

**ORAL CLONIDINE AND ANAESTHESIA: EFFECT OF ORAL CLONIDINE
PREMEDICATION ON HEMODYNAMIC CHANGES DURING LAPAROSCOPIC
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ABSTRACT

Background: Laryngoscopy and intubation are mandatory for patients undergoing general anesthesia. Direct laryngoscopy and intubation along with pneumoperitoneum with carbon dioxide (CO₂) insufflation for laparoscopic surgery cause afferent sympatho-adrenal response, this causes increase in blood pressure (BP), heart rate (HR) and cardiac arrhythmias in some patients. Oral Clonidine premedication has been recently shown to have a potential to prevent such harmful responses. **Aim:** To evaluate the efficacy of administration of oral Clonidine premedication to attenuate hemodynamic responses due to laryngoscopy, intubation and pneumoperitoneum during laparoscopic surgery. **Methods:** After taking informed consent, 200 patients were systematically randomised into two groups of 100 each. Patients were kept NPO 8 hours, after proper preanesthetic checkup before surgery. On morning of surgery Group C received Oral Clonidine 150mcg premedication 90 minutes prior to induction in the preoperative room and Group P, oral ranitidine 150mg (Pacebo) premedication 90 minutes before shifting the patient immediately afterwards to the operation room. **Results:** Oral Clonidine premedication in a dose of 150 mcg orally before laryngoscopy and intubation effectively attenuates hemodynamic responses during intubation and pneumoperitoneum during elective laparoscopic cholecystectomy. **Conclusion:** Oral Clonidine 150mcg premedication effectively attenuates hemodynamic responses during intubation and pneumoperitoneum during laparoscopic cholecystectomy.

KEYWORDS: Oral Clonidine, hemodynamic responses, Laparoscopic Cholecystectomy.

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, with an average increase in blood pressure by 20-40% and increase in heart rate by 20%.^[1] Pneumoperitoneum with carbon dioxide (CO₂) insufflation for laparoscopic surgery induces abrupt elevations of arterial pressure and systemic vascular resistance with no significant change in heart rate possibly due to an increase in intraperitoneal pressure and stimulation of the peritoneum by CO₂ and due to humoral mediators like catecholamines, prostaglandins, the renin-angiotensin system, and vasopressin which cause an increase in systemic vascular

resistance.^[2,3,4] These disturbances could be mediated both mechanically and humorally, mechanically by increased venous resistance, compression of the abdominal aorta contributing to the increase in cardiac afterload and tilting the patient to the head-up position reducing venous return.^[5] The centrally acting α_2 -adrenoceptor agonists like clonidine have been used with success to provide haemodynamic stability for patients undergoing surgery. Particularly in the case of patients with overt or underlying cardiac disease the actions of α_2 -adrenoceptor agonists, which include maintenance of stable systemic blood pressure and low heart rate and a reduction in overall oxygen consumption, can be expected to reduce the risk of procedure-related cardiac events.^[6] This ability of α_2 adrenoceptor agonists to inhibit central sympathetic outflow may benefit the patients undergoing various procedures like

bronchoscopy by reducing the incidence and severity of hemodynamic abnormalities especially in cardiac patients.^[7]

METHODS

After obtaining informed patient consent and approval from institutional ethical committee, this randomized control trial was conducted in a tertiary care medical college hospital. Study included 200 patients divided into two groups of 100 each, of ASA grade I and II of either sex between the age of 18-65 years, undergoing elective laparoscopic cholecystectomy under general anesthesia with endotracheal intubation after a detailed preanesthetic checkup.

Following patients were excluded from the study;

Anticipated difficult intubation ASA grade III or greater
History of consumption of antihypertensive drugs, sedatives, Hypnotics and antidepressants preoperatively
Pre-existing cardiovascular disease, significant respiratory, renal and hepatic disorder
History of drugs or alcohol abuse pregnant women.

Patients were prepared by 8 hours preoperative fasting. After obtaining informed consent, patients were randomly allocated into two groups using computer-generated Microsoft excel programme. The two groups of patients received the following treatment in the preoperative room.

Group C. Oral Clonidine 150mcg premedication 90 minutes before induction of anesthesia.

Group P. Oral Ranitidine 150mg premedication 90 minutes before induction of anesthesia.

The anesthesiologist in charge of intraoperative management of patient was not aware of the groups of patients and treatment given to before anesthesia in the preoperative room (Oral Clonidine 150mcg or Oral Ranitidine 150mg premedication). 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 and patients were shifted immediately to operation room along with proper monitoring of vitals, which is continued. Injection Ondansetron 0.1mg/kg and inj. Tramadol 1-2mg/kg was given at induction. After 3 minutes of preoxygenation, anesthesia was induced with Propofol 2.0 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, 0.6% Halothane and Atracurium 5mg as intermittent boluses with inj. Paracetamol 25-30 mg/kg for analgesia. During surgery CO₂ pneumoperitoneum was established and maintained

at a pressure of around 12-14 mm Hg by an automatic insufflation unit till the completion of surgery. EtCO₂ maintained between 25-35mmHg throughout. The surgical technique used was identical in the two groups. Arterial pressure and heart rate was measured before Premedication (baseline); before induction, 5min. after intubation, before pneumoperitoneum and at 5, 10, 15min, and 30 min after commencement of insufflations and at release of pneumoperitoneum.

At the end of the surgery residual neuromuscular blockade was reversed with injection Neostigmine 0.05mg/kg and injection Atropine 0.02mg/kg and patient extubated. All the observations made in the study were compared for each parameter within the groups. All the data obtained was analyzed and subjected to subsequent statistical analysis using, student Independent T- test were intergroup means were compared and Chi Square tests were non-parametric data was compared (SPSS Ver. 20).

RESULTS

We studied 200 patients divided into two groups of ASA grade I and II of either sex between age of 18-65 years, who underwent laparoscopic cholecystectomy under general anesthesia with endotracheal intubation. Parameters like heart rate, noninvasive blood pressure (SBP, DBP and MAP) were monitored before administration of study drug, after administration of study drug before induction, after intubation, before pneumoperitoneum and 5, 10, 15 and 30 minutes after pneumoperitoneum and lastly at ending of pneumoperitoneum in both groups.

The difference of age, sex, weight, ASA grading and duration of surgery were statistically non-significant. ($p > 0.05$ which is not significant)

Effect on Heart Rate**Table 1: The mean \pm SD and P values of heart rate in Group C and P are shown in Table No 1.**

| HEART RATE | | MEAN \pm SD GROUP C | MEAN \pm SD GROUP P | P VALUE |
|------------------|-----------------------------------|--------------------------|--------------------------|------------|
| Base-Line | | 80.0 \pm 3.86 | 79.0 \pm 4.07 | 0.076 |
| Before Induction | | 75.7 \pm 4.03 | 89.9 \pm 3.87 | <0.001* |
| After Intubation | | 89.1 \pm 4.14 | 108.9 \pm 3.59 | <0.001* |
| Pneumoperitoneum | Before Pneumoperitoneum | 77.7 \pm 4.05 | 87.4 \pm 3.91 | <0.001* |
| | 5 Minutes After Pneumoperitoneum | 76.1 \pm 3.83 | 91.0 \pm 3.98 | <0.001* |
| | 10 Minutes After Pneumoperitoneum | 75.4 \pm 3.98 | 94.4 \pm 4.37 | <0.001* |
| | 15 Minutes After Pneumoperitoneum | 75.4 \pm 3.55 | 97.2 \pm 4.58 | <0.001* |
| | 30 Minutes After Pneumoperitoneum | 74.8 \pm 4.26 | 95.7 \pm 4.08 | <0.001* |
| | After Release of Pneumoperitoneum | 74.7 \pm 4.47 | 94.1 \pm 4.94 | <0.001* |

Paired 't' test (NS: $p > 0.05$; Not Significant; $p < 0.05$; Significant; $p < 0.001$: Highly significant). Within group C and P heart rates were found to be statistically significant throughout the surgery right from before induction till release of pneumoperitoneum.

Effect on Systolic Blood Pressure**Table 2: The mean \pm SD and P values of SBP in Group C and P are shown in Table No 2.**

| SBP | | MEAN \pm SD GROUP C | MEAN \pm SD GROUP P | P VALUE |
|------------------|-----------------------------------|--------------------------|--------------------------|------------|
| Base-Line | | 119.4 \pm 3.45 | 120.3 \pm 4.43 | 0.112 |
| Before Induction | | 110.3 \pm 3.23 | 122.3 \pm 2.79 | <0.001* |
| After Intubation | | 120.0 \pm 2.42 | 145.0 \pm 3.15 | <0.001* |
| Pneumoperitoneum | Before pneumoperitoneum | 114.9 \pm 3.07 | 126.6 \pm 3.31 | <0.001* |
| | 5 Minutes After Pneumoperitoneum | 116.3 \pm 2.38 | 135.5 \pm 3.15 | <0.001* |
| | 10 Minutes After Pneumoperitoneum | 117.2 \pm 3.21 | 139.6 \pm 3.25 | <0.001* |
| | 15 Minutes After Pneumoperitoneum | 119.7 \pm 2.84 | 144.5 \pm 3.62 | <0.001* |
| | 30 Minutes After Pneumoperitoneum | 120.3 \pm 2.47 | 140.2 \pm 2.90 | <0.001* |
| | After Release of Pneumoperitoneum | 115.8 \pm 2.95 | 126.4 \pm 3.17 | <0.001* |

Paired 't' test (NS: $p > 0.05$; Not Significant; $p < 0.05$; Significant; $p < 0.001$: Highly significant). Within group C and P systolic blood pressure (SBP) were found to be statistically significant throughout the surgery right from before induction till release of pneumoperitoneum.

Effect on Dystolic Blood Pressure**Table 3: The mean \pm SD and P values of DBP in Group C and P are shown in Table No 3.**

| DBP | | MEAN \pm SD GROUP C | MEAN \pm SD GROUP P | P VALUE |
|------------------|-----------------------------------|--------------------------|--------------------------|------------|
| Base-Line | | 79.1 \pm 6.34 | 80.5 \pm 5.78 | 0.104 |
| Before Induction | | 73.1 \pm 3.19 | 83.5 \pm 3.13 | <0.001* |
| After Intubation | | 83.0 \pm 2.73 | 98.1 \pm 2.72 | <0.001* |
| Pneumoperitoneum | Before Pneumoperitoneum | 77.1 \pm 3.00 | 84.5 \pm 3.50 | <0.001* |
| | 5 Minutes After Pneumoperitoneum | 78.7 \pm 3.28 | 91.9 \pm 2.19 | <0.001* |
| | 10 Minutes After Pneumoperitoneum | 80.0 \pm 2.06 | 96.5 \pm 2.51 | <0.001* |
| | 15 Minutes After Pneumoperitoneum | 82.7 \pm 2.29 | 100.2 \pm 2.75 | <0.001* |
| | 30 Minutes After Pneumoperitoneum | 81.5 \pm 2.58 | 93.9 \pm 3.32 | <0.001* |
| | After Release of Pneumoperitoneum | 78.9 \pm 3.48 | 83.2 \pm 1.98 | <0.001* |

Paired 't' test (NS: $p > 0.05$; Not Significant; $p < 0.05$; Significant; $p < 0.001$: Highly significant). Within group C and P Diastolic blood pressure (DBP) were found to be statistically significant throughout the surgery right from before induction till release of pneumoperitoneum.

Effect on Mean Blood Pressure**Table 4: The mean \pm SD and P values of MAP in Group C and P are shown in Table No 4.**

| MAP | | MEAN \pm SD GROUP C | MEAN \pm SD GROUP P | P VALUE |
|------------------|-----------------------------------|--------------------------|--------------------------|------------|
| Base-Line | | 92.6 \pm 5.07 | 93.8 \pm 4.93 | 0.091 |
| Before Induction | | 85.5 \pm 2.39 | 96.4 \pm 2.31 | <0.001* |
| After Intubation | | 95.3 \pm 1.90 | 113.7 \pm 2.25 | <0.001* |
| Pneumoperitoneum | Before pneumoperitoneum | 89.7 \pm 2.46 | 98.5 \pm 2.65 | <0.001* |
| | 5 Minutes After Pneumoperitoneum | 91.3 \pm 2.30 | 106.4 \pm 1.84 | <0.001* |
| | 10 Minutes After Pneumoperitoneum | 92.4 \pm 1.60 | 110.9 \pm 2.12 | <0.001* |
| | 15 Minutes After Pneumoperitoneum | 95.0 \pm 1.79 | 115.0 \pm 2.44 | <0.001* |
| | 30 Minutes After Pneumoperitoneum | 94.5 \pm 1.85 | 109.3 \pm 2.40 | <0.001* |
| | After release of Pneumoperitoneum | 91.2 \pm 2.72 | 97.6 \pm 1.61 | <0.001* |

Paired 't' test (NS: $p > 0.05$; Not Significant; $p < 0.05$; Significant; $p < 0.001$: Highly significant). Within group C and P mean blood pressure (MBP) were found to be statistically significant throughout the surgery right from before intubation till release of pneumoperitoneum.

Whereas, within group C and P difference in heart rates, systolic blood pressure, diastolic b.p and mean arterial blood pressures at various intervals with respect to base-line were found to be statistically significant as shown in Table No 1,2,3 and 4 respectively, the results being comparable confirming the attenuating response of oral Clonidine premedication as comparable to placebo (oral Ranatidine) on haemodynamics during intubation and laparoscopic insufflations.

DISCUSSION

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 with an average increase in blood pressure by 20-40% and increase in heart rate by 20%.^[1] α_2 adrenoreceptor agonists inhibit central sympathetic outflow may benefit the patients undergoing various procedures like bronchoscopy by reducing the incidence and severity of hemodynamic abnormalities especially in cardiac patients.^[7] Clonidine premedication may be particularly well suited for elderly benefitting intraocular pressure (IOP), and hemodynamic profiles.^[8,14] Premedication with clonidine or fentanyl has effectively attenuated the intraoperative hemodynamic responses of laparoscopic cholecystectomy. The intraoperative hemodynamic stability with clonidine or fentanyl premedication might enable laparoscopic cholecystectomy in obese, hypertensive and cardiac compromised patients.^[9] Above results were similar to studies involving administration of Premedication with clonidine, which blunts the stress response to surgical stimuli and the lessen narcotic and reduce anaesthetic doses by increasing cardiac baroreceptor reflex sensitivity to increase in systolic blood pressure, and thus stabilises, blood pressure in patients undergoing laparoscopic surgeries.^[10] Similarly clonidine premedication before anaesthesia with isoflurane was helpful in decreasing bleeding during ear surgery by stabilizing haemodynamics.^[11] Also Clonidine reduces Venous plasma concentrations of

noradrenaline, adrenaline, growth hormone, vasopressin, and Cortisol levels during surgical stress.^[12]

Our above results were similar to studies involving administration of premedication with 150 μ g oral clonidine, finding it to be relatively safe as well as effective method that provides stable haemodynamics and protection against stress response triggered by pneumoperitoneum in patients undergoing laparoscopic cholecystectomy with added advantage of reduction in postoperative complications such as nausea-vomiting and shivering.^[13] Clonidine significantly reduced the intraoperative lability of systolic (P less than 0.01) and diastolic BP and heart rate (HR) (P less than 0.05), and resulted in significantly slower HR during recovery (P less than 0.01) improving perioperative hemodynamics and anaesthetics requirements.^[15] Significant hemodynamic derangements during pneumoperitoneum of laparoscopic surgery can be effectively attenuated by premedication with 1 μ g and 2 μ g/kg of intravenous clonidine 30 min before induction of anesthesia to attenuate the hemodynamic stress response of pneumoperitoneum and tracheal intubation/extubation in otherwise healthy patients is comparable to our study results.^[16] Also our results were similar to studies involving administration of Oral Clonidine 150mcg premedication before intubation and then introducing peritoneal insufflation by CO₂, therein attenuating the arterial pressure increase in laparoscopic cholecystectomy.^[17] This attenuation results from reduced neurohumoral changes with oral Clonidine in similar studies concluding use of clonidine blunts the stress response to surgical stimuli and the narcotic and anaesthetic doses are also reduced. In addition, clonidine increases cardiac baroreceptor reflex sensitivity to increase in systolic blood pressure, and thus stabilises, blood pressure in patients undergoing laparoscopic surgeries as found in our study.^[10] Also during laparoscopic cholecystectomy, carbon dioxide is commonly used to create pneumoperitoneum causing adverse cardiovascular effects leading to the release of catecholamines from both adrenergic nerve terminals and

the adrenal gland which Clonidine effectively blocks.^[17,18]

CONCLUSION

Oral Clonidine 150mcg premedication administered at induction attenuates haemodynamic responses at intubation and during pneumoperitoneum in laparoscopic cholecystectomy.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests regarding publication of this paper.

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