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Effect of oral Clonidine premedication before anaesthesia: Double blindprospective randomized study.

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Abstract:

Background: Haemodynamic fluctuations, higher myocardial oxygen demand and cardiac arrhythmia are undesirable but inevitable side effects of laryngoscopy and endotracheal intubate on. This is a concern in all patients especially in patients with coronary artery disease, valvular heart disease, elevated intracranial pressure and cerebrovascular disease.The induction of anesthesia, laryngoscopy, tracheal intubation and surgical stimulation often evoke cardiovascular responses characterized by alteration in systemic arterial blood pressure, heart rate and cardiac rhythm. The response following laryngoscopy and intubation often peaks at 1.2 minutes and return to baseline within 5 to 10 minutes. **Objective:**to study the influence of clonidine to attenuate the hemodynamic responses associated with laryngoscopy and endotracheal intubation. **Methodology:**The Present prospective Randomized control study was conducted on 60 patientswho underwent elective surgery under general anesthesia during the period of 1st February 2021 to 30th August 2021 at Karnataka Institute of Medical Sciences, Hubballi . Adult patients aged between 18-65 years belonging to ASA physical status 1and 2, of either gender undergoing surgical procedures under general anesthesia requiring endotracheal intubation were included in the study.. All the patients included in the study were randomized into 3 groups Group CL-1: Patients who received oral Clonidine premedication at the dose of 1 microgram per kg . Group CL-2: Patients who received clonidine premedication at the dose of 2microgram per kg .Group CS: Patients who received premedication with oral saline.**Results :**In the present study we had the mean age as 45.60 years, 43.45 years and 46.10 years in the Group CL-S, Group CL-2 and Group CL-1 respectively.In all groups, 60% of cases were Cormack-Lehane grade 1, 10 % were grade 2a and the rest were grade 2b. In the present study when we evaluated the heart rate, systolicblood pressure, diastolic blood pressure and the respiratory rate in various study groups we had at the time of induction; there was no

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statistical significance between the groups just before laryngoscope with a p value by ANOVA being more than 0.05. But immediately after intubation and 1 minutes, 3 minutes and 5 minutes after intubation there was a statistical significance between the groups with the p value by ANOVA more than 0.05. **Conclusion:**Administration ofclonidine provides haemodynamic stability and attenuates the stress response to laryngoscope and intubation.

KEYWORDS: Clonidine, Hemodynamic, Premedications, Intubation

INTRODUCTION

Haemodynamic fluctuations, higher myocardial oxygen demand and cardiac arrhythmia are undesirable but inevitable side effects of laryngoscopy and endotracheal intubate on [1-4] .This is a concern in all patients especially in patients with coronary artery disease, valvular heart disease, elevated intracranial pressure and cerebrovascular disease. [5, 6]

In 1951, King et al [7] highlighted this and since then, numerous pharmacological agents have been tried to attenuate ill desired hemodynamic response [8-12].

The induction of anesthesia, laryngoscopy, tracheal intubation and surgical stimulation often evoke cardiovascular responses characterized by alteration in systemic arterial blood pressure, heart rate and cardiac rhythm[1]. The response following laryngoscopy and intubation often peaks at 1.2 minutes and return to baseline within 5 to 10 minutes.

Though the sympathoadrenal responses are probably of little consequence in healthy patients, it is hazardous to those patients with hypertension, coronary heart disease, cerebrovascular disease, intracranial pathology and hyperactive airways. In such cases, reflex circulatory responses such as an increase in heart rate, systemic arterial pressure and disturbances in cardiac rhythm need to be suppressed [1-4].

Clonidine is a centrally acting alpha-2 adrenergic agonist. It acts on presynaptic alpha-2 receptors in the vasomotor center in the brain stem .This binding decreases presynaptic calcium a level, thus inhibiting the release of nor-epinephrine .The net effect is decrease in sympathetic tone, causing decrease in peripheral vascular resistance, thus lowering the blood pressure [13]

The induction of anesthesia, laryngoscopy, tracheal intubation and surgical stimulation often evoke cardiovascular responses characterized by alteration in systemic arterial blood pressure, heart rate and cardiac rhythm[1]. The response that follows laryngoscopy and intubation peaks at 1.2 minutes and returns to baseline within 5 to 10 minutes.

Though the sympathoadrenal responses are probably of little consequence in healthy patients, it is hazardous to those patients with hypertension, coronary heart disease, cerebrovascular disease, intracranial pathology and hyperactive airways. In such cases, reflex circulatory responses such as an increase in heart rate, systemic arterial pressure and disturbances in cardiac rhythm need to be suppressed.

Premedication with clonidine blunts the stress response to surgical stimuli and the narcotic and anesthetic dose can be reduced. Furthermore, perioperative myocardial ischemic events can be prevented by preoperative application of clonidine. Oral

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clonidine at a dose of 1.5-2 mcg/kg BW combines the advantages of benzodiazepines and opioids: anxiolysis, sedation and analgesia with stable hemodynamics and respiration [14-18]

Clonidine does not have opioid related side effects such as nausea and vomiting. Doses of up to 5 mcg/kg BW have been administered to young and healthy patients preoperatively in dental and maxillofacial surgery without significant side effects. However, lower doses of oral Clonidine should be an adequate oral premedication dose for young and healthy patients. Bradycardia is a contraindication for the use of clonidine[8].

Oral clonidine has lesser hypotensive effect,when compared to iv clonidine,whereas the anxiolytic effect is as good as iv clonidine. But a larger dose of clonidine can cause persistent hypotension, bradycardia which is not ideal for patient with ischemic heart disease and hypertensive patients [14-18].

A Study concluded that oral Clonidine given as premedication prior to the surgery blunts the stress response to laryngoscopy and intubation [15]

Hence, we propose to study the influence of clonidine to attenuate the hemodynamic responses associated with laryngoscopy and endotracheal intubation.

MATERIALS AND METHODS

Source of data

The Present prospective Randomized control study was conducted on 60 patients in who underwent elective surgery under general anesthesia during the period of 1st February 2021 to 30th August 2021 at Karnataka Institute of Medical Sciences, Hubballi.

Inclusion Criteria:

Adult patients aged between 18-65 years belonging to ASA physical status 1and 2,of either gender undergoing surgical procedures under general anesthesia requiring endotracheal intubation.

Exclusion Criteria:

1.Patients with hypertension
2.Ischemic heart disease
3.BMI >25
4. Patients on beta blockers
5. Patients with known or anticipated difficult airway are also excluded from the study.
6. Duration of Laryngoscopy>1Min
7.More than 1 attempt of intubation
8.Laryngoscopic grade >2B

Methods of collection of data

Plan of study:

This study was carried out strictly in compliance with the ethical guidelines laid down by Declaration of Helsinki and ICMR bioethical guidelines 2006. Ethical clearance was obtained from the Institutional Dissertation committee before commencing the study.

Patients who were posted for surgery under general anesthesia were evaluated to confirm that they met the inclusion and exclusion criteria. Those chosen, underwent

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pre-anesthetic checkup. A written informed consent was obtained from those patients who were willing to be a part of the study.

On the day prior to surgery, a thorough evaluation of all the patients was done again Standard premedication night prior to surgery and on morning of surgery included the following,

1.Tab Rabeprazole 20 mg -Night and morning of surgery

2.Tab Domperidone 10mg-Night and morning of surgery

Group CL-1 and Group CL-2 patients were premeditated with oral Clonidine 60 minutes prior to the surgery.

RANDOMISATION: All the patients included in the study were randomized into 3 groups

- Group CL-1: Patients who received oral Clonidine premedication at the dose of 1 microgram per kg
- Group CL-2: Patients who received clonidine premedication at the dose of 2microgram per kg
- Group CS: Patients who received premedication with oral saline.

INVESTIGATOR 1: Primary Investigator (consultant Anaesthesiologist) who is unaware as to which Group the patient belongs performs laryngoscopy and endotracheal intubation.

INVESTIGATOR 2: Consultant Anesthesiologist /Anesthesiology resident who gave the drugs as per protocol and notes down all the data.

INDUCTION SEQUENCE:

After shifting the patient inside the operating room noninvasive blood pressure, saturation probe and electrocardiogram monitoring with 5 leads were attached and baseline values were recorded.

All the patients were preoxygenated with 100% oxygen for 3mins and iv fentanyl 2 mcg/ kg was injected.

Anaesthesia was induced with I.V Propofol 2 mg per kg and loss of response to verbal stimuli was confirmed. On confirming, the ability to bag and mask ventilate, patient wasparalyzed with iv Vecuronium 0.1 mg/kg and anesthesia deepened with Isoflurane.

Patient was ventilated with Isoflurane and oxygen for 3 mins and muscle relaxation confirmed with PNS (TOF 0/4).

Consultant Anaesthesiologist (Investigator1) who was blinded to the drug given shall attempt direct laryngoscopy and endotracheal intubation.

Duration of laryngoscopy and intubation (from the time laryngoscope inserted till the end tidal CO2 is seen on the monitor) was noted, grade of laryngoscopy, heart rate, systolic, diastolic and mean blood pressures were noted at the time of induction, just before laryngoscopy, immediately after intubation and 1,3 and 5mins after intubation by investigator 2.

For patients in whom intubation time (laryngoscopy+intubation) was more than 1 min, were excluded from the study.

Statistical Analysis:

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The data was entered and managed in Excel. Data was analyzed using Student t test for continuous variable and Fisher`s exact test for categorical variable. Non- parametric test was used for data if they were not normally distributed. Numericaldata analysis was done using one-way ANOVA test. Intra Group variable was analyzed using repeated measures of ANOVA test.

OBSERVATION & RESULTS

In the present study we had the mean age as 45.60 years,43.45 years and 46.10 years in the Group CL-S, Group CL-2 and Group CL-1 respectively. There was no significant difference between the groups, the p value by ANOVA was more than 0.05 hence the groups are comparable.

In the present study we had the 10, 11 and 10 males and 10,9 and 10 females in the Group CS, Group CL-2 and Group CL-1 respectively. There was no significant difference between the groups, the p value by ANOVA was more than 0.05.Hence the groups are comparable.

In all groups,60% of cases were Cormack-Lehane grade 1, 10 % were grade 2aand the rest were grade 2b. All the groups were comparable with a p =1.

In the present study when we evaluated the heart rate, systolicblood pressure, diastolic blood pressure and the respiratory rate in various study groups we had at the time of induction; there was no statistical significance between the groups just before laryngoscope with a p value by ANOVA being more than 0.05. But immediately after intubation and 1 minutes,3 minutes and 5 minutes after intubation there was a statistical significance between the groups with the p value by ANOVA more than 0.05.Highest difference was notedimmediately after intubation. There was least variation in those who received 2 mg clonidine than those who received 1 mg clonidine as compared to the placebo saline group. Heart rate was higher in the saline group as compared to the test groups,clonidine 1 mcg group had a higher rate than clonidine 2 mcg group.

In group CL-1 and in group CL-2,after a slight fall of Mean Arterial Pressure following premedication (by 3.69% from baseline) and more during induction (by 17.05% from baseline), it remained persistently below baseline even during intubation, surgical incision, and till 45 minutes where the MAP was just above baseline by 0.50%.MAP showed maximum rise during reversal and extubation.

During inter group comparison it is clearly noticed that MAP values in both the groups CL-1 and CL-2 were significantly different ($P < 0.05$), MAP being significantly low in group CL-1 and in group CL-2 at all points when compared to the corresponding values in Group C. MAP values in group CL-2 were lesser than in group CL-1. The exaggerated fall in MAP in Clonidine group could be due to potentiation of hypotensive effects of propofol and fentanyl by Clonidine.

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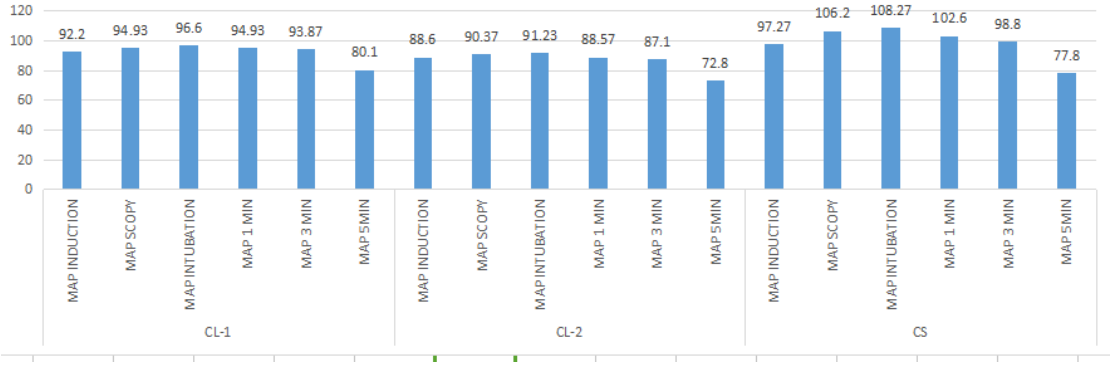

GRAPH 1: MAP DISTRIBUTION IN THE STUDY AT VARIOUS TIME

TABLE 1: THE SIGNIFICANCE OF HEMODYNAMIC VARIATIONS AT VARIOUS TIME INTERVALS

P VALUE	-at the time of induction	-just before laryngoscope	-immediately after intubation	-1minute after intubation	-3 minute after intubation	-5 minute after intubation
MAP	0.011	0.015	0.012	0.19	0.022	0.0001
DBP	0.031	0.035	0.023	0.036	0.0001	0.0001
SBP	0.025	0.02	0.013	0.01	0.0001	0.0001
HEART RATE	0.015	0.02	0.0001	0.0001	0.0001	0.0001

DISCUSSION

Haemodynamic fluctuations, higher myocardial oxygen demand and cardiac arrhythmia are undesirable but inevitable side effects of laryngoscopy and endotracheal intubation. This is a concern in all patients especially in patients with coronary artery disease, valvular heart disease, elevated intracranial pressure and cerebrovascular disease.

Various techniques and pharmacological agents have been used to counteract these detrimental effects. Clonidine, a centrally acting alpha-2 adrenergic agonist, which was first introduced into clinical practice as an antihypertensive medication, has been recently used for anaesthetic premedication, providing sedative, anxiolytic, and analgesic effects. Clonidine also attenuates hypertension, tachycardia, and nor-epinephrine release in response to stress induced by anaesthetic and surgical procedures.Even in a recent editorial, Longnecker who referred to marked haemodynamic responses in the peri-operative period as ‘alpine anaesthesia’, had suggested that clonidine may modify the valleys and peaks during this period.

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At present, the only clinically available Alpha-2 adrenergic agonist for oral use in our country is Clonidine.[14] Though mainly used as an anti-hypertensive agent, it has many properties of an ideal premedicant and also has beneficial effects on haemodynamics during stressful conditions like laryngoscopy and endotracheal intubation Clonidine, an imidazoline derivative, is well absorbed when given orally and is completely used in the body. The pharmacological effect of Clonidine appears in 1.5- 2 hours, with the peak level in 3 hours.[23,24]

This double blind prospective randomized study was undertaken to evaluate effectiveness of oral Clonidine premedication at 2 different doseSas a pre-anaesthetic medication and as a drug to attenuate the peri-operative haemodynamic alterations during elective surgeries. .

The dose of oral Clonidine as premedication in our study was approximately in the dose 1 and 2 microgram per kilogram (mcg/kg). Dose of oral clonidine, in various other studies ranged from 2 to 5 mcg/kg.

Aho et al[11]had compared 3 mcg/kg and 4.5 mcg/kg oral clonidine for suppression of haemodynamic response and they observed, rise in blood pressure and heart rate was less in both the groups but 4.5 mcg/kg of clonidine produced greater fall in MAP beforeinduction. Hence, they recommended 3 mcg/kg of clonidine for perioperative haemodynamic stability.

Yu et al, observed haemodynamic stability during pneumoperitoneum with 150 mcg oral Clonidine.[12]

During intergroup comparison, it was seen that mean HR in Group CL-2 was significantly low ($P < 0.05$) at all points after premedication with Clonidine.Thus, rise in HR in group CL-1 and in group CL-2 was significantly less as compared to that in Group C ($P < 0.001$).

In the present study when we evaluated the mean arterial pressure, in the various study groups we had at the time of induction there was no statistical significance between the groups just before laryngoscope with a p value by ANOVA was more than 0.05.but immediately after intubation and 1 minutes,3 minutes and 5 minutes after intubation there was a statistical significance between the groups with the p value by ANOVA was more than 0.05.Highest difference was noted atimmediately after intubation. There was least variation in those who received 2 mcg clonidine as those who received 1 mcg clonidine as compared to the placebo saline group.

Hemodynamic fluctuations during laryngoscopy and intubation was less in group CL than in group C which could be explained by the central and peripheral attenuation of sympathetic outflow by clonidine.

CONCLUSION

Administration ofclonidine provides haemodynamic stability and attenuates the stress response to laryngoscope and intubation.

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