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The Clinical Evaluation of Oral Clonidine as Premedication Used in Attenuating Cardiovascular Changes During Laparoscopy.

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ABSTRACT

Background: To evaluate oral clonidine as premedication used in attenuating cardiovascular changes during laparoscopy. **Methods**: The present study was carried out on 60 patients in the age group of 20-50 years of ASA grade I and II posted for elective laparoscopic surgery under general anesthesia. They were randomly divided in two groups of 30 patients each, receiving tablet Vit. C as placebo (group P) and tablet clonidine 150 microgram (group C) as premedication 90 min prior to induction of anesthesia. We compared both groups for changes in mean arterial pressure, ECG, HR, were recorded 2 hours prior to induction, immediately after intubation, after 5 minutes of insufflation of pneumoperitoneum and after 10 minutes of release of pneumoperitoneum. **Results:** Mean arterial pressure and mean heart rate increased immediately after intubation, 5 minutes after insufflation, and 10 minutes after release of pneumoperitoneum in both groups but rise was significantly greater in placebo group. **Conclusion**: We conclude that premedication with tablet clonidine 150microgram has been found relatively safe and effective method to provide stable hemodynamics intraoperatively and protection against stress response triggered by pneumoperitoneum in laparoscopic surgeries.

Keywords: Oral clonidine, premedication, cardiovascular changes, laparoscopy.

INTRODUCTION

Preanaesthetic medication has two fold purpose It serves to prepare a patient for anaesthesia by providing a state of acquiescence to the induction of anaesthesia and by obtunding nervous system activity.[1,2] It serves to contribute to anaesthetic state and reduce the anaesthetic drug requirement.

Clonidine As Preanaesthetic Medication

Clonidine , an alpha-2 adrenergic receptor agonist, in oral dose of 5 microgram/kg has been shown to be safe and effective drug to achieve preoperative blood pressure control in mild to moderate hypertension. Clonidine is a useful drug for premedication because it produces sedation and anxiolysis. Clonidine premedication has assured improved perioperative cardiovascular stability. Oral clonidine premedication attenuates cardiovascular response to laryngoscopy and intubation which appears to be Superior to either lidocaine or fentanyl pretreatment. It reduces the doses of commonly used intravenous induction agents. It effectively reduces peripheral sympathetic tone. Clonidine premedication results in significant reduction in plasma catecholamines level, either during rest or exercise. It has potent analgesic property. Clonidine premedication in narcotic based anaesthetic techniques reduces the dose requirements, as in patients undergoing coronary artery bypass surgery. It inhibits bronchospasmic response to noxious stimuli. Oral clonidine premedication in heavy smokers reduces their nicotine dependence and craving. It reduces the MAC values of inhalation agents. Laparoscopic surgery has advantages like cosmetic scar, less post-operative pain, decreased hospital stay, and obviously less mortality. But apart from these advantages; pneumoperitonium required for this procedure affects several systems leading to alternation in cardiovascular, respiratory, stress response and acid- base physiology.

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Pharmacology of Clonidine

Chemistry: Clonidine is centrally acting selective partial aplha -2 agonist (2220:1 alpha-2 to alpha-1) acts by virtue of its ability to decrease sympathetic nervous system out flow from the central nervous system.

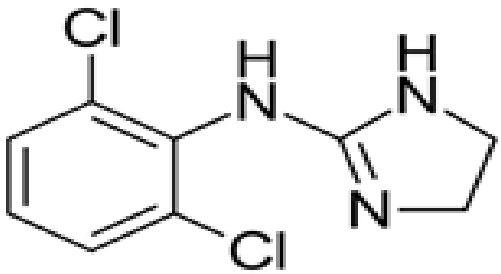

Figure 1: Clonidine

Alpha-2A receptor mediate sedation, analgesia and sympatholytic action. Whereas alpha-2B mediates vasoconstriction and possibly antishivering effects. The startle response may reflect activation of alpha-2c receptors. Alpha-2 receptors are present in the pontine locus ceruleus, an important source of sympathetic nervous system innervations of the forebrain and a vital modulator of vigilance.

Clonidine stimulates alpha-2 adrenergic inhibitory neurons in the medullary vasomotor centre. As a result, there is decrease in sympathetic nervous outflow from central nervous system (CNS) to peripheral tissues. Decreased sympathetic nervous system activity is manifested as peripheral vasodilatation and decrease in systemic blood pressure, heart rate and cardiac output. The ability of clonidine to modify the function of potassium channels in the CNS (cell membranes become hyperpolarized) may be the mechanism for profound decrease in anaesthetic requirements produced by clonidine.

Pharmacokinetics

Clonidine is rapidly absorbed after oral administration and reaches peak plasma concentration within 60 to 90 minutes. The elimination time of clonidine is between 9 to 12 hours, with approximately 50% metabolised in liver whereas rest is excreted unchanged in urine. The duration of hypotensive effect after a single oral dose is 8 hours.

Pharmacodynamics

Cardiovascular effects: The decrease in systolic blood pressure produced by clonidine is more prominent than the decrease in diastolic blood pressure.

Respiratory effects: Alpha-2 agonists have minimal depressant effect on ventilation and these agonists do not potentiate ventilatory depressant effect of opioids.

Side Effects: The most common side effects produced by clonidine are sedation and xerostomia.

1) Sedation
2) Bradycardia: Occasionally require treatment of bradycardia with IV anti-cholinergic.
3) Retention of sodium and water:
4) Rebound hypertension: In patients who were receiving > 1.2 mg of clonidine daily.
5) Skin rashes are frequent.
6) Impotence occurs occasionally on chronic use.
7) Orthostatic hypotension is rare

Clinical use

1) Preanaesthetic medication
2) Neuraxial analgesia.
3) Prolonging the effect of regional anaesthesia
4) Protection against perioperative myocardial infarction
5) Antihypertensive.
6) Diagnosis of pheochromocytoma.
7) Treatment of opioid and alcohol withdrawal syndrome
8) Treatment of shivering

MATERIALS AND METHODS

The present study was a prospective, randomized, placebo controlled double blind clinical study was conducted on 60 patients (30 in each group) in age group of 20-50 of ASA grade I / II of either sex, undergoing elective laparoscopic surgeries under general anesthesia. Patient receiving sedative or any other drugs affecting neurological or cardiovascular function, patient suffering from renal disease, known allergy to clonidine, difficult intubation, drug or alcohol abused were excluded from study. Study was carried out after getting approval from Institutional Ethics Committee. All patient were adequately investigated.

Simple random sampling was done with lottery method to divide patients in two groups, Group C and Group P. Informed consent was obtained for participation in the study from all patients and received tablet Vit. C by P group and tablet clonidine 150 mcg. by C group 90 minutes prior to induction of anesthetic with a sip of water. On the day of surgery, patient's NBM status was confirmed: patient was taken inside the operation theater and intravenous line was secured on the non- dominant hand. Monitoring was continued using pulse-oxymeter, non-invasive blood pressure monitor, cardioscope, and ETCO2 (after tracheal intubation). Pre- induction pulse rate and blood pressure recording were taken. ECG lead II was recorded. Printout out ECG was taken when there was a change of > 30% in the heart rate of any arrhythmia was noted. All patients receiving inj. ondansetron 80 mcg IV.Inj. midazolam 20 mcg /kg. IV and inj. fentanyl 1 mcg /kg. as premedication. Then they were pre-oxygenated for 3-5 minutes with 100% oxygen. They were induced with Inj. Thiopentone sodium 5 mg/kg. IV. Induction was confirmed with loss of eyelash reflex and inj. vecuronium 80 mcg/kg. IV was given and patient was ventilated for 3 min. Direct laryngoscopy was done and intubated with appropriate size portex cuffed endotracheal tube. After cuff inflation and confirmation of air

entry patients were maintained on O2 + N2O + isoflurane. Following induction of anaesthesia nasogastric tube was placed. Anesthesia was maintained with 50% O2 and N2O along with 0.4%-0.6% isoflurane and muscle relaxation was maintained using injection vecuronium IV. Controlled ventilation was done with closed circuit having soda lime canister. After creation of pneumoperitoneum patients were hyperventilated to maintain normocapnia. Mean intraabdominal pressure was kept at 13+1mmHg in both groups. Mean arterial pressure (MAP), ECG, HR, were recorded 2 hours prior to induction, immediately after intubation, after 5 minutes of insufflation of pneumoperitonium and after 10 minutes of release of pneumoperitonium.

Statistical Analysis

For analysis of this data SPSS Statistical software for social sciences software version of 20th was used. For finding statistical significance between two groups, unpaired t –test was applied to ascertain the pattern and magnitude of differences. P value <0.05 was considered as significant, and P value < 0.01 was considered as highly significant.

RESULTS

The cardiovascular response to the act of tracheal intubation is reflex phenomenon with afferent stimuli carried over both glossopharyngeal and vagal pathways. Such stimuli activate suprasegmental and hypothalamic sympathetic centre to cause a peripheral sympathoadrenal response with release of adrenaline and nor adrenaline (Brutein et al.1950). clonidine stimulates alpha-2 adrenergic inhibitory neurons in the medullary vasomotor centre. As a result there is decrease in sympathetic nervous outflow from central nervous system (CNS) to peripheral tissues. Decreased sympathetic nervous system activity is manifested as peripheral vasodilatation and decrease in systemic blood pressure, heart rate and cardiac output.

Changes in mean heart rate at various time interval

There was significant difference in heart rate immediately after intubation, at 5 minutes after insufflations of pneumoperitoneum and at 10 minutes after release of pneumoperitoneum in both groups. However as compared to clonidine group, placebo group patients showed significantly higher and sustained increase in heart rate immediately after intubation, at 5 minutes after insufflation of PNO and at 10 minutes after release of PNO.

03.33% of patients in the clonidine group and 56.67% of patients in the placebo group had tachyarrhythmia's [Table 5]. Only one patient in clonidine group had tachycardia which lasted for more than 05 minutes while 11 and 6 patients in placebo group had tachycardia which lasted more than 05 and 10 minutes respectively. 6.67% patients in clonidine group had bradyarrhythmia while none of the patient in placebo group had bradyarrhythmia. None of the patient in both the groups had other disturbances on ECG monitoring.

Table 1: Comparison of mean HR in both groups at various interval

		Mean	SD	P-value
Baseline (2hrs before induction)	Group C	86.00	16.20	0.9348 NS
	Group P	86.30	11.72	
Immediately after intubation	Group C	96.04	16.07	0.0031 S
	Group P	107.00	09.86	
5Min after insufflation of PNO	Group C	95.01	14.95	0.0001 S
	Group P	109.97	11.90	
10 min after release of PNO	Group C	87.03	16.19	0.0023 S
	Group P	99.67	14.45	

S: Significant | NS: Not significant

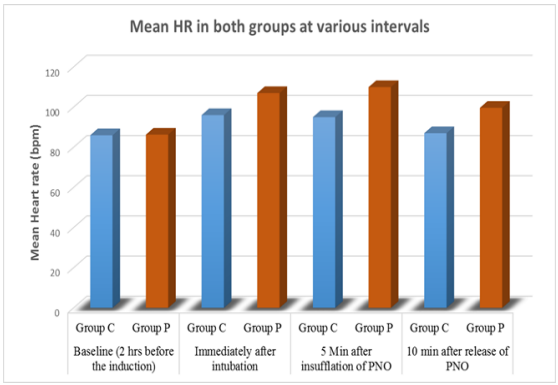

Figure 2: Bar diagram showing Heart rate changes at various time interval

X-axis group C (Clonidine) & P (placebo) Y- axis- mean heart rate (BPM)

Table 2: Arrhythmias Following Induction

Arrhythmias	Number Of Patients	
	'C' Group	'P' Group
Tachyarrhythmia's	01/30 (03.33%)	17/30 (56.67%)
Bradyarrhythmia's	02/30 (06.67%)	00/30

Changes in Mean Arterial Blood pressure at various time interval.

There was as significant increase in mean arterial blood pressure immediately after intubation and 5 minutes after insufflations of pneumoperitonium in both the groups. As compared to clonidine group, placebo group patients showed significantly higher and sustained increases in mean arterial blood pressure immediately after intubation and5 minutes after insufflations of pneumoperitonium.

DISCUSSION

Pneumoperitoneum used for laparoscopic procedure is a complex patho- physiologic phase with significant hemodynamic variation. Carbon dioxide is most commonly used as it is colorless, noncombustible, highly soluble and permeable in tissues thus reducing the risk of gas embolism. The

hemodynamic changes associated with pneumoperitoneum are the result of both increased intra- abdominal pressure and hypercarbia. Five minutes after the beginning of pneumoperitoneum, there is marked increase of vasopressin. Plasma concentrations of epinephrine, norepinephrine and renin are also increased during laparoscopy. The nature of changes in cardiovascular system associated with pneumoperitoneum include an increase in mean arterial pressure, decrease in cardiac output and increase in systemic vascular resistance which can lead to altered tissue perfusion. To attenuate this hemodynamic response, a wide variety of pharmacological agents and anaesthetic interventions like segmental spinal, combined epidural and general anesthesia are being used. Research fellows have tried esmolol, alpha 2 agonists, magnesium sulphate, nitroglycerine, and gasless approach to reduce the hemodynamic variations.

Table 3: Comparison of Mean Arterial Blood Pressure (mm of Hg)

Time		Mean	SD	P-value
2hrs before induction	Group C	90.87	09.22	0.5312 NS
	Group P	89..38	09.10	
Immediately after intubation	Group C	93.19	09.52	0.0001 S
	Group P	106.84	14.65	
5 min after insufflation of PNO	Group C	91.17	07.41	0.0000 S
	Group P	107.51	14.28	
10 Minutes after release of PNO	Group C	82.32	10.71	0.0004 S
	Group P	92.31	09.75	

S: Significant | NS: Not significant

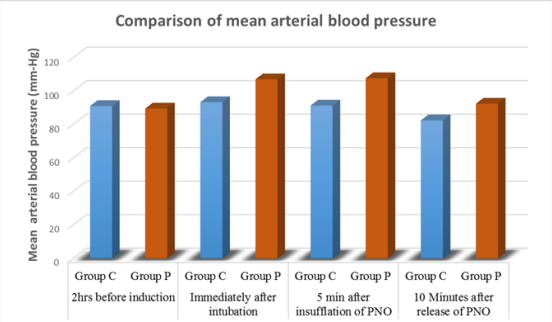

Figure 3: Bar diagram showing mean blood pressure changed at various interval X-axis group C (Clonidine) & P (placebo) Y- axis- mean Arterial Pressure (mmHg.)

Heart Rate

In our study, there was increasing heart rate after intubation in both the groups. As compare to clonidine group, placebo group patients showed significantly higher and sustained increase in heart rate at immediately after intubation, 5 minutes after insufflation of pneumoperitonium, 10 minutes after release of pneumoperitonium. Yuvesh Pasi et al. (2009) observed mean heart rate varied from 92±8 to 96±12 (Mean ±SD) in clonidine group while placebo group it varied from 94±13 to 111±17 (Mean ±SD), Shivinder Singh et al. (2011), M Das et al. (2007), was observed the similar mean heart rate variation during intubation and pnemoperitonium in laparoscopic surgery after use of oral clonidine as premedication. Wright P.M.C. et al. (1990) did the study to evaluate oral clonidine in a dose of 0.3 mg as a routine premedicant and observed that tachycardia in response to intubation was attenuated by clonidine (P less than 0.05).

Arterial Blood Pressure

When the mean arterial blood pressure between two groups were compared in our study, placebo group patients showed significantly higher and sustained increase in mean arterial pressure at immediately after intubation, 5 minutes after insufflations of pneumoperitonium and 10 minutes after release of pneumoperitonium. The percentage change in the mean arterial pressure immediately after intubation was 2.55% in the clonidine group as against 19.54 in the placebo group. Yuvesh passi et al. (2009) studies MAP ranged between 88±9 to 95±9 (Mean±SD) in clonidine (group A) and between 97±14 to 106±5 (Mean ±SD) in placebo (group B), Dhiraj Bhandari et al. (2012), M Das et al (2007), Goyagi T et al (1999), Kodaka M et el. (1997) and Ghignone M et al. (1987) obtained similar results. 40% patients in placebo group had hypertension while none of the patient in clonidine group had hypertension. None of the patient in our study experienced hypotension. The adverse effects in the postoperative period were less in the patients who had clonidine premedication in comparison with placebo premedication. In clonidine, the incidence of sedation was 13.33% and same in placebo group was 16.67%. Incidence of vomiting in placebo group patient was 13.33% as compared to none in clonidine group. None of the patient from both groups developed hypotension in postoperative period. Deepshikha C Tripathi et al (2011). Joseph Park, Jay Forrest, Rick Kolesar, Dolly Bhola, Scott Beattie and Chris Chu (1996), Das M (2007) obtained similar results. Dhiraj Bhandari et al. (2012) observed 28% patients required intraoperative NTG drip for control of hypertension in placebo group whereas no patient required NTG drip in clonidine group. Shivinder Singh et al. (2011) obtained similar result.

The adverse effect in the postoperative period were less in the patients who had clonidine premedication in comparison with placebo premedication. In clonidine group the incidence of sedation was 13.33 and same in placebo group was 16.67%. Incidence of vomiting in placebo group patient was 13.33 as compared to none in clonidine group. There was incidence of shivering in 26.67% patients in the placebo group compared to none in the clonidine group. None of the patient from both groups developed hypotension in postoperative period. .

Deepshikha C Tripathi et al. (2011), Joseph Park, Jay Forrest, Rick Kolesar. Dolly Bhola. Scott Beattie and Chris Chu (1996), Das M (2007) obtained similar result. Thus, oral clonidine 150 mcg. given 90 minutes prior to surgery-

1. Attenuate the cardiovascular response to laryngoscopy and pneumoperitoneum during laparoscopic surgery.
2. Reduces the postoperative rescue analgesic requirement.
3. Has fewer side effects.
4. Is cost effective, safe and acceptable to patient.

CONCLUSION

From our clinical study, it can be concluded that: Pneumoperitoneum used during laparoscopic surgeries causes sympathetic activation leading to alteration in hemodynamics. Premedication with 150 micrograms of oral clonidine in ASA I and II patients has been found to be relatively safe and effective method to provide stable hemodynamics intraoperatively as protection against stress response triggered by pneumoperitoneum in patients undergoing laparoscopic surgeries. Oral clonidine premedication also offers additional advantage of reduction of postoperative complications such as pain nausea –vomiting, and shivering. Hence 150 microgram of oral clonidine can reasonably be recommended as premedication for all surgeries.

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