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A study on oral clonidine *vis a vis* intravenous lignocaine for attenuation of hemodynamic response to laryngoscopy and endotracheal intubation

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ABSTRACT

Background: Hemodynamic change takes place during procedures like laryngoscopy and endotracheal intubation due to reflex sympathetic discharge caused by epipharyngeal and laryngopharyngeal stimulation before a surgery under general anesthesia. **Aims and Objectives:** The aim of the study was to compare the effectiveness of oral clonidine and intravenous lignocaine as premedicant to obtund the stress response due to such mandatory maneuvers. **Materials and Methods:** A prospective, randomized, double-blind, double dummy-controlled study was undertaken for 11 months at a tertiary care hospital in the eastern part of India. A total (n = 100) patient aged 30 to 50 years of either sex with ASA I and II waiting for elective abdominal surgery were randomized into two equal groups. Group C (n = 50) received (4μg/kg) of oral clonidine 90 minute before laryngoscopy and Group L (n = 50) received 1.5 mg/kg lignocaine 3 minute before laryngoscopy as active drugs and appropriate placebos were administered as double dummy technique. Comparable demographic and base line parameters like heart rate, systolic blood pressure and diastolic blood pressure were recorded at various time intervals. Similar anesthesia technique applied was in both the study arm. **Result:** Attenuation of systolic blood pressure, diastolic blood pressure, heart rate and mean arterial pressure was statistically highly significant ($p < 0.0001$) more in Group C as compared to Group L within first vital 10 minutes of intubation. **Conclusion:** Oral clonidine attenuates the stress response better than intravenous lignocaine during laryngoscopy and endotracheal intubation with minimum adverse effects.

Key words: Clonidine; Lignocaine; Cannulation; Stress response; Diminution

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INTRODUCTION

Laryngoscopy and tracheal intubation like awful stimuli producing pronounced sympathetic response is manifested as tachycardia and hypertension. Circulatory responses to laryngeal and tracheal stimulation were known since 1940 (Reid LC et al.).[1] These hemodynamic changes are generally transitory, variable and unpredictable without sequel. However, in patients with pre-existing coronary artery disease, hypertension and cerebrovascular disease, an increase in these circulatory parameters may precipitate myocardial ischemia, arrhythmias, infarction and even cerebral haemorrhage. These hemodynamic changes due to spontaneous sympathetic discharge resulting

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from epi-pharyngeal and laryngopharyngeal titillation is associated with increased plasma nor-adrenaline concentrations.[2] This increased sympatho-adrenal activity may result in hypertension, tachycardia and arrhythmias.[3,4] Hypertensive patients are more prone to have significant increases in blood pressure whether they have been treated beforehand or not.[5] Momentary hypertension and tachycardia are probably not a matter of concern in healthy individuals but either or both may be precarious to those with hypertension, myocardial inadequacy or cerebrovascular diseases. These laryngoscopic reactions in such individuals may predispose to development of pulmonary oedema[6] myocardial insufficiency[7] and cerebrovascular accident.[8] It is therefore mandatory in such individuals to blunt these harmful laryngoscopic reactions.

Numerous pharmacological strategies have been formulated to lessen the extent of hemodynamic response to laryngoscopy, including high doses of opioids,[9] local anaesthetics like lignocaine,[10] alpha- and beta-adrenergic blockers [11,12] and vasodilating drugs like nitroglycerine.[13] Topical anaesthesia with lignocaine applied to the larynx and trachea in a variety of ways remains a popular method used alone or in combination with other techniques.[14]

The ideal premedicant should be effective and pleasant to be taken orally, have analgesic and non-emetic properties, should not impair cardiovascular stability or depress respiration, should have antisialagogue effect and should effectively alleviate apprehension of the patient.

Intravenous lignocaine having centrally depressant and anti-arrhythmic character was found to reduce the pressor response to laryngoscopy and intubation. Alpha-2 adrenoceptor agonists have been used as premedicant because of their beneficial properties in anaesthesia. The only clinically available alpha-2 adrenergic agonist in our country are clonidine and dexmedetomidine of which clonidine is mainly used as an anti-hypertensive agent, but has many properties of ideal premedicant and also has beneficial effects on haemodynamic during stressful conditions like laryngoscopy and endotracheal intubation.[1] Moreover it attenuates stress responses to painful stimuli, improves the intraoperative hemodynamic stability, reduces the incidence of perioperative myocardial ischemic episodes in patients with suspected or documented coronary artery disease, and decreases anaesthesia requirements during surgery. In an earlier study where, intravenous lidocaine was compared with oral clonidine group, an ambiguous result was found comparing the attenuation of hemodynamic stress responses to laryngoscopy and tracheal intubation with comparatively more side effects observed in the clonidine group.[15] Where as in the study conducted by Marulasiddappa V et al. comparing intravenous lignocaine with intravenous clonidine for similar purpose concluded clonidine to be more effective premedicant.[16]

With the contrasting outcome from different studies conducted earlier, this study was planned and undertaken to compare the effect of intravenous lignocaine and oral clonidine as premedication on hemodynamic change to laryngoscopy and endotracheal intubation in elective surgeries.

MATERIALS AND METHODS

A prospective, randomized, double blinded, double dummy-controlled study was conducted on (n=100) patients of either sex aged 30 to 50 years with ASA grade I and II in a tertiary care hospital inthe eastern part of India, for a period of one 11 months (December 2011 to October 2012). After getting approval from the Institutional Ethical Committee, written informed consent were obtained from the patients with controlled hypertension selective for elective abdominal surgery under general anesthesia. Those who had congestive heart failure (CHF), arrhythmia, BMI ≥ 30, a history of allergies to the study drugs, diabetes, pregnancy, or intubation time more than 15 seconds were excluded. Patients were randomized using online software Random© into Group C (n=50) who received clonidine (4μg/kg) whereas the other Group L (n=50) received anti ulcer agent tablet Pantop© (40mg) as placebo 90 minutes before intubation and group L received 1.5 mg/kg lignocaine as active comparator and group C received normal saline as dummy drug administered in same shape of syringes, 3 minutes before intubation. Hence, the patients, and the anesthetist were unaware of the group allocation. Assessment of study data at the end was done by an independent anesthetist. The base line parameters like systolic blood pressure (SBP) diastolic blood pressure (DBP), heart rate (HR) and Mean Arterial Pressure (MAP) were recorded.

All the baseline parameters were measured at intubation, 1 minute, 3 minute and 10 minutes after intubation respectively. Bispectral Index (BIS) was used for monitoring the depth of anesthesia. The target BIS range was 40-60 for surgical anesthesia. After preoxygenation for 5 minutes, the study patients were given Inj.fentanyl citrate 2 mcg/kg intravenously and induction was done with Inj.propofol 2 mg/kg at a rate of 20 mg/5 second until BIS was below 60. Endotracheal intubation was facilitated with Inj.succinyl choline 1 mg/kg. Anesthesia was maintained with Inj.atracurium 0.5mg/kg as intermediate acting muscle relaxant in bolus and intermittent dose and nitrous oxide and oxygen at the ratio of 66% and 33% respectively. Isoflurane, an inhalational anesthetic was given to maintain the BIS at the range of 40-60. At end of the surgical procedure residual neuromuscular block was reversed

with Inj.neostigmine and Inj.glycopyrrolate in calculated dose. All the patients were shifted to post anesthetic care unit (PACU) after adequate reversal from muscle relaxant. Moist Oxygen was given to all the patients for 2 hours in PACU. Ramsay Sedation Score [17] Was assessed and post-operative blood pressure, heart rate, MAP were monitored for 24 hours for all the patients after surgery.

Statistical Analysis

All recorded data were analyzed using standard statistical methods as student's 't' test or chi square tests where applicable. A sample size of 50 patients in each study group was estimated to detect a 10% reduction in MAP with a power of 85% and drop out of 5%. Statistical analysis was performed using Graph Pad Prism 8©. Normality of the distribution of data was tested by the Kolmogorov-Simirnov test. A p value < 0.05 was considered to be statistically significant.

RESULTS

In total, out of 108 patients scheduled consecutively for elective abdominal surgeries, 5 were excluded due to fulfilling the exclusion criteria and 3 others for laryngoscopy duration of more than 15 seconds. Finally, 100 patients were allocated for statistical analysis. Demographic data were not statistically different between the study groups (Table 1). There was also no significant difference between the two groups of patients regarding HR, SBP and DBP before intubation at baseline before tracheal intubation (Tables 2-4).

There was a significant difference ($p<0.05$) in the heart rate at induction up to 10 minutes after induction between the two groups (Table 2). The patients in the clonidine group showed least variability whereas in the lignocaine group there was a gradual increase in heart rate of the patients. Intraoperative pulse rate of the patients was thoroughly monitored during the whole study period which didn't show any statistically significant change in either of the study arm and hence not represented in this section.

There was a highly significant difference ($p< 0.0001$) in the systolic BP between the two-study groups (Table 3) at the time of induction up to 10 minutes after induction. A gradual rise in systolic BP was noted in the lignocaine group as compared to clonidine group.

While comparing the difference of diastolic BP between the two-study group it was found to be highly significant ($p< 0.0001$) (Table 4) at the time of induction up to 10 minutes after induction. The diastolic BP considerable increased in the lignocaine arm as compared to clonidine arm.

When the mean arterial pressure (MAP) of the two groups were compared it was found that there was statistically highly

Table 1: Demographic characteristics of the patients in both groups

Variables	Group C (n=50)	Group L (n=50)	P value
Age (years)	38.96±5.264	38.02±5.129	0.368
Gender			
Male	24	25	
Female	26	25	
Weight (kg)	55.96 ±4.573	57.4 ±5.321	0.149

Data expressed in mean ± SD

Table 2: Comparison of the heart rate in both the groups

Parameter	Group C (n=50)	Group L (n=50)	P value
Baseline	85.38±6.376	87.20±8.298	0.143
At induction	90.32±7.880	105.40±8.983	0.003
1 min after induction	89.72±7.543	110.88±7.660	0.002
3 min after induction	88.02±7.633	111.62±7.850	0.005
10 min after induction	97.58±8.362	112.30±6.780	0.004

Data expressed in mean ± SD

Table 3: Comparison of the systolic blood pressure (mm of Hg) in both the groups

Parameter	Group C (n=50)	Group L (n=50)	P value
Baseline	119.44±6.952	119.20±7.114	0.865
At induction	109.88±7.880	139.90±8.983	<0.0001
1 min after induction	118.42±6.704	141.84±8.527	<0.0001
3 min after induction	120.82±6.407	142.68±8.213	<0.0001
10 min after induction	124.90±5.901	147.96±22.708	<0.0001

Data expressed in mean ± SD

Table 4: Comparison of the diastolic blood pressure (mm of Hg) in both the groups

Parameter	Group C (n=50)	Group L (n=50)	P value
Baseline	74.52±4.695	77.20±4.743	0.005
At induction	70.18±5.720	88.70±4.087	<0.0001
1 min after induction	74.74±4.993	90.22±3.688	<0.0001
3 min after induction	77.00±4.625	91.14±3.790	<0.0001
10 min after induction	78.92±4.009	91.88±3.931	<0.0001

Data expressed in mean ± SD

Table 5: Comparison of the mean arterial blood pressure (mm of Hg) in both the groups

Parameter	Group C (n=50)	Group L (n=50)	P value
Baseline	91.18±5.16	89.98±5.31	0.2546
At induction	83.2±4.93	105.88±5.15	<0.0001
1 min after induction	88.42±6.08	107.18±4.81	<0.0001
3 min after induction	91.34±4.26	108±4.79	<0.0001
10 min after induction	93.86±3.77	108.96±4.8	<0.0001

Data expressed in mean ± SD

Table 6: comparison of ramsay sedation score in both the study group

Parameter	Group C (n=50)	Group L (n=50)	P value
Ramsay sedation score	1.10	1.10	1.00

significant (p<0.0001) difference (Table 5) in MAP at the time of induction to till the first 10 minutes after induction.

Following completion of surgery Ramsay sedation score was observed to be close to cooperative, orientated and tranquil with no statistically significant difference in both the study groups (Table 6).

DISCUSSION

Laryngoscopy and intubation are associated with a rise in heart rate, blood pressure and incidence of cardiac arrhythmias. There are many elements that influence the cardiovascular variation associated with laryngoscopy and intubation. Age, drugs, type and duration of procedures influence the pressor response. With advancement in age, there is normal variation in the heart rate. Young patients show more extreme changes.[18] Marked fluctuations in haemodynamic response are often seen in geriatric patients.[19,20] In this study, we selected an optimal age range of 30 to 50 years in both study arm with comparable demographic profile and baseline parameters before induction. Readings were taken during laryngoscopy and tracheal intubation at 1, 3 and 10-minutes interval following laryngoscopy and tracheal intubation. We observed that following such manoeuvre, clonidine showed a favourable response towards attenuation of heart rate. A similar finding was evident in a study done by Roy. S. et al [21] where clonidine found to be highly significant in the attenuation of maximum rise in the heart rate when compared to a placebo. While comparing the systolic and diastolic blood pressure of the patients in his study, clonidine had a very significant edge over lignocaine in attenuation of hemodynamic status at various time intervals following induction. Altan et al [22] used clonidine 3 μg/kg intravenously over a period of 15 minutes before induction and 2μg/kg/hour by continuous infusion intraoperatively and found significant reduction in blood pressure. Marulasiddappa V et al.[16] used 2 μg/kg i.v. clonidine and found a significant lowering of heart rate like our study. Kumari et al[23] compared clonidine and midazolam as premedication agents. Clonidine administered before induction and during operation improves perioperative haemodynamic soundness. In the study conducted by Raval and Mehta[24] SBP and DBP came back to baseline 5 minutes after intubation. However, in this study, SBP and DBP remained above baseline even at 10 minutes after intubation in the clonidine group. Unlike the observation of Mohammadi SS et al [15] where there were no significant differences in the MAP in the two study group our study revealed a highly significant difference at the time of induction to till 10 minutes after induction in the clonidine arm as compared to lignocaine arm.

Limitations of the study

There are a few limitations of our study as we have not measured serum levels of stress markers such as cortisol and catecholamines during laryngoscopy and intubation and hence not able to compare the differences in the neuroendocrine responses to laryngoscopy and intubation between the two drugs. Haemodynamic changes associated with two stages i.e. direct laryngoscopy and passage of the tracheal tube into the trachea were not studied separately. Although the bioavailability of oral and intravenous routes of drug administration is different, such difference was not validated by pharmacokinetic study.

CONCLUSION

Oral clonidine appeared to attenuate hemodynamic status of patients in a much superior way than intravenous lignocaine following laryngoscopy and tracheal intubation for abdominal surgery. It is quite reasonable to study with increased sample size of patients to compare the effect of premedication by oral clonidine and other oral drugs with lidocaine on hemodynamic variables after laryngoscopy and tracheal intubation.

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SR, BBG-Concept, design of study and literature search, experimental studies; **AB, PP-**Data acquisition, data analysis, statistical analysis; **AB, DB-** Manuscript preparation; **SS-**Manuscript editing and manuscript review.

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