CAN CALCIUM AND SODIUM CHANNEL BLOCKERS ATTENUATE HEMODYNAMIC RESPONSES TO ENDOTRACHEAL INTUBATION?

Manjunath Honnavara Govindaiah[1], Venkatesh Gubbi Suryanarayana[1], Prima Vas[2], Jennifer Leigh Vlk[2], Sathees Beladakere Channaiah Chandra[2]*

Rajiv Gandhi University, Mysore Medical College, [1]Krishna Rajendra Hospital and Cheluvamba Hospital, India, Roosevelt University, [2]Department of Biological, Physical Sciences, Chicago, USA

Aim: Direct laryngoscopy and endotracheal intubation following induction of anesthesia almost always triggers powerful cardiovascular responses. The purpose of this study was to investigate the efficacy of diltiazem (calcium channel blocker), lidocaine (sodium channel blocker) and a combination of these two drugs in the attenuation of circular responses to endotracheal intubation in normotensive patients.

Methods: 120 Patients were randomly assigned to one of the following four groups. Group I received a single 0.2 mg/kg IV bolus of diltiazem 1 minute prior to laryngoscopy and intubation (n=30), Group II received a single 1.5 mg/kg IV bolus of lidocaine (n=30) 3 minutes prior and Group III received combination of these two drugs 1 minute prior to laryngoscopy and intubation (n=30). Group IV served as the control and received a single 5 mL IV bolus of normal saline. Changes in heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) were measured and then compared within and between groups. Rate pressure product (RPP) was calculated and evaluated as well.

Results:Either diltiazem or lidocaine alone blunts unwanted hemodynamic responses to intubation. However, significantly less circulatory responses were experienced by patients receiving both than those receiving either lidocaine or diltiazem alone.

Conclusion: Given the difference in the pharmacological mechanisms of these two drugs, the prophylactic therapy with combination of diltiazem+lidocaine is significantly more effective than any one alone for attenuating hemodynamic changes to laryngoscopy and tracheal intubation, without producing increased risk of hypertension.

Key words: Calcium channel, sodium channel, circulatory response, endotracheal intubation, hemodynamic change

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INTRODUCTION

Cardiovascular complications are one of the most common causes of anesthesia-related morbidity (1). The hemodynamic consequences of drugs and the techniques used for induction of anesthesia have been well documented (2-6). Laryngoscopy and endotracheal intubation are often mandatory for patients undergoing a variety of surgical procedures. It is well known that laryngoscopy and endotracheal intubation following induction of anesthesia is almost always associated with hemodynamic changes due to sympatho-adrenal stimulation (7,8). This increased sympatho-adrenal activity normally causes hypertension, tachycardia or myocardial ischemia in patients with coronary artery disease, intracranial tumors and previous myocardial infarction (9). This increase in blood pressure and heart rate are usually transitory, variable and unpredictable. Transitory hypertension and tachycardia are generally of no consequence in healthy individuals, but either or both may be hazardous to those with hypertension, myocardial insufficiency or

Correspondence:*Sathees B.C. Chandra, Ph.D*
Associate Professor of Biology/Genetics, Department of Biological, Chemical and Physical Sciences, Roosevelt University, 430 S Michigan Avenue, Chicago, IL 60605 USA
Phone: 8476197968, Fax: 8476198555
Email: schandra@roosevelt.edu

Table1. Study participant's demographic data (values represent means ± SD)

	Control (Saline)	Group 1 (Diltiazem)	Group 2 (Lidocaine)	Group 3 (Diltiazem+ Lidocaine)
n	30	30	30	30
Sex (M/F) Ratio	15/15	13/17	16/14	18/12
Age (yr)	38 ± 10.2	43.5 ± 9.6	40 ±10.6	42 ± 11.3
Weight (kg)	56.4 ± 5.33	68.7 ± 10.17	65.9 ± 10.25	69.4 ± 11.3

cerebrovascular diseases (10).

Many pharmacological methods have been devised to reduce the extent of hemodynamic events including high dose of opioids such as fentanyl, remifentanil, alfentanil (11-13), alpha- and beta-adrenergic blockers (14,15), and vasodilatation drugs like nitroglycerine (16). Each of these drugs has a unique advantage and disadvantage in blunting the pressor response to intubation.

During the last decade, calcium and sodium channel blockers has been utilized to mitigate the hemodynamic responses to intubation. Diltiazem is one of the calcium channel blockers being used as antianginal, antiarrythmic and antihypertensive agent. Lidocaine (lignocaine) is a common local anesthetic and a sodium channel blocker known to reduce pressor response to intubation. Although these two drugs have been used in various studies alone or combined with other opioids, only two reports have so far examined the benefits of combining both calcium and sodium channel blockers. The first study looked at the combination of these two drugs only in hypertensive patients (10). Based on an English-translated abstract, a second study by Lee et al. (17) also appeared to look at the combination of these two drugs. However in their work, the researchers only measured the heart rate and mean arterial pressure which sharply contrasted with what we found in our study. The present work was undertaken to compare the effect of diltiazem, lidocaine and combination of these two drugs on blunting the hemodynamic responses to endotracheal intubation in normotenseive patients. Because the mechanism for control of hemodynamic changes is different between these two drugs (18,19), we hypothesized that significantly less circulatory responses would be experienced by patients receiving both than receiving either lidocaine or diltiazem alone.

MATERIAL AND METHODS

This study was undertaken at K.R.Hospital attached to Government Medical College, Mysore, coming under Rajiv Gandhi University of Health sciences, Bangalore, Karnataka state, India. Following institutional approval by the ethical committee at Mysore Medical College, informed consent was obtained from 120 patients. The study population consisted of randomly selected ASA physical status I or II male and female adults, between the ages of 18-60 yr, which were scheduled for various elective surgical procedures. Patients having pre-existing systemic disorders, ischemic heart disease, hypertensive heart disease, diabetes mellitus, bronchial asthma, previous myocardial infarction, renal disease, cerebrovascular insufficiency or association with any co-morbid disease were excluded from the study.

Study design

Each patient was randomly assigned to one of four study groups. Group I received a single 0.2 mg/kg IV bolus of diltiazem diluted to 5 mL with normal saline 1 minute prior to laryngoscopy and intubation (n: 30). Group II received a single 1.5 mg/kg IV bolus of lidocaine (lignocaine) diluted to 5mL with normal saline 3 minutes prior to laryngoscopy and intubation (n:30). Group III received a combined single IV bolus containing both 0.2 mg/kg of diltiazem and 1.5 mg/kg lidocaine diluted to 5mL with normal saline 1 minute prior to laryngoscopy and intubation (n:30). Group IV served as control and received a single 5ml IV bolus dose of normal saline given 1 minute before laryngoscopy and intubation (n=30). Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) were recorded via a

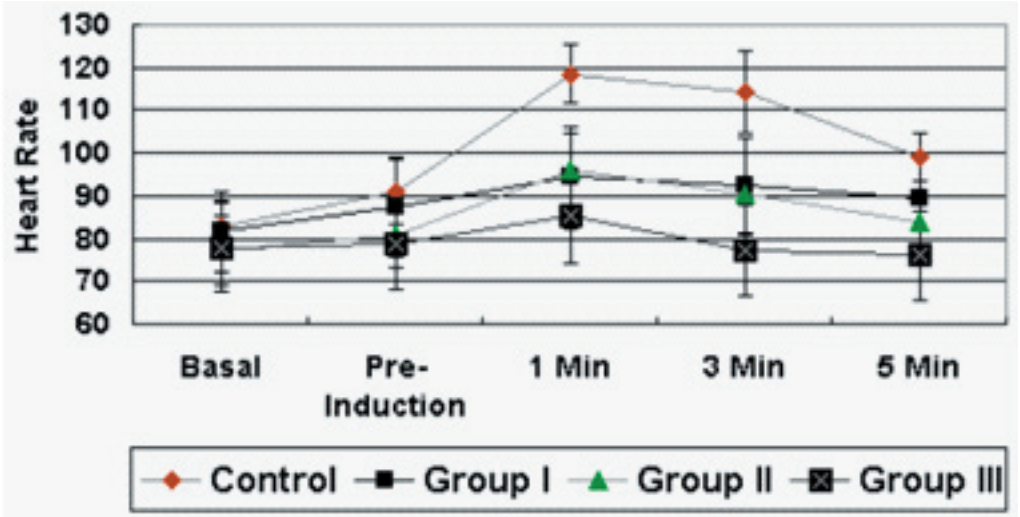

Figure 1. Changes in Heart Rate with standard deviations in each group. All values are expressed as mean ±SD. Group I: diltiazem; Group II:lidocaine and Group III: diltiazem+lidocaine. p<0.05 vs. control and p<0.001 between Group III vs Group I/ Group II after intubation

Siemens SC-7000 multi-channel monitor for each patient prior to administration of the study drug, at pre-induction and after intubation at the time increments of 1, 3 and a maximum of 5 minutes as after surgery has commenced, multiple factors like various surgical stimuli may also play role in hemodynamic response. Rate Pressure Product (RPP) was calculated and evaluated as well. The rate pressure product was calculated by multiplying heart rate with systolic blood pressure.

Pre-surgical Protocol

The day prior to surgery all patients underwent a pre-anesthetic evaluation with special consideration to elicit a history of hypertension, diabetes mellitus, chest pain, dyspnoea, convulsions, and wheezing, myocardial infarction, as well as previous anesthetic history and drug sensitivity. Patient information collected during the pre-anesthetic evaluation also included nutritional status, weight, airway assessment by the Mallampatti scoring system, and a detailed examination of the cardiovascular, respiratory and central nervous system, which included measured hemoglobin (Hb%), bleeding and clotting time, urine analysis, blood sugar FBS/ RBS, blood urea, serum creatinine, ECG, chest radiography, and blood/Rh typing. Patients were advised to fast the night prior to surgery and were premedicated with a single oral dose of 150mg ranitidine and 0.5 mg alprozolam the night before surgery.

Surgical Protocol

1 mg Midazolam and 15mg Pentazocine was given to all the patients before induction as Pre-medication. The patients were preoxygenated for three minutes using 100% oxygen by facemask with Mapleson A circuit. In the operating room, an 18-gauge intravenous cannula was inserted and an infusion of dextrose with normal saline was started. The patients were connected to the Siemens multi-channel monitor and HR, SBP, DBP, and MAP was recorded. After recoding the baseline reading (basal), the study drug (0.2 mg/kg IV bolus of diltiazem, 1.5 mg/kg IV bolus of lidocaine or combination of both) or the control placebo (5 mL normal saline) was administered as follows. Anesthesia was induced with Thiopentone 5 mg/kg as 2.5% solution and endotracheal intubation was facilitated with succinylcholine 1.5 mg/kg administered one minute prior to laryngoscopy and intubation. Laryngoscopy was performed one minute after the study drug in Group I (after induction with Thiopentone) and 3 minutes after the study drug in Group II (before induction) and one minute after the study drugs in Group III (after induction). The patients were intubated using appropriate sized cuffed endotracheal tubes. Upon bilateral equal air entry confirmation,

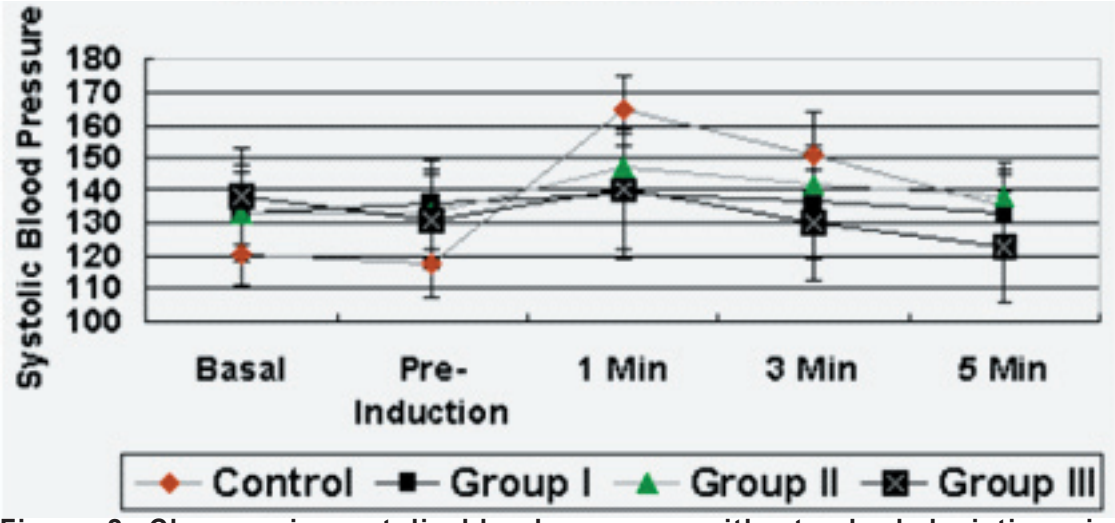

Figure 2. Changes in systolic blood pressure with standard deviations in each group. All values are expressed as mean ±SD. Group I: diltiazem; Group II:lidocaine and Group III: diltiazem+lidocaine. p<0.05 vs. control and p<0.001 between Group III vs Group I/Group II after intubation

the endotracheal tube was fixed and the patients mechanically ventilated using a Bains system. Anesthesia was maintained using 66% nitrous oxide and 33% oxygen. Neuromuscular blockade was maintained with 0.06 mg/kg vecuronium bromide. Anesthesia was reversed with 0.05 mg/kg neostigmine IV bolus and 0.02 mg/kg atropine IV bolus.

Data Analysis

Summary statistics of patient gender, age and weight for all three groups and control were reported as means± standard deviation. Intra- and inter-group analysis for heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and Rate Pressure Product (RPP) were statistically evaluated using one-way ANOVA and Paired T-tests using both StatPlus™ v2, and Minitab™, where $p<0.05$ was considered significant, and $p<0.001$ considered highly significant.

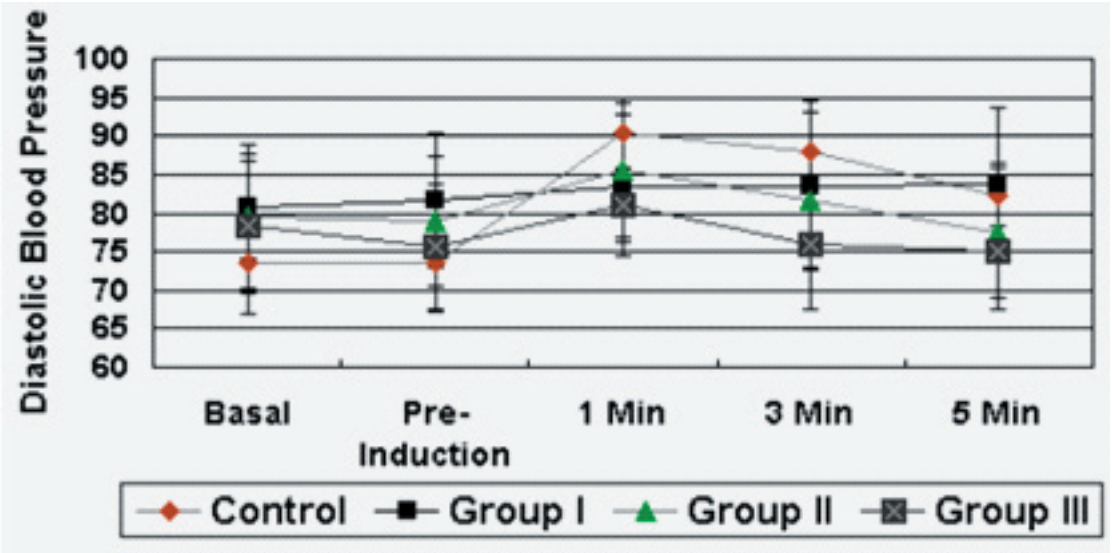

Figure 3. Changes in diastolic blood pressure with standard deviations in each group. All values are expressed as mean ±SD. Group I: diltiazem; Group II:lidocaine and Group III: diltiazem+lidocaine. p<0.05 vs. control and p<0.001 between Group III vs. Group I/Group II after intubation

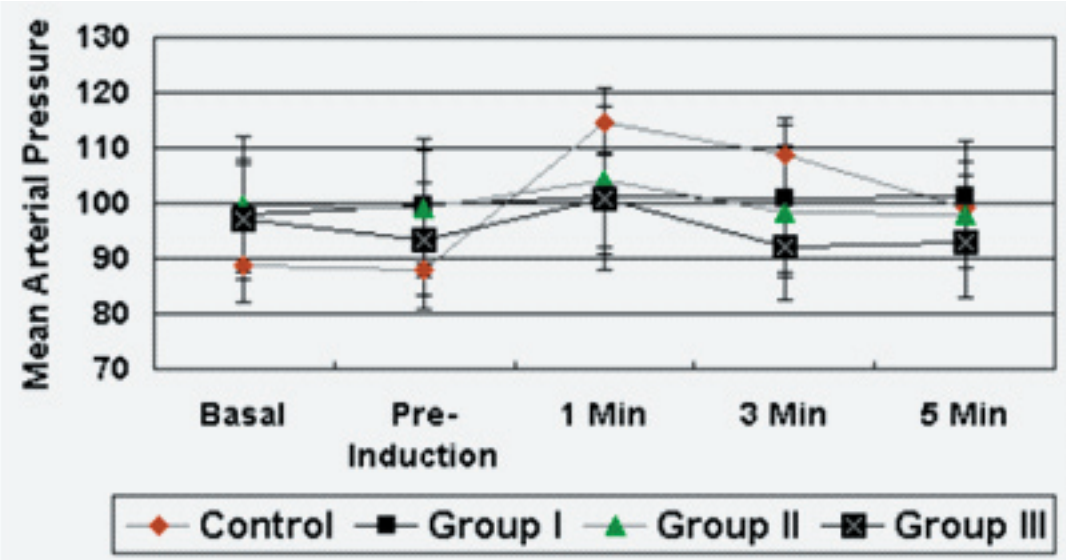

Figure 4. Changes in mean arterial pressure with standard deviations in each group. All values are expressed as mean ±SD. Group I: diltiazem; Group II:lidocaine and Group III: diltiazem+lidocaine. p<0.05 vs. control and p<0.001 between Group III vs. Group I/Group II after intubation

RESULTS

The demographic characteristics of each group were similar (Table 1). There were no statistical differences observed with respect to number of patients in each group, sex ratio or age. However, the average age of patients in the control group was lower than that of the other three groups, due to random inclusion of four 20 years old patients in that group.

Heart Rate (HR)

Attenuation of heart rate related hemodynamic response to tracheal intubation by a single bolus of diltiazem, lidocaine or combination of both was observed at all time points (Figure 1). The diltiazem group had a highly significant mean heart rate, 1 minute after intubation, at 22% below the control (n:30, t=11.32, p<0.001), suggesting that a single 0.2 mg/kg bolus injection of diltiazem 1

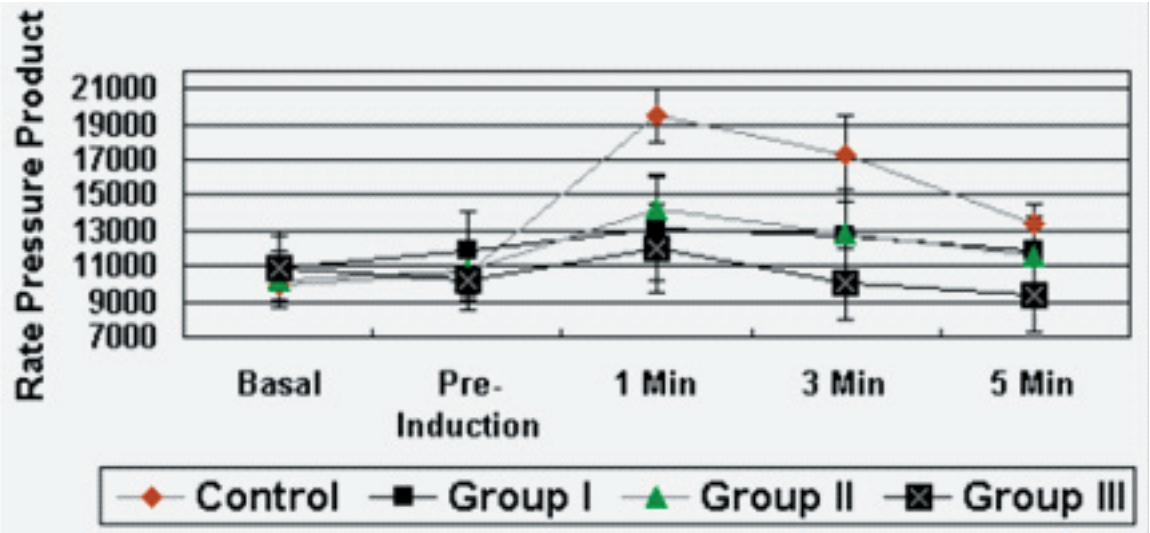

Figure 5. Changes in rate pressure product with standard deviations in each group. All values are expressed as mean ±SD. Group I: diltiazem; Group II:lidocaine and Group III: diltiazem+lidocaine. p<0.05 vs. control and p<0.001 between Group III vs. Group I/Group II after intubation

minute prior to intubation was sufficient to attenuate the hemodynamic response due to tracheal intubation. The lidocaine group also had a highly significantly lower mean heart rate 1 minute after intubation (n:30, t=12.07, p<0.001), 3 minutes after intubation (t=9.61, p<0.001) and again at 5 minutes post-intubation (t=8.77, p< 0.001). The diltiazem+lidocaine combination group had a highly significant mean heart rate, 1 minute after intubation, at 33% below the control (n=30, t=13.20, p<0.001), suggesting injecting diltiazem along with lidocaine 1 minute prior to intubation was more effective in attenuating the hemodynamic response due to tracheal intubation. Further, significant attenuation was also observed 3 minutes after intubation (t=13.72, p<0.001) and again at 5 minutes post-intubation (t=9.86, p< 0.001) in the combination group.

Systolic Blood Pressure (SBP)

Highly significant attenuation of systolic blood pressure was observed in the diltiazem group as compared to the equivalent control measured values (n: 30, p<0.001) (Figure 2). The greatest difference between measured points was at 1 min after intubation, where a 17% decrease from control levels was observed (t=7.05, p<0.001). Attenuation of the SBP pressor response to intubation in the lidocaine group was highly significant (n:30, p<0.001), except at 5 minutes post-intubation (n:30, t=1.02, p=0.318). SBP response to intubation was significantly attenuated in the diltiazem+lidocaine group (n:30, p<0.001) as compared to the equivalent control measure values. The greatest difference between measured points was at 1 min after intubation, where a 16% decrease was observed in the combination group.

Diastolic Blood Pressure (DBP)

Highly significant attenuation of diastolic blood pressure was observed in the diltiazem group as compared to the equivalent control measured values (n:30, p<0.001), except at 5 minutes after intubation (n:30, t=0.67, p=0.50) (Figure 3). Attenuation of the DBP pressor response to intubation in lidocaine group was significant (n:30, p<0.001) at all time points. The greatest difference between measured points was at 3 minutes after intubation, where a 8% decrease from control levels was observed (t=3.64, p<0.001). DBP response to intubation was highly significantly attenuated in the diltiazem+lidocaine group (n:30, p<0.001). The greatest difference between measured points was at 3 minutes after intubation, where a 15% decrease from control levels was observed in the combination group (t=6.38, p<0.001).

Mean Arterial Pressure (MAP)

A significant attenuation of mean arterial pressure was observed in the diltiazem group (n:30, p<0.001) except at 5 minutes after intubation (n:30, t=0.74, p=0.46) (Figure 4). Attenuation of the MAP pressor response to intubation in the lidocaine group was significant (n:30, p<0.001) at all time points except at 5 minutes after intubation (n:30, t=0.68, p=0.49). MAP response to intubation was significantly attenuated in the diltiazem+lidocaine group (n:30, p<0.001) at all time points. The greatest difference between measured points was at 3 minutes after intubation, where a 17% decrease from control levels was observed in the combination group (t=7.70, p<0.001).

Rate Pressure Product (RPP)

Attenuation of the RPP pressor response to intubation in the diltiazem group was significant (n=30, p<0.001) at all time points (Figure 5). Attenuation of the RPP pressor response to intubation in the lidocaine group was highly significant (n:30, p<0.001) at all time points. RPP response to intubation was highly significantly attenuated in the diltiazem+lidocaine group (n:30, p<0.001) at all time points. The greatest difference between measured points was at 3 minutes after intubation, where a 53% decrease from control levels was observed in the combination group (t=14.38, p<0.001).

Diltiazem+lidocaine group vs. diltiazem or lidocaine group

Highly significant attenuation of HR, SBP, DPB and MAP was observed in the diltiazem+lidocaine group as compared to the equivalent diltiazem or lidocaine measured values at 1 minute, 3 minutes and at 5 minutes after intubation (n: 30, p<0.001). Attenuation of the RPP pressor response to intubation in the diltiazem+lidocaine group was highly

significant (n:30, p<0.001) at all time points compared to equivalent diltiazem or lidocaine measured values.

DISCUSSION

In designing this experiment, our primary objective was to study the combination of calcium and sodium channel blockers on hemodynamic changes due to tracheal intubation in normotensive patients. Our results consistently show that either diltiazem or lidocaine alone blunts unwanted hemodynamic responses to intubation. However, significantly less circulatory responses was experienced by patients receiving both than receiving either lidocaine or diltiazem alone.

In the control group, markedly high cardiovascular changes occurred after one minute following laryngoscopy and intubation. In our study, 0.2 mg/kg diltiazem given a minute before intubation sufficiently reduced the circulatory responses in normotensive patients. Our results are in agreement with previous reports (18,20-23) that calcium channel blockers can, in fact, attenuate hypertension associated with tracheal intubation. Surprisingly, Lee et al. (17) found, when diltiazem alone was administered it did not attenuate heart rate. This might be explained by dosage differences (0.3 mg/kg) and timing of administration of drugs. In the other study, drug was given 90 seconds before laryngoscopy as opposed to the 60 seconds in the current study. The use of calcium blockers can be best utilized when their peak effects corresponds to that of pressor responses. It has been reported before that, MAP begins to increase about 15 seconds after laryngoscopy and reaches peak value around 45 seconds if no treatment is administered to patients (24). That's why, in our study, diltiazem was administered 1 minute before laryngoscopy.

In the current investigation, patients receiving diltiazem had a highly significant mean heart rate 22% below the control, mean arterial pressure at 13% below, systolic blood pressure at 17% below and rate pressure product at 39% below the control 1 minute after intubation. The RPP levels close to 20,000 are normally associated with angina and myocardial ischemia (25,26). RPP after intubation rose to 19500 in control group, after a minute, but was reduced to 13200 in the diltiazem group. Diltiazem blunts hemodynamic response to laryngoscopy and intubation by acting as a potent vasodilator and/or by relaxing vascular muscles, resulting in dilation of blood vessels and facilitating blood pressure reduction (10,27). Diltiazem also prevents/blocks the release of catecholamines, which reduces sympathetic nervous system reactions (28). By slowing conduction of normal electrical impulse through the AV node, diltiazem increases the time needed for each beat, normally resulting in reduced myocardium oxygen consumption (6).

It was also determined that intravenous administration of the sodium channel blocker, lidocaine, considerably attenuated unwanted pressor response to laryngoscopy and tracheal intubation when given 3 minutes before laryngoscopy. Patients receiving lidocaine had a highly significant mean heart rate at 21% below the control, systolic blood pressure at 11%, mean arterial pressure at 10% and rate pressure product at 31% below the control 1 minute after intubation. The similar decline in the hemodynamic changes occurred in the lidocaine-administered group 3 minutes after intubation. However, little difference was noted in the circulatory responses between control and lidocaine groups 5 minutes after intubation. The results of various studies, in the last decade, on the effect of hemodynamic responses to tracheal induction have varied considerably. Many studies have reported beneficial effect (29-33), while others showed no effect (5,34-36). The difference in the results of various studies involving lidocaine, to some extent, can be explained by differences in study designs including variations in patient population, age, and dose and timing of drug administration in relation to intubation (37). In addition, techniques used for induction, method of measurement of circulatory responses as well as use of various methods for statistical analysis of data (34) are contributing towards mixed effect of lidocaine in various studies.

Sodium blockers such as lidocaine attenuate hemodynamic response to laryngoscopy and intubation by one or combination of following mechanisms: lidocaine acts mainly by inhibiting sodium influx in the voltage gated sodium channels in the neuronal cell membrane. When the influx of sodium is interrupted, signal

conduction is inhibited (38). It also acts by decreasing the sensitivity to heart muscle to electrical pulses. This will in turn slow down conduction of electrical signals in the heart muscles, and therefore helps to restore a regular heart beat rhythm (39). The beneficial effect of lidocaine on the hemodynamic changes may also due to its direct cardiac depression and peripheral vasodilatation properties (10,40), its ability to suppress airway reflexes elicited by irritation of tracheal mucosa, and its analgesic as well as antiarrythmia properties (41,42).

The hemodynamic changes in HR, SBP, DBP, MAP and RPP, from baseline values one minute after tracheal intubation, in diltiazem+lidocaine group were always highly significantly less than those in diltiazem or lidocaine alone. The patients receiving combination of calcium and sodium blockers had highly marked mean heart rate at 33% below the control, systolic blood pressure at 16%, mean arterial pressure at 14% and rate pressure product at 47% below the control 1 minute after intubation. The similar decline in the hemodynamic changes occurred at both 3 and 5 minutes after intubation. Interestingly, the patients receiving combination of these two drugs had highly significant mean HR at 15% below and RPP at 22% below the diltiazem group measured at 3 minutes after intubation. Similarly, the combination group had highly significant mean HR at 13% below and RPP at 23% below lidocaine group at 3 minutes after intubation. Similar declines in SBP, DBP and MAP for the combination group was recorded. Our results are in agreement with the hypertensive studies by Fujii et al. (10). Given the difference in the pharmacological mechanisms of diltiazem and lidocaine, it was not unexpected that a combination of both drugs was found to be more effective than when administered alone. However, Lee et al. (17) reported that administration of a combination of diltiazem+lidocaine was no more effective than that of injection of diltiazem alone. Nevertheless, at the time of this publication, an English translation of the abstract for the Lee et al. (17) study was not available, so a direct comparison of study details could not be made.

One of the earlier studies (10) looked at the efficacy of these two drugs in hypertensive patients. Our study involving normotensive patients exhibited some similarities and differences, in terms of HR, MAP & RPP values, with that of previous study. In the hypertensive patients, the HR increased immediately after tracheal intubation in both lidocaine and diltiazem groups and remained elevated for three minutes. MAP and RPP also increased and remained elevated for two minutes in lidocaine-administered group. However in diltiazem group, MAP did not increase but RPP increased immediately after tracheal intubation. In the diltiazem+lidocaine group, they observed no increases in HR, MAP or RPP. Our study showed substantial increase in HR, but no increase in MAP and a slightly higher RPP values immediately after tracheal intubation in the combination group. In the present study in the diltiazem group, the HR increased immediately after tracheal intubation and remained elevated for 5 minutes. HR also increased in the lidocaine, but remained elevated only for 3 minutes. Nevertheless, both studies demonstrated higher effectiveness of combinations of drugs for attenuating the cardiovascular responses.

In conclusion, the present data suggests that diltiazem and lidocaine when injected alone can blunt the cardiovascular responses to laryngoscopy and tracheal intubation successfully. However, the prophylactic therapy with combination of these two drugs is significantly more effective than any one alone for attenuating hemodynamic changes to laryngoscopy and tracheal intubation in normotensive patients, without increased risk of hypertension. The dosage and timing of administration of drugs are important factors that determine whether they will have beneficial effect on the laryngoscopy and tracheal intubation, therefore further research is necessary to elucidate the effects of calcium and sodium channel blockers. The dilitiazem+lidocaine combination appears to be very effective and safe and should be viewed as potential treatment strategy for attenuating hemodynamic changes during induction of anesthesia.

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