

## Role of Antiarrhythmics in Attenuation of Haemodynamic Responses.

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### Abstract

**BACKGROUND:** Laryngoscopy and intubation are mandatory for patients undergoing general anesthesia. Direct laryngoscopy and intubation causes afferent vagal stimulation and efferent sympatho-adrenal response, this causes increase in blood pressure (BP), heart rate (HR) and cardiac arrhythmias in some patients. These reflex changes in cardiovascular system are most marked and lead to average increase in blood pressure by 20-40% and increase in heart rate by 20%.<sup>[1]</sup> Usually these changes are well tolerated by healthy individuals. However these changes may be fatal in patients with hypertension, coronary artery disease, intracranial hypertension and aneurysms.<sup>[2]</sup> Certain antiarrhythmics like class Ib antiarrhythmic Mexiletine and class II metoprolol have been studied to attenuate this sympatho-adrenal haemodynamic (pressor) response during intubation.

**AIM:** Role of antiarrhythmics like class Ib antiarrhythmic Mexiletine and class II metoprolol to attenuate haemodynamic (pressor) response during intubation.

**METHODS:** We performed a randomly controlled prospective hospital study, including sixty patients. Patients 25 -45 years of age were taken randomly of both the sexes which were of ASA status 2 to 3, planned for elective surgeries under general anesthesia. After taking informed consent, 60 patients were systematically randomised into three groups A, B and C of 20 each. Patients were kept NPO 8 hours prior and given Tablet Diazepam 0.2mg/kg 2 hr before and buprenorphine 2.5 microgram/kg im 1 hr before surgery on morning of surgery. Group A received 10ml volume of isotonic 0.9%N.S iv. 5 minutes before induction as control, Group B received Mexiletine 150 mg i.v 5 minutes before induction and lastly Group C received metoprolol 2 mg i.v 5 minutes before induction of anaesthesia.

**RESULTS:** In our study heart rate and blood pressure were studied at intubation, 1, 3 minute and 10 minutes time. We concluded both Mexiletine and Metoprolol before induction effectively attenuates haemodynamic responses to laryngoscopy and intubation, though Mexiletine does it more effectively than metoprolol.

**CONCLUSION:** Mexiletine and Metoprolol belonging to class Ib and class II antiarrhythmics respectively administered before induction effectively attenuates haemodynamic responses to laryngoscopy and intubation

**KEY WORDS:** Mexiletine, Metoprolol, Antiarrhythmics, Pressor responses

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### I. Introduction

Laryngoscopy and intubation are mandatory for patients undergoing general anesthesia. Direct laryngoscopy and intubation causes afferent vagal stimulation and efferent sympatho-adrenal response, this causes increase in blood pressure (BP), heart rate (HR) and cardiac arrhythmias in some patients. These reflex changes in cardiovascular system are most marked and lead to average increase in blood pressure by 20-40% and increase in heart rate by 20%.<sup>[1]</sup> Usually these changes are well tolerated by healthy individuals. However these changes may be fatal in patients with hypertension, coronary artery disease, intracranial hypertension and aneurysms.<sup>[2]</sup> The present study was designed primarily to study the effects of Mexiletine and Metoprolol on patient's hemodynamic responses at induction and intubation.

## II. Methods

A hospital based prospective observational study was conducted at the Government Medical College, Srinagar. After obtaining approval from Hospital Ethics Committee, a written informed consent was taken from the patients for participation in this study.

### Exclusion criteria

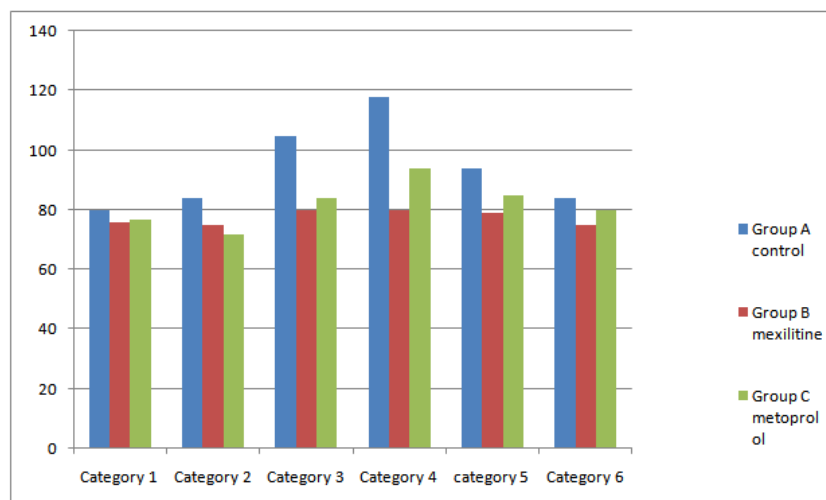
- Anticipated difficult intubation.
- ASA grade III or greater.
- History of Htn, bradycardia and heart blocks preoperatively.
- Pre-existing cardiovascular disease, significant respiratory, renal And hepatic disorder.
- History of drugs( Beat blockers, antiarrhythmics) or alcohol abuse.
- Pregnant women.

Sixty patients were included in the study. The selected individuals were systematically randomised into three groups A, B and C of 20 each. Patients were kept NPO 6 hours prior and given Tablet Diazepam 0.2mg/kg 2 hr before and bupenorphine 2.5 microgram/kg im 1 hr before surgery on morning of surgery. Group A received 10ml volume of isotonic 0.9%N.S iv. 5 minutes before induction as control , Group B received Mexiletine 150 mg i.v 5 minutes before induction and lastly Group C received metoprolol 2 mg i.v 5 minutes before induction of anaesthesia.

During the administration of the preoperative medication patients pulse, blood pressure, and oxygen saturation were monitored. The anesthesiologists in charge of intraoperative management and those responsible for postoperative observation of patient were not aware of the treatment given before anaesthesia in the preoperative room .After this a Ringer lactate infusion at rate of 10ml /kg was started through the intravenous 18G or 20G cannula inserted in a peripheral vein . Injection Ondansetron 0.1mg/ kg and Fentanyl 0.5 µg/kg was given 5 minutes before induction. After 3 minutes of preoxygenation, anaesthesia was induced with Thiopental 5 mg/kg body weight over 30 seconds and injection Atracurium 0.5 mg/kg body weight. All intubations were performed after 3 min, by experienced anesthesiologist. The duration of laryngoscopy and intubation was limited to minimum possible time being similar to all patients. Depending upon the type and duration of surgery all the patients were maintained with 33% Oxygen, 66% Nitrous oxide, 0.4% Halothane and Atracurium 5mg as intermittent boluses. The surgical technique used was identical in the two groups. Arterial pressure and heart rate was measured before induction (baseline); during intubation and 1, 3 and 10 min. after intubation. At the end of the surgery residual neuromuscular blockade was reversed with injection Neostigmine 0.05mg/kg and injection Glycopyrolate 0.01mg/kg and patient extubated. All the observations made in the study were compared for each parameter within the group and intergroup comparison. All the data obtained was analyzed and subjected to subsequent statistical analysis using, student Independent T- test were intergroup means were compared, paired T- tests for intragroup comparisons and Chi Square tests were non-parametric data was compared.

## III. Results

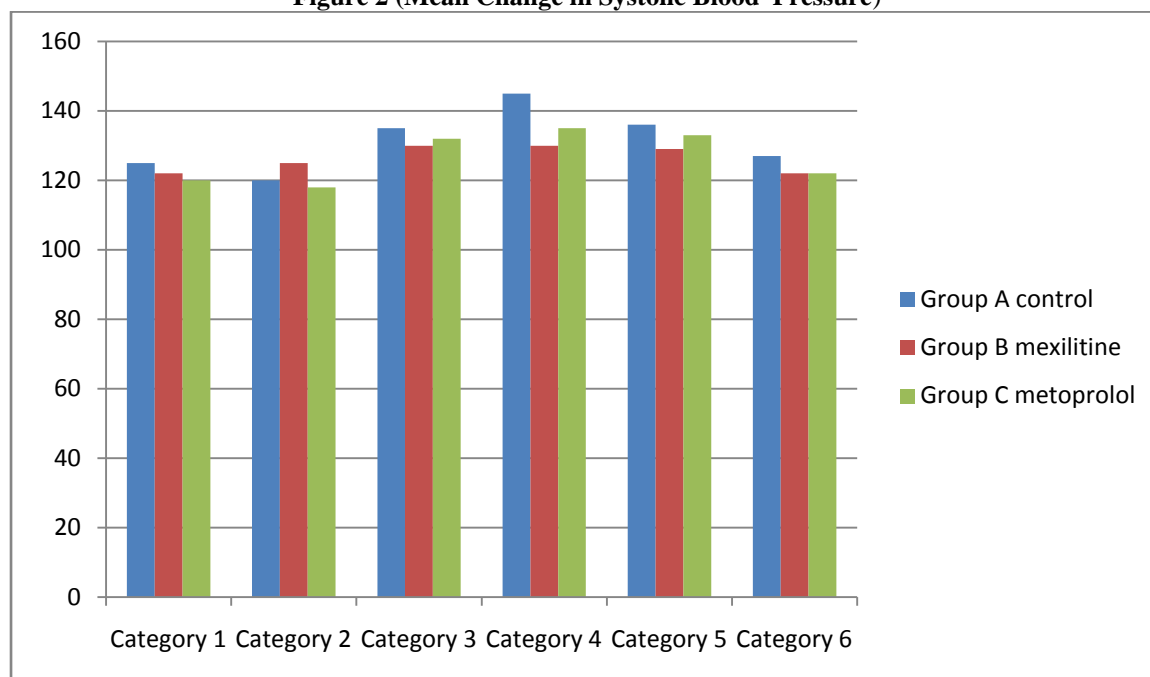
Mean age, sex, mean body weight were measured in all groups and no significant variations were observed.



**Category 1:** Before pre-treatment, **Category 2:** Before Induction, **Category 3:** During Intubation, **Category 4:** One min. following Intubation, **Category 5:** three min. following Intubation, **Category 6:** Ten min. following Intubation

**Figure 1** shows **heart rates** at various stages. Significant control on heart rate is shown in mexilitine and metoprolol group as compared to normal Saline (control) group. Also it depicts mexilitine does control heart rate better than metoprolol group.

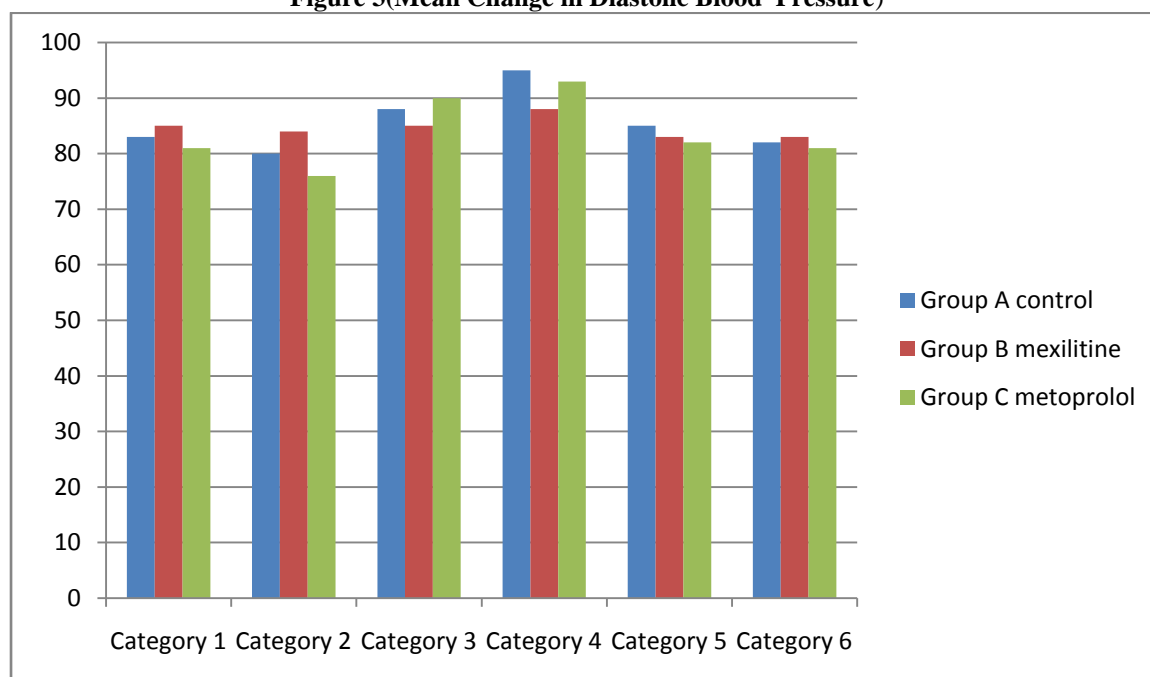
**Figure 2 (Mean Change in Systolic Blood Pressure)**



**Category 1:** Before pre-treatment, **Category 2:** Before Induction, **Category 3:** During Intubation, **Category 4:** One min. following Intubation, **Category 5:** three min. following Intubation, **Category 6:** Ten min. following Intubation

Figure 2 shows changes in Systolic blood pressures( mmHg) in the 3 groups. Showing that both drugs attenuates the increase in Systolic Blood pressure caused by laryngoscopy and intubation but Mexilitine is more effective in doing so.

**Figure 3(Mean Change in Diastolic Blood Pressure)**



**Figure 3** shows changes in Diastolic blood pressures( mmHg) in the 3 groups. Showing that both drugs attenuates the increase in Diastolic Blood pressure caused by laryngoscopy and intubation as compared to control ( Normal Saline). Mexilitine is more effective in doing so.

#### IV. Discussion

Laryngoscopy and intubation causes afferent vagal stimulation and efferent sympatho-adrenal response, this causes increase in blood pressure (BP), heart rate (HR) and cardiac arrhythmias in some patients. These reflex changes in cardiovascular system are most marked and lead to average increase in blood pressure by 20-40% and increase in heart rate by 20%.<sup>[1]</sup> Usually these changes are well tolerated by healthy individuals. However these changes may be fatal in patients with hypertension, coronary artery disease, intracranial hypertension and aneurysms.<sup>[2]</sup> Certain antiarrhythmics like class Ib antiarrhythmic Mexilitine and class II metoprolol have been studied to attenuate this sympatho-adrenal haemodynamic (pressor) response during intubation.

Plasma levels and the effect of orally administered metoprolol on the resting arterial blood pressure and heart rate have been studied during acute and steady-state conditions in patients with mild hypertension. The patients receiving an 80-mg dose had a mean maximum plasma level of about 100 ng/ml plasma in single-dose studies and about 140 ng/ml plasma during steady-state conditions. The corresponding values for the patients on the 50-mg dose were about 60 and 100 ng/ml plasma, respectively. metoprolol markedly reduced the heart rate after the single dose as well as at steady state.<sup>(3)</sup>

Metoprolol is as effective as propranolol in the reduction of angina attacks and improvement in exercise tolerance during chronic therapy in patients with uncomplicated angina pectoris. It is now appropriate to study the effects of metoprolol in patients with coronary artery disease in whom the harmful effects of non-selective beta-blockade heretofore have precluded optimal therapy with beta-blocking drugs.<sup>(4)</sup>

Mexilitine a antiarrhythmic is quite effective in the management of ventricular dysrhythmias both inside operation theatre as well as outside.<sup>(5)</sup>

The efficacy of intravenous mexilitine in attenuating the cardiovascular responses to laryngoscopy and tracheal intubation was studied in 30 normotensive patients undergoing elective surgery. The patients were randomly allocated to one of three treatment groups: saline (n = 10); 2 mg/kg mexilitine (n = 10); and 3 mg/kg mexilitine (n = 10). The placebo/mexilitine was administered immediately before induction of anaesthesia using 5 mg/kg thiopentone and tracheal intubation was facilitated with 0.2 mg/kg vecuronium; laryngoscopy lasting 30 s was attempted 2 min after induction of anaesthesia. All groups showed a significant (P less than 0.05) increase in mean arterial pressure and heart rate associated with tracheal intubation. The increase in mean arterial pressure was significantly (P less than 0.05) smaller in patients receiving 3 mg/kg mexilitine compared with those receiving either saline or 2 mg/kg mexilitine. There was no significant attenuation in heart rate in either of the mexilitine treatment groups compared with the saline group. It is concluded that 3 mg/kg mexilitine given intravenously provides a simple and effective method for attenuating the pressor response to laryngoscopy and tracheal intubation.<sup>(6)</sup>

Likewise Cardiovascular responses to anaesthesia beta-adrenoreceptor blockade with metoprolol provides a simple and effective method for attenuating the pressor response to laryngoscopy and tracheal intubation.<sup>(7)</sup>

Cardiovascular responses to endotracheal intubation were recorded in three groups of 15 subjects each. Following induction, group B and C received Mexilitine 200 mg oral and Mexilitine 150 mg i.v., respectively, in addition to nitrous oxide in oxygen for maintenance. Arterial pressure, heart rate and rate-pressure products were monitored during intubation and at 1, 3 and 10 min after intubation. In group A which did not receive Mexilitine intubation was associated with increases in heart rate, mean arterial pressure and rate- pressure product. In group B (oral Mexilitine) there was no rise in arterial pressure but increases in heart rate and rate-pressure product occurred. In group C no changes in these parameters occurred after intubation. ECG changes were also negligible in the group receiving i.v. Mexilitine.<sup>(8)</sup>

Mexilitine is a type I antiarrhythmic drug that is structurally similar to lidocaine. Mexilitine has considerable potential for causing neurologic, cardiac, or gastrointestinal side effects. However, mexilitine does not undergo clinically significant first-pass metabolism and, thus, has good oral bioavailability. Mexilitine has a large and variable volume of distribution and an elimination half-life ranging from 6 to 12 hours. Mexilitine disposition is probably altered in patients with heart failure, liver disease, and severe renal dysfunction. Efficacy and toxicity are not well correlated with mexilitine serum concentrations. Mexilitine is as effective as traditional antiarrhythmics in the treatment of premature ventricular contractions. However, in patients with drug-refractory inducible ventricular tachycardia, mexilitine is usually ineffective when used alone. When mexilitine is combined with other antiarrhythmic agents, a significantly higher percentage of patients with this difficult arrhythmia have a good response. Mexilitine is a potentially important addition to the existing

antiarrhythmic drugs currently available, but its place in the clinical setting and in therapeutic drug monitoring is not well defined at this time.<sup>(9)</sup>

Mexiletine is an antiarrhythmic agent with structural and electrophysiologic properties similar to those of lidocaine. Mexiletine decreases ventricular automaticity while shortening both action potential duration and effective refractory period. The drug may be administered orally or intravenously. Hepatic metabolism is the major route of elimination. The elimination half-life is approximately 10 hours, but longer in patients with acute myocardial infarction, chronic congestive heart failure or hepatic insufficiency. Mexiletine suppresses ventricular ectopy in the acute phase of myocardial infarction. The drug is effective for some patients in whom lidocaine has failed. It suppresses chronic ventricular ectopy and is well tolerated in approximately two-thirds of stable outpatients treated with this agent. In that population, mexiletine is comparable in efficacy to quinidine, procainamide and disopyramide. It is effective in 30-50% of patients with ventricular arrhythmias refractory to other antiarrhythmic drugs. In patients with refractory arrhythmias, the efficacy of mexiletine may be enhanced by combination with propranolol, quinidine or amiodarone. Adverse reactions limit use of mexiletine in approximately 20% of patients. Gastrointestinal and central nervous system side effects are the most common. Mexiletine does not depress myocardial function. Aggravation of arrhythmias is uncommonly observed. The usual intravenous dose of mexiletine is 150-250 mg over at least 10 minutes. Long-term oral dosages are usually 200-300 mg 3 or 4 times daily.<sup>(10)</sup>

**Conflict of Interests:** The authors declare that there is no conflict of interests regarding publication of this paper.

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