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To study the effects of low dose oral clonidine premedication in attenuating the haemodynamic response to laryngoscopy and intubation

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Abstract
Background: 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
Aim: Efficacy of low dose of clonidine in attenuating the haemodynamic response to intubation. Comparing two doses of oral clonidine in attenuating haemodynamic response to intubation.
Materials and Methods: The study will be conducted on 60 patients who will be undergoing elective surgery under general anesthesia during the period of 2017 to 2019.
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.
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.
Duration of laryngoscopy and intubation (from the time laryngoscope inserted till the end tidal CO_2 is seen on the monitor) was noted, grade of laryngoscopy, heart rate, systolic diastolic and mean blood pressures are noted at the time of induction, just before laryngoscopy, immediately after intubation and 1,3 and 5mins after intubation by investigator 2.
Results: In the present study when we evaluated the heart rate,SBP,DBP,MAP. There was least variation HR, SBP, DBP and MAP, in those who received 2 mg clonidine as those who received 1 mg clonidine as compared to the placebo saline group
Conclusion: administration of clonidine provides haemodynamic stability and attenuates the

stress response to laryngoscope and intubation.

Keywords: Clonidine, pressor response, hemodynamic response to laryngoscopy

Introduction

Haemodynamic fluctuations, higher myocardial oxygen demand and cardiac arrhythmia are undesirable but inevitable side effects of laryngoscopy and endotracheal intubation [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 [8-10].

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

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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 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. Clonidine does not have opioid related side effects such as nausea and vomiting. Doses of up to 5 microg/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 clonidine8.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

A Study conducted the authors concluded that oral Clonidine given as premedication prior to the surgery blunts the stress response to laryngoscopy and intubation

Here we propose to study the influence of clonidine to attenuate the hemodynamic responses

associated with laryngoscopy and endotracheal intubation.

Aim

Efficacy of low dose of clonidine in attenuating the haemodynamic response to intubationIncrease in Blood pressure heart rate in response to stress of intubation will be studied.
Comparing two doses of oral clonidine in attenuating haemodynamic response to intubation

Materials and Methods
Source of data

The study will be conducted on 60 patients in our institution, who will be undergoing elective surgery under general anesthesia during the period of 2020 to 2021

Type of study

Prospective, randomized comparative study.

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. Laryngoscope 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 preanesthetic 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 was paralyzed 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 CO_2 is seen on the monitor) was noted, grade of laryngoscopy, heart rate, systolic diastolic and mean blood pressures are noted at the time of induction, just before laryngoscopy, immediately after intubation and 1,3 and 5mins after intubation by investigator 2.
For pts.In whom intubation time (laryngoscopy+intubation) is more than 1 min were excluded from the study.

Sample size calculation

With reference to previous conducted study by Abhishek Chatterjee *et al.* in 2015 of I.V. lignocaine versus oral clonidine for attenuation of hemodynamic response to laryngoscopy and endotracheal intubation.To detect a mean difference of heart rate of 5 beats per minutes, (with standard deviation of 5) we need sample size of 17 in each Group (with power of 80% and alpha error of 0.05) While considering 10% dropouts in each Group we include 20

subjects in each.

Results

In the present study when we evaluated the heart rate 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 mg clonidine as those who received 1 mg clonidine as compared to the placebo saline group.
In the present study when we evaluated the systolicblood 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 mg clonidine as those who received 1 mg clonidine as compared to the placebo saline group.
In the present study when we evaluated the diastolic blood 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 mg clonidine as those who received 1 mg clonidine as compared to the placebo saline group.
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 mg clonidine as those who received 1 mg clonidine as compared to the placebo saline group.

Table 1: Pulse distribution in the study at various time

Group	HR-at the time of induction	HR-just before laryngoscope,	HR-immediately after intubation	HR -1minute after intubation by investigator	HR-3 minute after intubation by investigator	HR-5 minute after intubation by investigator
Group CL-1 MEAN	65.45	75.45	71.50	67.55	66.55	71.50
Group CS MEAN	75.93	92.80	94.80	96.80	98.80	64.60
Group CL-2 MEAN	69.30	65.35	63.70	63.90	64.55	65.35
p value (ANOVAs)	0.05	0.0030	0.0001	0.0001	0.0001	0.0001

Table 2: Systolic blood pressure distribution in the study at various time intervals

Group	SBP-at the time of induction	SBP-just before laryngoscopy,	SBP-immediately after intubation	SBP -1minute after intubation by investigator	SBP-3 minute after intubation by investigator	SBP-5 minute after intubation by investigator
Group CL-1 MEAN	114.55	111.55	109.55	107.55	107.55	110.55
Group CS MEAN	114.80	104.80	95.40	96.53	97.13	83.47
Group CL-2 MEAN	115.95	113.95	112.60	111.95	111.70	110.40
p value (ANOVAs)	0.056	0.0060	0.0030	0.0001	0.0001	0.0001
statistically significance	ns	S	S	s	s	S

Table 3: Diastolic blood pressure distribution in the study at various time intervals

Group	DSBP-at the time of induction	DSBP-just before laryngoscopy,	DSBP-immediately after intubation	DSBP-1minute after intubation by investigator	DSBP-3 minute after intubation by investigator	DSBP-5 minute after intubation by investigator
Group CL-1 MEAN	83.40	81.40	79.40	77.40	75.40	79.40
Group CS MEAN	83.33	71.33	69.33	67.33	65.33	65.33
Group CL-2 MEAN	84.45	82.45	80.45	78.45	76.45	75.70
p value (ANOVAs)	0.89	0.0001	0.0001	0.0001	0.0001	0.0001

Table 4: Map distribution in the study at various time intervals

Group	MAP-at the time of induction	MAP-just before laryngoscope,	MAP-immediately after intubation	MAP-1minute after intubation by investigator	MAP-3 minute after intubation by investigator	MAP-5 minute after intubation by investigator
Group CL-1 MEAN	93.78	91.45	89.45	87.45	86.12	89.78
Group CS MEAN	93.82	82.49	78.02	77.07	75.93	71.38
Group CL-2 MEAN	94.95	92.95	91.17	89.62	88.20	87.27
p value (ANOVAs)	0.91	0.0470	0.0034	0.0001	0.0001	0.0001
statistically significance	ns	S	S	s	S	S

Discussion

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

At present, the only clinically available Alpha-2 adrenergic agonist for oral use in our country is Clonidine. 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.

This double blind prospective randomized study was undertaken to evaluate effectiveness of oral Clonidine premedication at 2different doseS as 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.*[16] 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 before [17]induction. So they recommended 3 mcg/kg of clonidine for perioperative haemodynamic stability.

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. this rise in HR in group CL-1 and in group CL-2was 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 mg clonidine as those who received 1 mg clonidine as compared to the placebo saline group.

In group n group CL-1 and in group CL-2after a slight fall following premedication (by 3.69% from baseline) and more during induction (by 17.05% from baseline), MAP 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 were significantly different (P <0.05), MAP being significantly low in n group CL-1 and in group CL-2at all points when compared to the corresponding values in Group C.WITH n group CL-1 lesser than group CL-2. The exaggerated fall in MAP blood pressure Clonidine group could be due to potentiation of hypotensive effects of propofol and fentanyl by Clonidine.Also the exaggerated rise in blood pressure recorded 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.

These are comparable with the studies below

Kotwani DM *et al.*[18] who concluded that Oral clonidine premedication (150 micrograms) is safe and provides perioperative hemodynamic stability in ASA I and II patients undergoing laparoscopic cholecystectomy, and hence can be recommended as a routine premedication for laparoscopic procedures.

Conclusion

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

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