International Journal of Health Sciences and Research
www.ijhsr.org ISSN: 2249-9571

Original Research Article

Comparison of Diltiazem and Lignocaine in Attenuating Hemodynamic Responses during Extubation in Patients Undergoing Laparoscopic Cholecystectomy

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Received: 15/06/2016 *Revised: 24/06/2016* *Accepted: 27/06/2016*

ABSTRACT

Objective: To compare the effects of intravenous diltiazem and intravenous lignocaine on blunting the hemodynamic responses to endotracheal extubation in patients undergoing elective laparoscopic cholecystectomy.
Materials and Methods: Ninety patients were randomly divided into 3 groups: In the control group patients received saline; in the diltiazem group patients received 0.2 mg/kg diltiazem IV; and in the lignocaine group patients received 1.0 mg/kg lignocaine IV .These drugs were given 2 minutes before tracheal extubation. Values for Heart Rate (HR), SBP (Systolic Blood Pressure), DBP (Diastolic Blood Pressure), and MAP (Mean Arterial Pressure) were recorded, on arriving in the operating room, immediately at the end of the surgery, at the time of injection of the study drugs, at tracheal extubation, and at 1 minutes, 2 minutes, 3 minutes, 4 minutes and 5 minutes after extubation.
Results: During extubation in the control group HR, SBP, DBP and MAP increased significantly when compared to baseline levels (at the end of surgery). Both lignocaine (1.0 mg/kg) and diltiazem (0.2 mg/kg) successfully alleviated these increases. The suppressive effect of diltiazem was greater than that of lignocaine.
Conclusion: 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 IV or 0.2 mg/kg diltiazem IV. And the use of diltiazem attenuated these responses more than that of lignocaine.

Key words: Hemodynamic response, endotracheal extubation, diltiazem, lignocaine, laparoscopic cholecystectomy.

INTRODUCTION

Endotracheal extubation is associated with reflex sympathetic discharge caused by epipharyngeal and laryngopharyngeal stimulation resulting in hypertension, tachycardia and arrhythmias. [1,2] In addition many other stimuli affect these hemodynamic changes including pain from wound and emergence from anaesthesia. [3]

Laparoscopic cholecystectomy despite being a minimally invasive surgery produces significant hemodynamic changes resulting from the combined effects of pneumoperitoneum, patient position, anesthesia, and hypercapnia from the absorbed CO_2. [4] Hemodynamic changes induced by the pneumoperitoneum, and more particularly the increased systemic vascular resistance, outlast the release of the pneumoperitoneum. [5] Thus, at the end of

the procedure, even when intra-peritoneal pressure has returned to normal, the heart rate and arterial pressure remain elevated. [6,7] These changes may add on to the changes provoked by extubation. These increases in blood pressure and heart rate are transitory, variable, and unpredictable, but may lead to imbalances between myocardial O_2 demand and supply. [8] This may prove hazardous to the patients with hypertension, myocardial insufficiency or cerebrovascular diseases. [2]

Various methods have been used to control the cardiovascular responses to extubation. The non-pharmacological methods include smooth and gentle extubation with a shorter duration of laryngoscopy. Drugs like esmolol, [9] fentanyl, [10] diltiazem, [11] verapamil [3] and local anaesthetics like lignocaine [12,13] have been used alone or in combination [14,15] to reduce the extent of hemodynamic events. Similarly, the cardiovascular responses to tracheal extubation have been prevented by extubation of trachea with the patient in a deep plane of anaesthesia by use of inhalation or IV anaesthetics agents.

Several studies have shown that diltiazem with its direct vasodilation and a direct negative chronotropic and dromotropic property is effective in maintaining perioperative hemodynamic stability. [3,11] Lignocaine with its well established centrally depressant and antiarrhythmic effect has been used as a bolus or perioperative infusion to minimize the pressor response to extubation. [12,13]

The present study was undertaken to compare the effect of intravenous diltiazem and intravenous lignocaine on blunting the hemodynamic response to endotracheal extubation in patients undergoing laparoscopic cholecystectomy.

MATERIALS AND METHODS

After getting institutional approval and written informed consent, ninety patients aged 20-60 years of either sex belonging to ASA physical status I or II planned for elective laparoscopic cholecystectomy were included in this prospective, randomized, double blind placebo-controlled study. Patients with severe systemic diseases, patients with cerebrovascular insufficiency, patients with hypersensitivity to local anesthetic and study drugs, patients concomitantly taking drugs like digoxin, propranolol and theophylline and those having predicted difficult tracheal intubation were excluded from the study.

On arrival to the operating room, an 18 gauge intravenous (IV) cannula was inserted and an infusion of Ringer lactate wasted. All patients were premedicated with injection glycopyrrolate 0.2 mg IV, midazolam 0.04 mg/kg IV and ondansetron 0.1 mg/kg. Intraoperatively, continuous monitoring of electrocardiography (ECG), oxygen saturation (SPO_2), heart rate (HR), non-invasive blood pressure (NIBP), end tidal carbon dioxide concentration ($etCO_2$) was done. All patients received injection tramadol 100 mg slowly IV preinduction. General anaesthesia was induced with injection thiopentone 5mg /kg as 2.5% solution and endotracheal intubation facilitated with succinylcholine 1.5mg/kg. After confirming bilateral equal air entry, appropriate sized cuffed endotracheal tube was secured. Anaesthesia was maintained with oxygen and 0.5-1% isoflurane. Muscle relaxation was achieved with intermittent boluses of injection atracurium bromide. All patients received injection diclofenac aqueous 75 mg slow IV infusion to supplement analgesia after the start of the surgery. Minute ventilation was adjusted to maintain normocapnia ($etCO_2$ between 35 and 40 mmHg). During laparoscopy, intra-abdominal pressure was limited to 10-12 mmHg.

At the end of the surgery, the inhalational anesthetics used for maintenance of anesthesia were stopped and the CO_2 was carefully evacuated by manual compression of the abdomen with open trocars. The HR, SBP, DBP and MAP values were recorded. These served as baseline values. The muscle relaxation was

reversed with injection neostigmine 0.05mg/kg IV and glycopyrrolate 0.01 mg/kg IV. Three minutes after giving reversal, patients were randomly allocated to one of the three groups and study drugs were given as follows:

Group I - patients received normal saline as a placebo IV 2 minutes before extubation and served as control (n=30)

Group II - patients received injection diltiazem 0.2 mg /kg IV 2 minutes before extubation (n=30)

Group III - patients received injection lignocaine 1mg/kg IV 2 minutes before extubation (n=30)

Drug solution was prepared by an anaesthesiologist who had not participated in the study, and drug was filled in precoded 5ml syringes. The observing anaesthesiologist was unaware of the treatment to which each patient was randomized.

Heart rate (HR), Systolic blood pressure (SBP), Diastolic blood pressure (DBP) and Mean arterial blood pressure (MAP) were recorded in all patients at following time intervals:

1. At the end of the surgery serving as baseline.
2. Then after giving reversal at 1minutes & 2 minutes.
3. At the time of administration of study drug.
4. 1 minute after administration of study drug.
5. At the time of extubation.
6. After extubation at 1 minute (E1), 2 minutes (E2), 3 minutes (E3), 4 minutes (E4) and 5 minutes (E5).

Occurrence of any adverse events was recorded. Hypotension was defined as fall in SBP<80 mmHg and bradycardia was defined as fall in HR<50 beats per minute. Hemodynamic fluctuations were to be managed accordingly. Ondansetron (4 mg IV) was administered on complaint of nausea and vomiting.

Statistical analysis

All data were compiled and statistical analysis was carried out. Continuous data were summarized as Mean±SD while discrete data in percentage (%). Comparision between the groups were performed with one way Analysis of Variance (ANOVA) and unpaired t test for parametric data and chi-square test for non-parametric data. A p value < 0.05 was considered to be statistically significant, p < 0.001 highly significant and p >0.05 non-significant. All analysis were performed using computer software GraphPad InStat [DATASET1.ISD])

RESULTS

Table-1 shows that the three groups were comparable with respect to age and ASA physical status. In all the groups, the percentage of females was higher than males.

Table 1: Basic characteristics of the three groups

Characteristics	Group I	Group II	Group III	P value
Age(years)				
Mean±SD	40.1±13.202	40.4±11.886	41.57±10.464	>0.05
Sex				
Males	7(23.3%)	7(23.3%)	6(20%)	>0.05
Females	23(76.7%)	23(76.7%)	24(80%)	
ASA Physical Status				
Grade I	14(46.7%)	16(53.3%)	15(50%)	>0.05
Grade II	16(53.3%)	14(46.7%)	15(50%)	

Heart Rate Table-2 shows changes in Mean Heart Rate (Mean± SD) in beats/minute, in all 3 groups at baseline (at the end of surgery) and at 1, 2, 3, 4 and 5 minutes after extubation. At 1 minute after extubation, there was a significant increase (p < .0001) in HR from baseline values in Group I (control) as compared to increase in HR in Group II (diltiazem) and Group III (lignocaine). The heart rate in diltiazem group was significantly lower than control

group and lignocaine group up to 5 minutes after extubation.

Systolic blood pressure (SBP): Table-3 shows a statistically significant increase in systolic blood pressure from the baseline value one minute after extubation in Group I (control) and significant decrease in Group II (diltiazem) and Group III (lignocaine). The SBP in diltiazem group remained significantly lower than in control and lignocaine group up to four minutes after extubation.

Table 2: Comparision of Heart Rate (Mean± SD) among the three groups

Time	Group I	Group II	Group III	P value
Baseline	92.53±11.190	90±8.009	91.77±9.888	>0.05* >0.05† >0.05ǂ
E1	114.57±9.024	90.73±6.612	94.27±7.465	<0.001* <0.001† >0.05ǂ
E2	111.93±9.425	81.73±4.806	88.8±6.467	<0.001* <0.001† <0.001ǂ
E3	107.43±9.449	78.57±4.470	85.73±6.762	<0.001* <0.001† <0.001ǂ
E4	103.63±9.122	74.67±4.147	84.47±5.722	<0.001* <0.001† <0.001ǂ
E5	99.53±8.803	72.93±4.417	82.83±5.682	<0.001* <0.001† <0.001ǂ

*Level of significance between Group I and Group II; † Level of significance between Group I and Group III; ǂ Level of significance between Group II and Group III.

Table 3: Comparision of Systolic Blood Pressure (Mean± SD) among the three groups

Time	Group I	Group II	Group III	P value
Baseline	127.03±5.726	127.37±7.595	126.40±7.811	>0.05* >0.05† >0.05ǂ
E1	134.23±7.219	115.87±6.257	123.80±6.825	<0.001* <0.001† <0.001ǂ
E2	131.40±6.441	113.80±6.099	122.70±6.924	<0.001* <0.001† <0.001ǂ
E3	127.23±4.812	111.83±5.890	118.50±5.224	<0.001* <0.001† <0.001ǂ
E4	123.10±3.889	110.43±4.960	116.80±5.641	<0.001* <0.001† <0.001ǂ
E5	120.37±4.263	108.53±5.198	108.57±4.644	<0.001* <0.001† >0.05ǂ

*Level of significance between Group I and Group II; † Level of significance between Group I and Group III; ǂ Level of significance between Group II and Group III

Diastolic Blood Pressure: Table-4 shows a statistically significant increase in diastolic blood pressure from the baseline values one minute after extubation in Group I (control) and Group III (lignocaine), and highly significant decrease in Group II (diltiazem). The diastolic blood pressure remained significantly lower in diltiazem group up to 5 minutes after extubation.

Mean Arterial Blood pressure (MAP): Table-5 shows a significant increase in MAP from the baseline values one minute after extubation in Group I (control) and Group III (lignocaine), while a significant decrease in Group II (diltiazem). The MAP in diltiazem group was significantly lower up to 5 minutes after extubation**.**

Table4: Comparision of Diastolic Blood Pressure (Mean± SD) among the three groups.

Time	Group I	Group II	Group III	P value
Baseline	83.67±4.405	81.47±4.911	82.2±4.294	>0.05* >0.05† >0.05ǂ
E1	91.97±3.952	79.4±3.276	84.7±3.993	<0.001* <0.001† <0.001ǂ
E2	89.7±3.761	78.5±3.192	83.7±3.734	<0.001* <0.001† <0.001ǂ
E3	87.3±3.415	77.47±3.213	80.97±3.643	<0.001* <0.001† <0.001ǂ
E4	85.4±3.944	76.13±3.579	79.57±3.245	<0.001* <0.001† <0.01ǂ
E5	83.8±3.556	75.1±3.556	79.83±3.354	<0.001* <0.001† <0.001ǂ

*Level of significance between Group I and Group II; † Level of significance between Group I and Group III; ǂ Level of significance between Group II and Group III

Table 5: Comparision of Mean Arterial Blood Pressure (Mean± SD) among the three groups

Time	Group I	Group II	Group III	P value
Baseline	98.1±3.994	96.83±4.976	96.87±3.857	>0.05* >0.05† >0.05ǂ
E1	106±4.034	91.6±3.510	97.67±3.356	<0.001* <0.001† <0.001ǂ
E2	103.6±4.014	90.27±2.993	96.63±3.306	<0.001* <0.001† <0.001ǂ
E3	100.57±2.921	88.93±3.039	93.47±3.148	<0.001* <0.001† <0.001ǂ
E4	98.03±3.285	87.6±3.212	91.97±2.977	<0.001* <0.001† <0.001ǂ
E5	96±2.889	86.27±3.151	89.47±2.874	<0.001* <0.001† <0.001ǂ

*Level of significance between Group I and Group II; † Level of significance between Group I and Group III; ǂ Level of significance between Group II and Group III

Nausea was a common complaint in all the three groups. No patient developed profound hypotension (SBP < 80 mm Hg) or bradycardia (HR < 50 beats per minute) severe enough to require treatment.

DISCUSSION

Tracheal extubation is a stressful period and the cardiovascular changes during extubation are due to multifactorial stimuli, including wound pain, emergence from anesthesia and tracheal irritation. [1,3] Pneumoperitoneum during laparoscopic surgery leads to significant hemodynamic changes such as an increase in MAP and systemic vascular resistance (SVR). [6] The correction of these changes is gradual and outlasts the release of intra-abdominal pressure. [5] Thus, at the end of surgery, these changes add on to the changes provoked by tracheal extubation. The resulting hyperdynamic state could conceivably lead to a precarious hemodynamic situation in patients with cardiac disease. [16]

The effect of diltiazem and lignocaine in controlling hemodynamic changes during extubation has been studied. In a recent study, Ali et al [7] in showed the efficacy of lignocaine given as single bolus dose before induction in providing hemodynamic stability in patients undergoing laparoscopic cholecystectomy. Similarly, Jain et al [17] demonstrated that lignocaine given as IV bolus followed by perioperative infusion reduced the

hemodynamic changes during intubation, extubation as well as attenuated post-operative pain following laparoscopic cholecystectomy. In our study we compared the efficacy of intravenous diltiazem with intravenous lignocaine given as IV bolus before extubation in controlling the hemodynamic responses during extubation in patients undergoing laparoscopic cholecystectomy.

In our study there was a marked rise in HR (23.5%), SBP (5%), DBP (9%) and MAP (8%) from baseline values at 1 minute following tracheal extubation in Group I (control) patients where saline was used.

In Group II where diltiazem was used there were significantly less rise in HR (1.1%) and fall in SBP (8.6%), DBP (2.4%) and MAP (5.2%) at 1 minute following extubation compared to baseline values and these parameters remained stable up to 5 minutes after extubation. The probable effects of diltiazem are due to its direct vasodilator and its negative chronotropic and dromotropic properties. There are studies which have established the role of diltiazem in controlling cardiovascular response to intubation [18] as well as extubation. [3,11,19] Other studies have compared diltiazem with drugs like verapamil, [3] nicardipine [18] and metoprolol. [19] Nishina et al [11] in their study compared the effect of two different doses of diltiazem 0.2 mg/kg and 0.1mg/kg with lignocaine 1 mg/kg during extubation in patients undergoing elective abdominal gynaecologic surgery and showed that the inhibitory effect on cardiovascular responses was greatest with diltiazem 0.2 mg/kg while the extent of attenuation by diltiazem 0.1 mg/kg was similar to lignocaine 1 mg/kg. Also they mentioned that diltiazem 0.3 mg/kg caused hypotension in their preliminary study. In view of this in the present study we employed 0.2 mg/kg of diltiazem to attenuate the stress response and to minimize the side effects of the drug.

In Group III where lignocaine was used, we observed a rise in HR (3.2%), DBP (3.6%), MAP (1%) and fall in SBP (2.3%) compared to the baseline values. These values indicate that lignocaine significantly suppressed the increases in HR and arterial pressure during extubation compared to control group. The beneficial effect of lignocaine is attributed to its suppression of airway reflexes, depression of autonomic nervous system and peripheral vasodilatation. [17] Khan RM et al [13] studied the circulatory changes during extubation of the trachea with or without prior xylocaine (1 mg/kg IV) in patients having coronary artery disease or 2 or more cardiac risk factors. They observed that the circulatory changes in xylocaine group were statistically insignificant as compared to highly significant rise in rate pressure product in the control group. Bidwai et al [2] demonstrated that IV lignocaine 1 mg/kg given 2 minutes before extubation prevented coughing and increases in blood pressure and pulse rate during and after extubation. Other studies have reported better results with combination of lignocaine with other drugs like verapamil [13] or prostaglandin E1. [11] In our study also the attenuating effect of lignocaine was less when compared to that of diltiazem, which is similar to the finding of Nishina et al. [11]

The onset of antihypertensive action of diltiazem (0.2mg/kg) occurs within approximately 30 sec after a single IV injection, with a peak effect occurring at 1.5-2 minutes. The decision to give the drug 2 minutes prior to tracheal extubation was based on this data. The same holds true regarding intravenous lignocaine. None of the patients in our study developed profound hypotension (SBP<80 mmHg) or bradycardia (HR< 50 beats per minute) severe enough to require pressor or sympathomimetic drugs. Incidence of nausea was not statistically different among the three groups.

We concluded that diltiazem 0.2 mg/kg IV and lignocaine 1 mg/kg IV given 2 minutes before extubation significantly attenuated the pressor response to extubation in patients undergoing laparoscopic cholecystectomy. Also, when

intravenous lignocaine and diltiazem were compared we noticed that diltiazem gave better protection than lignocaine. We studied patients with ASA physical status I and II and without any cardiovascular disease. However, further studies are required to evaluate the advantage, beneficial effects and adverse effects of diltiazem and lignocaine in comparison with other drugs when used for the purpose of attenuating the hemodynamic changes associated with extubation in patients with coronary artery disease and cerebrovascular disease specifically in patients undergoing laparoscopic cholecystectomy.

CONCLUSION

Both lignocaine and diltiazem are effective in attenuating the pressor response to extubation in patients undergoing laparoscopic cholecystectomy. The suppressive effect of diltiazem is more than that of lignocaine given IV 2 minutes before tracheal extubation.

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How to cite this article: Thanvi A, Tak ML, Naithani U. Comparison of diltiazem and lignocaine in attenuating hemodynamic responses during extubation in patients undergoing laparoscopic cholecystectomy. Int J Health Sci Res. 2016; 6(7):82-89.

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