

# Clinical Efficacy Of Combination Of Diltiazem And Lidocaine In Attenuating Hemodynamic Changes During Tracheal Intubation And Comparing The Response When They Are Used Alone.

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## Abstract

**Background:** Tracheal intubation produces transient hemodynamic pressor responses which may be unpredictable. Diltiazem-lidocaine combination is hypothesized to attenuate these responses better than when they are used alone. **Aims:** To compare the clinical efficacy and safety of diltiazem-lidocaine combination in attenuating pressor response to tracheal intubation with lidocaine and diltiazem alone. **Settings and Design**

: prospective double blind, randomised clinical trial of efficacy and safety **Methods and Materials:** 120 ASA grade I&II patients were randomly divided into four groups (using a random sequence generator) of 30 each according to the drug given before intubation to attenuate the hemodynamic response to intubation: saline in control group, diltiazem in D group, lidocaine in L group and both diltiazem and lidocaine in DL group. The person A prepared the drugs, B injected the drug and C evaluated the response; B and C were thus unaware of the drug given. **Statistical analysis used**

: Demographic profiles were evaluated statistically using CHI square test. Changes in haemodynamic parameters were compared using paired t test within the group. Inter group comparison was done by one way analysis of variance (ANOVA).

**Results:** The attenuation of hemodynamic response occurred maximal in DL group followed by lidocaine and diltiazem group respectively ( P value < 0.001 till 5 minutes postintubation for BP and HR). Lidocaine controlled both heart rate and blood pressure better than Diltiazem as there was reflex tachycardia to some extent in D group due to reflex sympathoadrenal stimulation. Diltiazem-Lidocaine combination controlled both these parameters to optimal levels. **Conclusions**

: The primary outcome of the study is that Diltiazem-Lidocaine combination is safe and effective in attenuating pressor response to tracheal intubation . We recommend its routine use before intubation

## INTRODUCTION

The peri-intubation period is one of the moments of most stress during general anaesthesia. Laryngoscopy and tracheal intubation is invariably associated with certain haemodynamic and cardiovascular changes such as transient hypertension, tachycardia which may result in a wide variety of cardiac arrhythmias. These changes are usually transitory but variable and unpredictable<sup>1</sup>. Many methods have been devised to reduce the extent of such haemodynamic events during intubation. Some of them like deep level of anaesthesia, use of beta blockers and agents like phentolamine, sodium nitroprusside and nitroglycerine are effective but require continuous intraarterial monitoring.<sup>2,3,4</sup>

Lidocaine has been used for attenuation of cardiovascular responses to intubation since a long time.<sup>5</sup> It acts by inhibiting sodium channels in the neuronal cell membrane, decreasing the sensitivity of the heart muscles to the electrical impulses, has direct cardiac depression and peripheral vasodilatation properties. It also suppresses airway reflexes and its analgesic as well as anti-arrhythmic properties.<sup>6</sup>

Diltiazem also attenuates the cardiovascular response to intubation by blocking voltage sensitive L type channels and inhibiting calcium entry mediated action potential in smooth and cardiac muscle cells. It also controls hypertension by its peripheral vasodilating action.<sup>7</sup>

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Because the pharmacological mechanism of action is different for diltiazem and lidocaine, a combination of these two drugs is hypothesized to be more effective than each drug used alone for attenuation of cardiovascular response to intubation.<sup>7,8</sup>

### **METHODS**

This prospective double blind randomized study was conducted over a period extending from august 2009 to august 2011 after obtaining approval of institutional ethics committee. 120 patients, ASA physical status I /II , aged 18-65 years ,of either sex undergoing elective surgery under general anaesthesia were selected for this study. Informed consent was taken from all the patients. Patients with ASA grade more than II, history of hypertension, diabetes, cardiac disease and bronchial asthma, patients on Beta blockers and history of allergic reaction to drugs under study were excluded from the study.

Patients were divided randomly in to four groups of 30 each using a computer generated random sequence generator and the study drug was given as under:

Group C (control group): 20 ml normal saline in 2 syringes of 10 ml each was given 1 minute prior to laryngoscopy.

Group D (Diltiazem group): 0.2 mg/kg diltiazem diluted to 10 ml and 10 ml of normal saline was given 1 minute prior to laryngoscopy.

Group DL (Diltiazem- Lidocaine group): 0.2 mg/kg diltiazem made to a total volume of 10 ml and 1.5mg/kg lidocaine diluted to 10 ml was given 1 minute prior to laryngoscopy.

Group L (Lidocaine group): 1.5mg/kg lidocaine diluted to 10 ml and 10 ml of normal saline was given 1 minute prior to laryngoscopy.

Person A made the drugs. Person B injected the drugs and observed the response (SBP, DBP, HR and SPO<sub>2</sub>) and person C who was an experienced qualified anaesthesiologist, intubated the patient. Both B and C were kept unaware of the drug injected.

All the patients were premedicated with inj midazolam 1mg IV, 5 minutes before induction. Injection fentanyl 2 mcg/kg was given 2 minutes before induction. Anaesthesia was induced with injection propofol followed by injection atracurium. This was followed by injection of the study drug

1 minute before laryngoscopy. Patients were intubated using cuffed endotracheal tube ( size was standardised to be 7 for females and 8 for males) by an experienced anaesthesiologist so as to keep the intubation time less than 30 seconds. After tracheal intubation, anaesthesia was maintained with nitrous oxide, oxygen (50:50) and isoflurane upto 0.5 MAC. Ventilation of lungs was adjusted so as to maintain ETCO<sub>2</sub> between 35 and 45 mmHg.

Non invasive Monitoring included heart Rate (HR), systolic blood pressure(SBP), diastolic blood pressure(DBP), mean arterial pressure (MAP), and spO<sub>2</sub> (O<sub>2</sub> saturation) at baseline, postinduction , pre intubation, immediately after intubation and at 1minute, 2 minutes, 3 minutes, 5 minutes and 10 minutes after intubation. No surgical stimulus was given for 10 minutes post intubation. Data was collected and the results were subjected to statistical analysis before making conclusions and results. Demographic profile that included Age, Weight, Height and BMI were evaluated statistically using CHI square test. Within the group, changes in haemodynamic parameters with respect to baseline were compared using paired t test. Inter group comparison of haemodynamic parameters were done by one way analysis of variance (ANOVA).

### **RESULTS**

The mean age, weight, height and body mass index (BMI) and ASA status in all four groups were comparable (p value 0.141, 0.159, 0.462 ,0.065 and 0.96 respectively).

The baseline Systolic BP (table 1) and MAP (table 2) is comparable in all the four groups (p value 0.254 and 0.083 respectively). There was significant rise in both systolic BP and MAP in control group as compared to D, L & DL group (peak rise at 1minute post intubation).The respective P value was <0.001 in all the groups. However the percent attenuation of SBP was better in DL group at 0, 1 and 2 minutes as compared to D & L group (figure1 &2). The D and L groups were comparable at all the times. Both SBP and MAP returned to normal after 3 minutes postintubation.

The baseline HR was comparable in all the four groups (p value 0.076). There was significant rise in HR in C & D group as compared to baseline at 0 and I minutes( table 3),while there was significant attenuation of HR in both DL and L group as compared to baseline at 0 and 1 minute. Although there was no significant difference in attenuation of HR between DL & L group ( P value 0.08) and L group was better in terms of percent attenuation than DL group till

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2 minutes postintubation as can be seen in figure 3.

Similarly, there was significant rise in RPP ( rate pressure product) in control group as compared to D, L & DL group till five minutes postintubation with peak changes at one minute postintubation (p value 0.001) (table 4). However the percent attenuation of RPP is significantly better in DL group followed by L group followed by D group (figure 4) till 5 minutes postintubation as compared to the control group.

**Figure 1**

Table 1: Comparison of Systolic Blood Pressure in between the groups

time	Systolic Blood Pressure				P value
	Group C Mean ± SD	Group D Mean ± SD	Group L Mean ± SD	Group DL Mean ± SD	
t0	132.07 ±15.43	131.77±14.0	134.13±13.97	127.43±7.74	0.254
t1	112.27±14.80	142.20±18.4	109.3±10.6	111.10±9.32	0.461
t2	97.80±14.62	93.90±9.9	94.6±8.8	95.5±9.50	0.541
0 min	146.87±19.7	110.30±13.4	114.77±16.6	104.2±5.79	<0.001
1min	133.87±15.4	113.47±18.24	116.57±16.9	102.70±7.49	<0.001
2min	125.67±17.2	110.27±13.1	103±15.2	100.2±6.13	<0.001
3min	118.17±15.5	107.5±12.3	107.77±14.4	100.6±6.21	<0.001
5min	114.67±18.01	103.93±9.9	108.63±13.8	101.23±5.56	<0.001
10min	109.20 ±14.2	103.57±8.04	108.40±13.4	101.30±5.07	0.014

T0: Baseline, T1: Posinduction, T2: Preintubation

**Figure 2**

Table 2: Comparison of Mean Arterial Pressure in between the groups

Time	Mean Arterial Pressure				P value
	Group C Mean ± SD	Group D Mean ± SD	Group L Mean ± SD	Group DL Mean ± SD	
T0	98.4±10.7	95.0±10.8	100.8±10.4	95.56±6.39	0.083
T1	83.08±12.2	88.68±6.4	82.3±9.2	83.87±9.24	0.882
T2	71.18±12.1	67.06±8.8	68.5±6.8	71.12±8.64	0.24
0 min	108.2±19.2	80.7±12.6	87.1±14.2	79.03±8.00	<0.001
1min	99.7±17.8	82.5±15.07	88.6±13.9	79.66±8.19	<0.001
2min	91.7±15.01	79.7±10.9	84.4±13.0	78.46±8.08	<0.001
3min	87.2±14.8	77.3±11.2	80.8±11.8	77.44±7.20	0.004
5min	84±14.3	73.3±8.6	81.18±11.5	77.36±6.47	0.001
10min	79.5 ±11.7	75.4±7.04	81.64±10.8	78.25±6.24	0.069

T0: Baseline, T1: Posinduction, T2: Preintubation

**Figure 3**

Table 3: Comparison of Heart Rate in between the groups

Time	Heart Rate				P value
	Group C Mean ± SD	Group D Mean ± SD	Group L Mean ± SD	Group DL Mean ± SD	
T0	79.43±12.4	85.17±9.6	84±7.3	85.4±9.57	0.076
T1	74.8±14.0	78.43±9.2	73.87±7.9	77.4±11.47	0.602
T2	72.13±12.5	74.6±9.9	70.83±10.9	78.7±10.54	0.034
0 min	93.73±14.1	96.23±15.1	84.63±12.8	88.23±8.71	0.003
1min	91.9±15.3	91.7±14.1	83.77±15.4	87.13±9.12	0.048
2min	84.2±13.9	86.1±12.3	79.27±11.7	81.8±9.72	0.148
3min	80.13±14.2	80.73±13.2	74.73±10.5	79.03±10.50	0.228
5min	76.57±14.6	74.5±10.2	72.93±12.1	75.4±10.49	0.691
10min	70.53±13.8	70.2±10.8	69.7±10.3	69.9±10.62	0.993

T0: Baseline, T1: Posinduction, T2: Preintubation

**Figure 4**

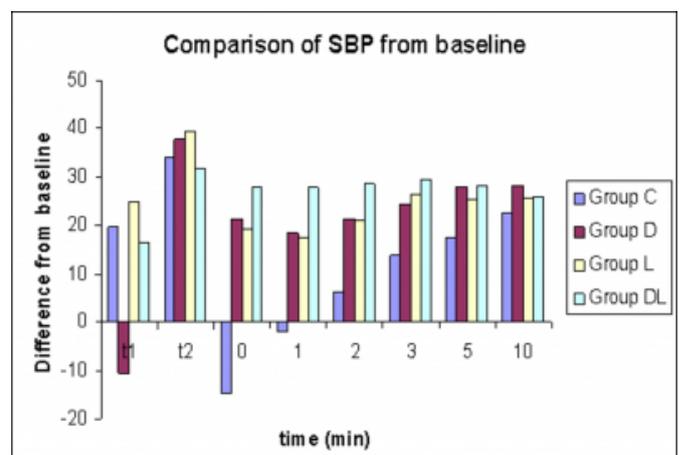
Table 4: Comparison of RPP in between the groups

Time	RPP				P value
	Group C Mean ± SD	Group D Mean ± SD	Group L Mean ± SD	Group DL Mean ± SD	
T0	10498.4±2094.2	11299.67±2249.7	11269.03±1531.1	10900±1521.72	0.30
T1	8381.33±1754.4	10796.27±1432.3	8071.57±1246	8620.07±1607.4	0.40
T2	7096.37±1708.1	7024.97±1284.2	6703.27±1197.2	7520.10±1264.7	0.15
0 min	13578.27±3313.5	10660.57±2272.7	9796.93±2363.4	8792.3±1061.6	<0.001
1min	12374.83±2933.1	10529.73±2883.3	9880.3±2678.1	8680.03±1275.04	<0.001
2min	10700±2700.7	9587.3±2235.3	9050.03±2197.1	8104.2±1154.8	<0.001
3min	9593.3±2700.7	8743.3±2079.2	8131.1±1951.1	7741.3±1173.6	0.004
5min	8903.97±2683.7	7785.63±1591.2	8025.6±2139.7	7491.6±1208.8	0.04
10min	7804.3±2247.4	7308.53±1529.1	7620.07±1799.17	7096.3±1214.6	0.41

T0: Baseline, T1: Posinduction, T2: Preintubation

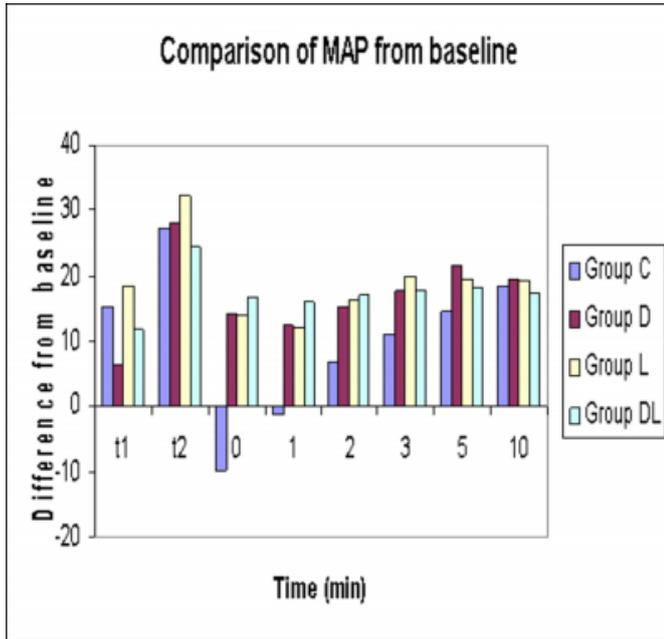
**Figure 5**

Figure 1: Comparison of SBP From Baseline



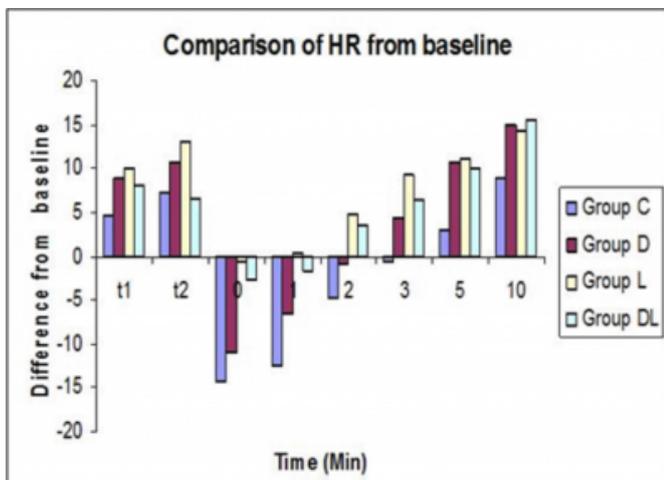
**Figure 6**

Figure 2: Comparison of MAP From Baseline



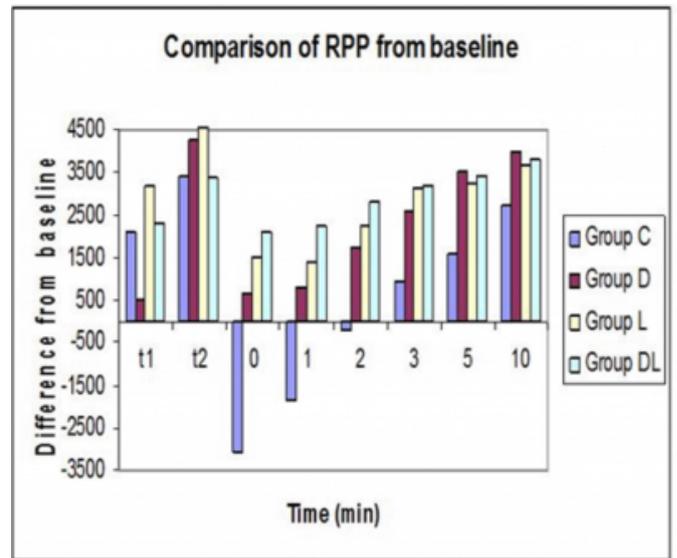
**Figure 7**

Figure 3: Comparison of HR From Baseline



**Figure 8**

Figure 4: Comparison of RPP From Baseline



**DISCUSSION**

Laryngoscopy and endotracheal intubation are considered as one of the most critical event during general anaesthesia. They provoke a transient, but marked sympathetic and sympathoadrenal response manifesting as hypertension and tachycardia. A variety of anaesthetic techniques and drugs are available to control the haemodynamic response to laryngoscopy and intubation<sup>3,9</sup>. Some of these are drugs are lidocaine (via various routes like intratracheal<sup>4</sup>, local spray over vocal cords, intravenous), beta blockers (esmolol), calcium channel antagonist (diltiazem), opioids (morphine, fentanyl, sufentanil, alfentanil, remifentanil) and alpha2 adrenergic agonist (clonidine). Diltiazem and lignocaine have different mechanisms of attenuating these pressor responses and a combination of these two drugs is more effective in attenuating both heart rate and blood pressure than when they are used alone.

The mean systolic blood pressure, Diastolic blood pressure and Mean arterial pressure amongst the Control (C) group at baseline were 132.07 ±15.43, 81.6±9.8 and 98.4±10.7 mmHg respectively. After intubation there was a significant rise in BP from the baseline. SBP increased by 14.8 mmHg (11.21%) (p value 0.001), DBP rose by 7.26 mmHg (8.9%)(p value 0.011), and MAP by 9.7mmHg (9.8%) (p value 0.011). The readings approached baseline and started coming down at 2minutes postintubation. These results are similar to the results of Vijaylakshmi et al<sup>10</sup> and Anila D Malde etal<sup>1</sup>. However in some studies<sup>11,12,13,14</sup> where no opioid analgesic was used at the time of induction the rise in SBP,

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DBP & MAP is much more than that observed in our study.

In the Diltiazem group of our study the mean SBP, DBP and MAP at baseline were  $131.77 \pm 14.0$ ,  $76.6 \pm 10.3$  and  $95.0 \pm 10.8$  respectively. Post intubation highly significant attenuation of SBP, DBP and MAP occurred from baseline (p value  $< 0.001$ ). The percentage fall of SBP, DBP & MAP were 14.5%, 14.4% and 15.7 % respectively. Similar results have been reported by Manjunath et al<sup>26</sup>, Santosh kr et al,<sup>a</sup> and Mikawa et al<sup>16</sup>. Y fujii et al<sup>17</sup> reported that in the Diltiazem group MAP did not increase after tracheal intubation from baseline.

In Lidocaine group the mean SBP, DBP and MAP at baseline were  $134.13 \pm 13.97$ ,  $80.17 \pm 9.5$  and  $100.8 \pm 10.4$  respectively. With respect to SBP, DBP and MAP, the attenuation was significant from baseline at all the times (p value  $< 0.001$ ). The percentage fall of SBP, DBP & MAP postintubation was 14.9%, 8.7% and 13 % respectively. The results are in concurrence with Manjunath et al<sup>11</sup>, Anila D Malde et al<sup>1</sup> and Hyong Yong Shin et al<sup>18</sup> who also observed attenuation of SBP, DBP and MAP response to intubation with lidocaine.

In Diltiazem- Lidocaine group of our study the mean SBP, DBP and MAP pressure at baseline were  $127.43 \pm 7.74$ ,  $79.63 \pm 6.91$  and  $95.56 \pm 6.39$  respectively. With respect to SBP, DBP and MAP, the attenuation was significant from baseline at all the times (p value  $< 0.001$ ). The percentage fall of SBP, DBP & MAP postintubation were 18.1%, 12.6% and 16.8 % respectively. Manjunath et al<sup>11</sup> reported highly significant attenuation of SBP, DBP, MAP when a combination of Diltiazem and lidocaine group was used. Rupakar et al<sup>7</sup> reported nonsignificant rise of 4.6 mmhg of MAP in DL group while Y Fujii et al<sup>17</sup> observed that combination of Diltiazem- Lidocaine prevents the increase in hemodynamic variables like MAP, RPP and Heart rate.

Among our study groups, significant differences were observed in SBP between C & D group till 5 minutes after intubation and C & L group till 3 minutes post intubation (P Value  $< 0.001$ ). Both L & D groups were comparable at all the times. Significant differences were observed in between C & DL group (P Value  $< 0.001$ ), D & DL group (P value  $< 0.001$ ), and L & DL group (P value  $< 0.001$ ) till five minutes after intubation. The results showed that attenuation of SBP was significantly more in the Combination DL group. Rupakar et al<sup>7</sup> and Y Fujii et al<sup>17</sup> also found that combination of Diltiazem- Lidocaine produces more

significant attenuation of cardiovascular response to laryngoscopy and tracheal intubation than lidocaine or diltiazem used alone.

After intubation there was a significant rise in HR in C group, by 14 beats/minute (17.7%) from the baseline (p value 0.001). However in in the D group also, there was significant rise in HR by 11 beats/minute (12.9%) from the baseline (p value 0.001). Similarly Santosh kr et al<sup>15</sup> reported significant rise in heart rate immediately after intubation, at 1 min and at 3 minutes after intubation. These findings are also consistent with that of Mikawa et al<sup>6</sup> who said that IV diltiazem (0.2 and 0.3 mg/kg) given 1 minute before laryngoscopy failed to protect against the increase in heart rate after laryngoscopy. The fact that diltiazem does not prevent the increase in heart rate in a single bolus dose 0.2mg/kg or 0.3mg/kg has been reported by various investigators like Safar et al<sup>19</sup>, Tamura et al<sup>20</sup> and Michael Joyal<sup>21</sup> et al. This is because diltiazem causes reflex sympathoadrenal stimulation by hypotension which masks the direct negative chronotropic effect. The mean heart rate in L group at baseline was  $84 \pm 7.6$  beats per minute. After intubation there was no significant rise in HR from the baseline. In the DL group, There was maximum rise of 3 beat/ min postintubation. Similarly, results have been reported by Rupakar et al<sup>7</sup>, Manjunath et al<sup>11</sup> and Y fujii et al<sup>17</sup> in their DL group. The results showed that attenuation with respect to heart rate was equivalent in both L and DL groups as compared to D group.

With respect to RPP, there was significant rise in RPP in control group when compared with rest of the three groups. There was attenuation of RPP in all the three groups but the attenuation was maximum in DL group followed by L group and D group respectively. Levels of RPP in excess of 20,000 are more commonly associated with angina and myocardial ischemia<sup>22,23</sup>. In this study RPP following tracheal intubation was not  $> 20,000$  in any group, suggesting that critical increases in RPP may be avoided by diltiazem, lidocaine or diltiazem-lidocaine combination. The changes in RPP from baseline values immediately after tracheal intubation in group DL were also less than those in groups D and L. This suggest that diltiazem- lidocaine combination is more effective than diltiazem or lidocaine alone for attenuation of cardiovascular responses to laryngoscopy and tracheal intubation.

Most of the earlier studies did not use any drugs other than induction agent and relaxant in their control group.

<sup>11,12</sup> However we used 2 mcg/ kg of fentanyl along with induction agent in the control group as a result of which the pressor response in control group of our study is of lesser magnitude than in the literature reviewed. Keeping patient safety in mind, fentanyl was co-administered in all the four groups. Hence the group which did not receive diltiazem or lidocaine over and above fentanyl served as a control in our study.

In the patients with coronary artery disease or those with risk factors for CAD, myocardial ischemia may occur during induction- intubation sequence. Because HR is a major determinant of myocardial oxygen balance, the lack of efficacy of diltiazem in controlling tachycardia may limit its usefulness but simultaneous use of fentanyl and lidocaine helps to overcome this disadvantage and works towards the benefit of patient by achieving attenuation of both HR and BP response.

No arrhythmia, evidence of myocardial ischemia or hypoxemia was observed in any of the groups. There were no serious complications after laryngoscopy and tracheal intubation in any patient.

The primary outcome of the study is that a combination of diltiazem and lidocaine can be safely used as a routine before intubation to attenuate the potentially harmful hemodynamic responses. The secondary outcome is that diltiazem in the dose of 0.2mg/kg can also be used to blunt these hemodynamic responses (though to lesser extent than the combination) as compared to other studies where 0.3mg/kg has been used<sup>6,11</sup>.

## CONCLUSION

The data from our study suggests that diltiazem and lidocaine when injected alone can blunt the cardiovascular responses to laryngoscopy and tracheal intubation successfully. However, the primary hypothesis that with combination of these two drugs is significantly more effective than any one alone for attenuating haemodynamic changes to laryngoscopy and tracheal intubation in normotensive patients, without increased risk of hypertension holds good. The diltiazem and lidocaine combination appears to be very effective and safe and should be viewed as potential treatment strategy for attenuating hemodynamic changes during induction of anaesthesia, laryngoscopy and tracheal intubation.

The limitation of the study is its use only in ASA grade I &

II patients.

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