C	
Weight	63.4±8.7	61.1±10.3	63.3±7.0	0.466

SD=Standard deviation

Table 3: Heart rate comparison between three groups at various intervals

	Group (mean±SD)			*P*
	Group A	Group B	Group C	
Prereversal	109.9±8.0	110.3±10.6	109.1±11.0	0.866
Postextubation				
1 min	99.3±8.4	100.9±10.9	106.2±11.9	0.019*
2 min	91.9±8.1	94.2±8.9	103.7±12.2	<0.001*
3 min	85.3±7.0	87.4±6.6	101.1±11.8	<0.001*
5 min	78.3±5.7	81.5±6.0	99.4±11.8	<0.001*
10 min	71.9±5.3	74.6±5.5	97.7±12.0	<0.001*

*Significant. SD=Standard deviation

Mean SBP in three groups is shown in Table 4. At prereversal, significant difference in SBP was observed between three groups. During postextubation, significant difference in SBP was observed from 2 to 10 min between three groups. *Post hoc* Bonferroni analysis showed that the difference in mean SBP was statistically significant between Group C in comparison with Group A and Group B from 2 min postextubation to 10 min. There was no significant difference in SBP between Group A and Group B at all the intervals.

Mean DBP in three groups is shown in Table 5. At prereversal, no significant difference in DBP was observed between three groups. During postextubation, significant difference in DBP was observed from 1 to 10 min between three groups. *Post hoc* Bonferroni analysis showed that the difference in mean SBP was statistically significant between Group C in comparison with Group A and Group B from 1 min postextubation to 10 min. There was also significant difference in DBP between Group A and Group B at 2 and 3 min intervals.

Mean MAP in three groups is shown in Table 6. At prereversal no significant difference in MAP was observed b/w three groups. During postextubation significant difference in MAP was observed from 1 to 10 min between three groups. *Post hoc* Bonferroni analysis showed that the difference in mean SBP was statistically significant between Group C in comparison with Group A and Group B from 1 min postextubation to

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Table 4: Systolic blood pressure comparison between three groups at various intervals

	Group (mean±SD)			*P*
	Group A	Group B	Group C	
Prereversal	160.5±12.3	155.8±9.6	153.2±9.6	0.016*
Postextubation				
1 min	151.1±12.3	147.1±9.6	151.5±10.0	0.167
2 min	142.5±11.0	140.1±9.2	149.7±10.5	<0.001*
3 min	135.5±10.8	133.7±8.7	147.9±10.3	<0.001*
5 min	127.4±9.4	127.5±8.4	146.2±10.1	<0.001*
10 min	119.0±8.6	118.4±7.4	144.6±10.1	<0.001*

*Significant. SD=Standard deviation

Table 5: Diastolic blood pressure comparison between three groups at various intervals

	Group (mean±SD)			*P*
	Group A	Group B	Group C	
Prereversal	102.1±6.4	104.2±7.4	103.9±7.1	0.379
Postextubation				
1 min	93.1±5.3	96.5±5.1	101.7±7.2	<0.001*
2 min	86.9±5.2	90.7±4.2	100.2±7.3	<0.001*
3 min	81.0±6.3	84.7±5.2	98.8±7.1	<0.001*
5 min	75.3±6.4	78.7±6.1	97.2±7.3	<0.001*
10 min	69.4±6.4	72.2±6.5	95.5±7.5	<0.001*

*Significant. SD=Standard deviation

Table 6: Mean arterial pressure comparison between three groups at various intervals

	Group (mean±SD)						*P*
	Group A		Group B		Group C		
Prereversal	121.5	6.7	121.4	7.1	120.3	7.3	0.731
Postextubation							
1 min	112.5	6.2	113.1	5.5	118.1	7.4	0.001*
2 min	105.3	6.1	107.0	4.8	116.6	7.6	<0.001*
3 min	99.1	6.6	101.0	5.5	115.1	7.5	<0.001*
5 min	92.5	6.4	94.7	6.1	113.5	7.7	<0.001*
10 min	85.7	6.1	87.4	6.0	111.9	7.9	<0.001*

*Significant. SD=Standard deviation

Table 7: SpO_2 comparison between three groups at various intervals

	Group (mean±SD)			*P*
	Group A	Group B	Group C	
Prereversal	100.0±0.0	100.0±0.0	100.0±0.0	-
Postextubation				
1 min	100.0±0.0	100.0±0.0	100.0±0.0	-
2 min	100.0±0.0	100.0±0.0	100.0±0.0	-
3 min	100.0±0.0	100.0±0.0	100.0±0.0	-
5 min	100.0±0.0	100.0±0.0	100.0±0.0	-
10 min	100.0±0.0	100.0±0.0	100.0±0.0	-

SD=Standard deviation

10 min. There was no significant difference in MAP between Group A and Group B at all intervals.

No difference in SPO_2 was observed between three groups at all the intervals as shown in Table 7.

Discussion

Significant increase in HR, SBP, DBP, MAP, cardiac index, and systemic vascular resistance is observed in response to tracheal extubation, which persist into the recovery period.[6] Extubation irritates airways, causing cough or strain which in turn increases both BP, HR.[7]

Various attempts have been made to attenuate the pressor response by the use of drugs such as deep anesthesia induced by inhalational anesthetics, sympathetic blockers (beta-blockers), α_2 agonists, calcium channel blockers (verapamil, diltiazem, and nicardipine), intratracheal local anesthetic instillation, intracuff lidocaine, i.v. lignocaine, short-acting opioids, such as fentanyl, alfentanil remifentanil, and prostaglandin-E1.

Lidocaine, a sodium channel blocker, attenuates the hemodynamic response to tracheal extubation by inhibiting sodium channels in the neuronal cell membrane, decreasing the sensitivity of the heart muscles to electric impulses. It is also a direct cardiac depressant and peripheral vasodilator. It also supresses airway reflexes. It has analgesic as well as anti-arrhythmic properties.

Diltiazem, a calcium channel blocker, attenuates hemodynamic response by blocking voltage-sensitive L type channels and inhibiting calcium entry-mediated action potential in smooth and cardiac muscle. It also has peripheral vasodilation property. The onset and duration of action of diltiazem are rapid and short. The MAP begins to decrease 20–40 s after administration of diltiazem i.v. with a peak effect at 1.5–2 s.[8]

Tracheal extubation increases 20% or more in both HR and SBP in 70% of the patients. The exact mechanism of these cardiovascular responses is unknown, but it is believed to be associated with the release of catecholamines which causes increase in HR, myocardial contractility, and systemic vascular resistance, beginning at 1 min and continuing until 10 min after extubation due to significant increase in the plasma concentration of adrenaline, but not noradrenaline, after tracheal extubation.[9]

Combined diltiazem and lignocaine attenuate exaggerated hemodynamic responses to tolerable levels than each drug administered alone because these two drugs attenuate tachycardia and hypertension by different mechanisms.

Lignocaine minimizes the incidence and severity of cough, breath holding, bronchospasm following extubation.[10]

Diltiazem is benzodiazepine derivative of slow calcium channel blocker, blockade of slow calcium channels by calcium channel blockers results in slowing of HR, reduction in myocardial contractility, decreased speed of conduction

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of cardiac impulses through the atrioventricular node, and vascular smooth muscle relaxation.[11]

Lignocaine selectively binds to H subunit of sodium channels in the inactivated-closed state and stabilize these channels in this configuration and prevent there change to rested-closed or activated-open state in response to nerve stimulation. It decreases myocardial automaticity.

In our study, mean weight and age of individuals showed no statistically difference among the groups. In our study, at prereversal, no difference in HR, SBP, DBP, and MAP was observed between three groups. Whereas postextubation significant difference in HR, SBP, DBP, and MAP heart were observed from 1 to 10 min between three groups. The difference in HR, SBP, DBP, and MAP were statistically significant between Group C in comparison with Group A and Group B from 1 min postextubation to 10 min. There was no significant difference in HR, SBP, DBP, and MAP between Group A and Group B at all the intervals. The rise in HR was more persistant than other two groups in recovery period.

At prereversal, $P = 0.866$, no difference in HR was observed between three groups whereas postextubation significant difference in HR was observed from 1 to 10 min $P < 0.001$ between three groups showed that the difference in mean HR was statistically significant between Group C in comparison with Group A and Group B from 1 min postextubation to 10 min. There was no significant difference in HR between Group A and Group B at all the intervals.

At prereversal, $P = 0.016$ significant difference in SBP was observed between three groups. During postextubation, significant difference in SBP was observed from 2 to 10 min $P < 0.001$ between three groups showed that the difference in mean SBP was statistically significant between Group C in comparison with Group A and Group B from 2 min postextubation to 10 min. There was no significant difference in SBP between Group A and Group B at all the intervals.

At prereversal $P = 0.379$, no significant difference in DBP was observed between three groups. During postextubation, significant difference in DBP was observed from 1 to 10 min $P < 0.001$ between three groups showed that the difference in mean SBP was statistically significant between Group C in comparison with Group A and Group B from 1 min postextubation to 10 min. There was also a significant difference in DBP between Group A and Group B at 2 and 3 min intervals.

At prereversal $P = 0.731$, no significant difference in MAP was observed between three groups. During postextubation, significant difference in MAP was observed from 1 to 10 min $P < 0.001$ between three groups which showed that the difference in mean SBP was statistically significant between Group C in comparison with Group A and Group B from 1 min postextubation to 10 min. There was no significant difference in MAP between Group A and Group B at all intervals.

These results are consistant with other studies. Thanvi *et al*. evaluated the impact of tracheal extubation on changes in 90 patients. In the control group, patients received saline; in the diltiazem group, patients received 0.2 mg/kg diltiazem i.v.; and in the lignocaine group, patients received 1.0 mg/kg lignocaine i.v. These drugs were given 2 min before tracheal extubation. Values of HR, SBP, DBP, and MAP were recorded at 1, 2, 3, 4, and 5 min after extubation. The pressor responses and tachycardia occurring in patients undergoing laparoscopic cholecystectomy during emergence from anesthesia and tracheal extubation can be blocked by a bolus dose of 1.0 mg/kg lidocaine i.v. or 0.2 mg/kg diltiazem i.v. and the use of diltiazem attenuated these responses more than that of lignocaine.[12]

Savitha *et al*. studied in 90 patients scheduled for elective surgical procedures and they were randomly divided into three groups of 30 each, Group 1 (control-saline), Group 2 (lignocaine 0.5 mg/kg), and Group 3 (lignocaine 1 mg/kg). They were administered study drug 2 min before extubation. Study concludes that lignocaine 1 mg/kg is superior to 0.5 mg/kg in attenuating the hemodynamic responses to tracheal extubation. For postextubation, cough suppression (100%) lignocaine 1 mg/kg was ideal.[13]

Jain and Khan studied the effect of perioperative i.v. infusion of lignocaine on hemodynamic responses to intubation, extubation, and postoperative analgesia and concluded that the administration of lignocaine infusion attenuates the rise in pulse rat and MAP during the peri-intubation and peri-extubation period. Infusion of lignocaine also significantly increased the mean pain-free period postoperatively.[14]

In our study, there was no difference in SPO_2 observed between three groups at all the intervals, and there were no complications such as hypotension, bradycardia, laryngospasm, bronchospasm, or breath holding.

Strength and recommendations of our study

Strength of our study is we have used a calcium channel blocker to attenuate extubation response which was not being done in most of the places, and it is not expensive and found to be safe with minimal hemodynamic effects. We can make this as a recommendation or protocol in all institutions.

Limitations of our study

We have not used depth of anesthesia monitoring; it could have contributed in timing of extubation.

Conclusion

The attenuation of exaggerated hemodynamic responses to extubation by diltiazem 0.1 mg/kg or diltiazem 0.2 mg/kg with lignocaine 1 mg/kg were similar and effective compared to placebo group with lignocaine 1 mg/kg alone. Combined diltiazem and lidocaine are more effective prophylaxis than lidocaine alone for attenuating the cardiovascular responses to tracheal extubation.

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Conflicts of interest

There are no conflicts of interest.

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