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Original Research Article

# Effects of clonidine premedication on perioperative hemodynamic response, anesthetic requirements and postoperative analgesia for patients undergoing laparoscopic gynecological surgeries: A randomized study

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ABSTRACT

**Background and Objectives:** The creation of carbon dioxide ($CO_2$) pneumoperitoneum is frequent in laparoscopy, but has significant effect on the cardiopulmonary function of the patient. Clonidine by its central sympatholytic action reduces perioperative hemodynamic instability and has several advantages in the postoperative period, hence we consider it to be an effective premedication to contain the stress response to intubation and laparoscopy.

**Materials and Methods:** With informed consent, 56 patients scheduled for elective laparoscopic gynecological surgeries under general anesthesia were randomly allocated into two groups to receive premedication with either oral Clonidine 100 $\mu$g (Group I, n = 28) or Vitamin C as placebo (Group II, n = 28) 90 minutes prior to induction. A balanced general anesthesia was used to manage these patients. Hemodynamic parameters, Sevoflurane concentration, pain and sedation scores, time to request analgesics, 24hr cumulative analgesic requirements and adverse effects between the two groups were collected as data and compared using Two sample t-test and Fisher's exact test.

**Results and Conclusion:** When compared to the control group, oral Clonidine was found to be considerably superior significantly (p =0.00) in terms of maintaining stable hemodynamics (i.e. In group I, Mean HR ranged from 76.11±12.21 to 94.57±13.75, while in group II, it ranged from 79.04±7.11 to 112.00±12.75 and MAP ranged from 83.07±6.50 to 93.64±14.09 in group I, while in group II, it ranged from 88.04±9.03 to 116.14±13.23), having a Sevoflurane sparing effect and having a longer time (6.5 ± 1.6 hours) between the first request for analgesia postoperatively. In patients undergoing laparoscopic gynecological surgeries, administration of oral Clonidine 100$\mu$g as a premedication improves perioperative hemodynamic stability and reduces the intraoperative anesthetic and post-operative analgesic requirements.



## 1. Introduction

In this modern era of the 21$^{st}$ century, laparoscopic surgeries are performed on a daily basis and has replaced open abdominal surgeries with its smaller incision, because it offers cosmetic benefits as well as a reduction in hospital days, postoperative pain, postoperative ileus, morbidity and overall cost. During laparoscopy, the formation of carbon dioxide ($CO_2$) pneumoperitoneum and shift of the patient's position from supine to Trendelenburg or reverse Trendelenberg, affects homeostatic systems leading to alteration in cardiovascular and pulmonary physiology, acid-base disturbances and stress responses. These pathophysiological changes are characterized by an increase in intra-abdominal pressure, blood pressure, systemic and pulmonary vascular resistances. 10-30%

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decrease in cardiac output has also been reported.[1–3] These changes propose new anesthetic challenges to maintain the hemodynamic stability. To tackle this, various anesthetic techniques and pharmacological agents such as opioids,[4] esmolol,[5] Sodium Nitroprusside, Nitroglycerin,[6] lignocaine,[7] Pregabalin,[8,9] and Magnesium sulfate[10] are being used but the success rate is limited.

"Clonidine is a combined $\alpha_1$ and $\alpha_2$ adrenoceptor agonist with a predominant $\alpha_2$ action ($\alpha_1$: $\alpha_2$=1:220). It has an elimination half-life range from 6 to 24 hours with a mean of 12 hours. It exerts central sympatholytic action[11] with severe other perioperative beneficial features like anxiolysis, analgesia, sedation and improved hemodynamic stability in response to intubation and surgical stress. Furthermore they reduce the anesthetic/opioid requirements. Clonidine also improves the sensitivity of cardiac baroreceptor reflexes to increase systolic pressure and stabilizes blood pressure"[12] thus may offer benefits in the prophylaxis and treatment of perioperative myocardial ischemia.[13]

Shivender Singh et al[14] and Deepshika et al[15] used oral Clonidine 150$\mu$g and found to have postoperative sedation, bradycardia and hypotension. Hence we considered low dose Clonidine 100$\mu$g with excellent absorption and ease of administration to be an effective drug in the anesthetic management of patients undergoing laparoscopic gynecological procedures. The present study was aimed to evaluate the effects of oral Clonidine premedication on hemodynamic response to intubation and laparoscopy, anesthetic requirements to maintain anesthesia and postoperative pain modulation in patients undergoing laparoscopic gynaecological surgeries.

## 2. Materials and Methods

A prospective, randomized, single-blind, comparative study was conducted on patients undergoing laparoscopic gynecological surgeries at Cosmopolitan Hospitals, Trivandrum, a tertiary care center after approval from the Hospital research and ethical committee. After obtaining informed written consent the study was conducted on 56 adult patients who were randomly divided into two groups (I and II) of 28 each using simple randomization by a random number table.

Group I - Clonidine 100 $\mu$g per orally was given 90 min before induction.

Group II - Vitamin C tablets (placebo) 100 mg per orally were given 90min before induction.

Sample size was calculated using the formula

$$\frac{n = 2\ x\ \{[Z\alpha + Z\beta]\ x\ \sigma\}^2}{\delta^2}$$

Where n is the sample size, $\sigma$ is the standard deviation of the Heart rate, $\delta$ is the difference in the average Heart rates of the two groups, $\alpha$ is the type 1 error, here taken as 1%, $\beta$ is the type 2 error, here taken as 5%. From the study done by Shivender Singh et al[14] the heart rate was used to calculate the sample size. Here, $\sigma$ = 12.16; $\delta$ = 15; $Z\alpha$ = 2.58; $Z\beta$ = 1.64. So, on applying the above formula n = 23, this was upsized to 25. As nonparametric methods were used for statistical analysis, we added 10% extra patients to achieve the power of efficacy. So the sample size was 28 patients in each of the arms (Total of 56 patients).

Females of American Society of Anesthesiology (ASA) grades I and II, between 20-60 years of age, who were scheduled for laparoscopic gynecological surgeries under general anesthesia were chosen as the study population. Patients who are not meeting the eligibility criteria, absence of patient consent, patients with history of renal dysfunction, Atrioventricular block, severe valvular dysfunction, coronary artery disease, recent myocardial ischemia or infarction, bronchial asthma, chronic obstructive pulmonary disease(COPD), Clonidine allergy, hypertension, diabetes mellitus, drug dependence, concomitant use of methyldopa, Benzodiazepines, Beta blockers, monoamine oxidase inhibitors (MAOI), tricyclic antidepressants (TCA) or opioids were excluded from the study.

Detailed preoperative evaluation was done to optimize the patient prior to surgery. Demographic data such as age, height and weight were collected. All patients were given tablets Alprazolam 0.5mg and pantoprazole 40mg per orally on the night before the day of surgery. On the morning of planned surgery, an oral Clonidine tablet 100$\mu$g or Vitamin C tablet with 50ml of clear fluids was given to Group I and Group II patients respectively. Baseline heart rate and mean arterial pressure was measured before ingestion of the study drug in all patients. Then the patients were kept in a preoperative room for observation. An 18G IV cannula was secured in the right forearm vein and started preloading with 10ml/kg of crystalloid solution.

About one and half hours later, the patients were taken to the operating table and pre-induction monitors like ECG, Pulse oximeter ($SPO_2$) and non-invasive blood pressure (NIBP) were connected and measured. After induction and intubation, intraoperative End Tidal Carbon Dioxide ($ETCO_2$), end tidal inspired and expired concentration of Sevoflurane was measured by using a multi-parametric monitor (Drager).

Patients were given premedication with Inj.Granisetron 1mg IV, Inj.Midazolam 0.05mg/kg IV, Inj. Glycopyrrolate 0.2mg IV and Inj. Fentanyl 2$\mu$g/kg IV. Preoxygenation was done with 8L/min of 100% oxygen via mask and induced with inj. Propofol 2mg/kg IV and Inj. Atracurium 0.5mg/kg IV following which the patients were ventilated for 3 minutes via a mask with oxygen along with 2% Sevoflurane using a circle absorber. All the patients were intubated with the same investigator with suitable size Macintosh laryngoscope blades and cuffed oral endotracheal tubes in a single attempt with ease. Bilateral air entry was checked with a stethoscope and the endotracheal tube was fixed.

Then a 16FG nasogastric tube was inserted and fixed. Pressure points were padded and eyes were covered with wet gauze. Inj.Diclofenac sodium 75mg was given to all patients after intubation.

General anesthesia was maintained with 1.5–2% Sevoflurane and Nitrous oxide ($N_2O$) 67% with oxygen 33% mixture and was titrated to maintain the MACage[16] of Sevoflurane with $N_2O$ between 0.9 and 1.19 according to age of the patient. Maintenance doses of Inj. Atracurium 0.1mg /kg IV was given for muscle relaxation every 20 minutes during the surgery. Sevoflurane concentration was adjusted to maintain the Heart rate and mean arterial pressure at 20% above or below the baseline. Depth of anesthesia was measured clinically by change in Heart rate and Blood pressure. Intraoperative hydration was maintained with crystalloids using the Holliday Segar method. Volume control Ventilation was applied to maintain $ETCO_2$ between 35-40mmHg throughout the procedure by altering tidal volume and respiratory rate.

The selected patients underwent either Total laparoscopic hysterectomy (TLH), laparoscopic myomectomy or laparoscopic ovarian cystectomy under general anesthesia. After positioning, under strict aseptic precautions the patient's abdomen was painted and draped. $CO_2$ pneumoperitoneum was created through a Veress needle in the sub-umbilical region following which the surgery was proceeded. The intra-abdominal pressure was monitored and strictly maintained between 12-14mmHg. The average duration of surgery for TLH/laparoscopic myomectomy was 120 minutes and laparoscopic ovarian cystectomy was 60- 90 minutes.

Residual neuromuscular blockade was reversed with Inj. Neostigmine 50$\mu$g/kg IV and Inj.glycopyrrolate 0.2mg IV for each mg of neostigmine at the end of surgery. The Nasogastric tube was removed after proper suctioning of the NG tube. Extubation after oral suctioning was done once the patients were awake, warm and conscious. Patients were transferred to the recovery room and were given supplemental $O_2$ via mask. NIBP, $SPO_2$ and Respiratory rate were monitored in the recovery room for 2 hours after which they were shifted to the post anesthetic care unit.

Throughout the surgery, the hemodynamic variables (i.e) Hearts rate (HR), Mean Arterial Pressure (MAP), end tidal Sevoflurane inspiratory and expiratory concentrations were noted using automatic multi-parameter monitor (Drager) at (1). Baseline, (2). 1 minute after intubation, (3). 5 minutes after intubation, (4). At the time of skin incision, (5). After creation of pneumoperitoneum, (6). 15 minutes after insufflation, (7). 30 minutes after insufflation, (8). 15 minutes after release of pneumoperitoneum, (9). At the end of surgery.

In the event of severe hemodynamic variations (hypertension, bradycardia, hypotension) interventions other than adjusting Sevoflurane concentration were carried out in both groups. They were as follows:

1. A mean arterial pressure below 60mmHg was regarded to be hypotension and was treated with IV crystalloids and bolus of 6mg mephentermine, which were repeated when required.
2. A mean arterial pressure above 120mmHg lasting more than 5 minutes was treated with IV infusion of nitroglycerin 0.5-5$\mu$g/kg/min.
3. A heart rate of below 50 beats/min was regarded to be bradycardia and was treated with 0.6mg IV bolus of Atropine.

During the postoperative period, a 10-cm visual analog scale (VAS) was used to assess pain. Pain levels range from 0 to 10 with Zero indicating no pain and 10 denoting unbearable pain. The Ramsay sedation score, which ranges from 1 to 6 was used to assess sedation. At 30 minutes, 60 minutes, 90 minutes and 120 minutes after surgery, the VAS score, sedation score, and adverse events such as hypotension, nausea, vomiting, bradycardia, bradypnea and hypertension that occurred were documented. The time from completion of surgery to the time when the first dose of analgesia was provided at patients' request (i.e VAS >4) was recorded as the time of the first analgesic request (TAR). A combination of Inj.Tramadol 50mg IV and inj. Metoclopramide 10mg IV was given as rescue analgesia and the total dose required for postoperative analgesia in 24 hours was also noted.

The SPSS statistical package (version 16.0) was used for the statistical analysis. Continuous variables were expressed as mean ± standard deviation ($\bar{x}\pm\sigma$) and categorical variables as percentages. Comparison of categorical variables between two groups was tested using the chi-square test. Continuous variables were compared using Student's t-test. p value <0.05 was considered statistically significant. All statistical tests were two sided.

Two sample t-test was used to statistically analyze demographic variables (age, weight, height), hemodynamic variables (Heart rate, Mean arterial pressure), Sevoflurane concentration requirement, Time to the first dose of analgesic request (TAR) postoperatively, 24-hour cumulative analgesic requirement, VAS and sedation score. Fisher's exact test was used to analyze adverse events.

## 3. Results

There were no significant differences (p >0.05) in demographic variables (age, height, weight) between the Clonidine group (Group I) and the Vitamin C (placebo) group (Group II) (Table 1). This indicates that the two groups are more or less homogeneous and hence comparable. Of these 56 cases, 33 cases were TLH, 17 cases were laparoscopic myomectomy and 6 cases were laparoscopic ovarian cystectomy.

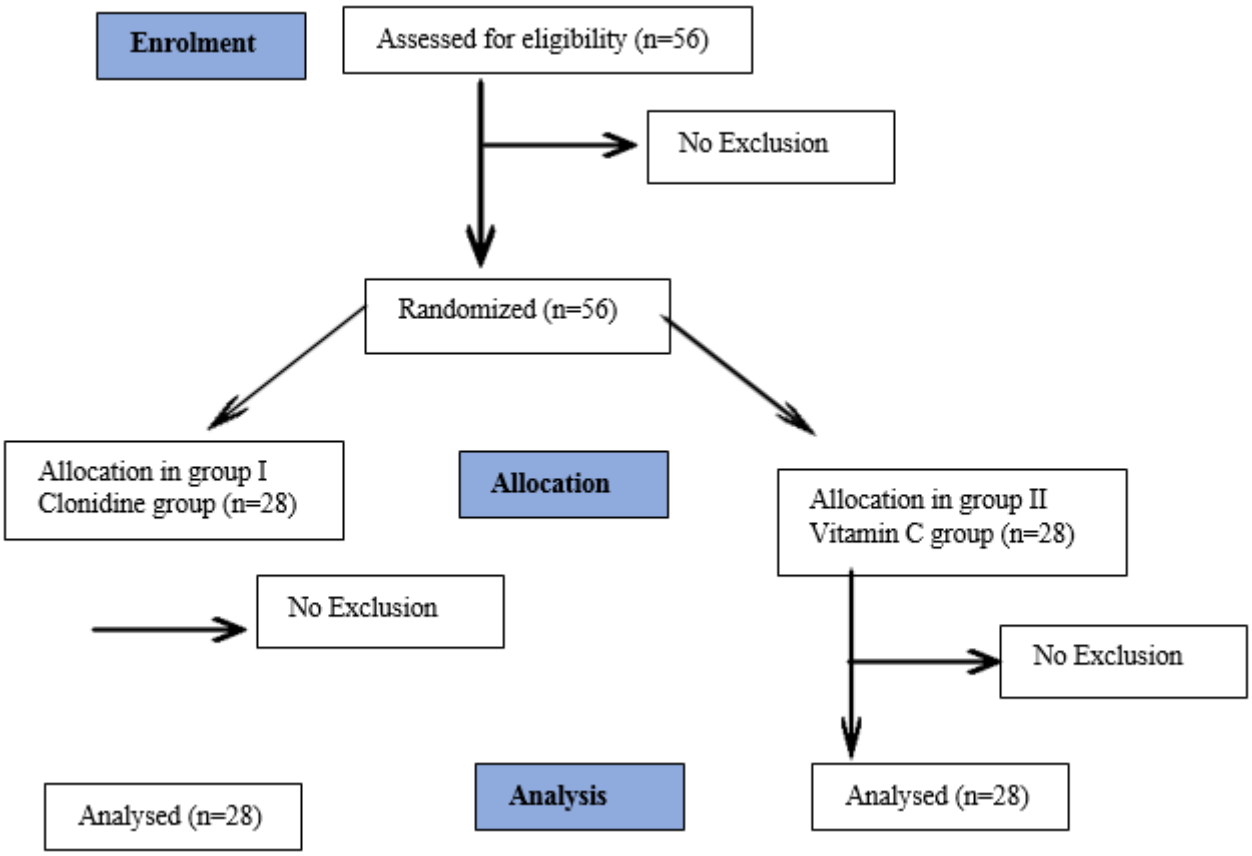


Diagram 1: Consort diagram

The ASA grading distribution between the two groups was comparable. The p value was >0.05 which means statistically insignificant. Group I accounted for 64.3% of ASA grade I and 35.7% of ASA grade II patients whereas Group II accounted for 53.6% of ASA grade I and 46.4% of ASA grade II patients (Table 1).

From Table 2, the baseline HR between the two groups before ingestion of premedication drugs (Clonidine or vitamin C) was comparable. There were no statistical differences (p >0.05) between the groups. There was an increase in HR at 1 minute following intubation with the difference becoming statistically significant (p <0.05) after 5 minutes only. In comparison to group II, the mean HR was lower and stable in group I at all times perioperatively. In group I, Mean HR ranged from 76.11±12.21 to 94.57±13.75, while in group II, it ranged from 79.04±7.11 to 112.00±12.75. The difference in mean HR between the two groups was statistically significant from 5 minutes after intubation to 15 minutes after release of pneumoperitoneum.

From Table 3, the baseline MAP between the two groups before ingestion of premedication (Clonidine or vitamin C) was comparable. There were no statistical differences (p >0.05) between the groups. In both groups, the highest spike in MAP occurred at one minute after intubation and at the start of pneumoperitoneum. In comparison to group II, the MAP was lower and stable in group I perioperatively. In group I, MAP ranged from 83.07±6.50 to 93.64±14.09, while in group II, it ranged from 88.04±9.03 to 116.14±13.23. The difference in the MAP values was significant at all time intervals between the groups except 30 minutes after insufflation when it became insignificant.

The Sevoflurane concentration needed to maintain stable hemodynamics was higher in group II (Vitamin C), after 5 minutes of intubation to all points of time until the end of surgery and there was a statistically significant difference between the groups (p <0.05) (Figure 1). The Sevoflurane concentration needed to maintain stable hemodynamics was higher in group II, after 5 minutes of intubation to all points of time until the end of surgery and there was a statistically significant difference between the groups (p <0.05) (Figure 1).

Group I patients were slightly sedated at 30 minutes following surgery when compared to Group II, but there were no statistically significant differences measured at 30 min intervals until 2 hours after surgery (p >0.05). (Table 4)

**Table 1:** Demographic data

| Data | Group I (n=28) ($\bar{x}\pm\sigma$) | Group II (n=28) ($\bar{x}\pm\sigma$) | p |
|---|---|---|---|
| Age (years) | 41.89±9.22 | 43.71±7.23 | 0.414 |
| Height (cm) | 158.9±4.7 | 158.3±6.8 | 0.350 |
| Weight (kg) | 63.3±8.2 | 64.2±8.8 | 0.638 |
| ASA I | 64.3% | 53.6% | 0.415 |
| ASA II | 35.7% | 46.4% | |

Heart Rate (HR)

**Table 2:** Heart Rate (HR)

| Heart Rate (HR) | Group I(n=28) ($\bar{x}\pm\sigma$) | Group II(n=28) ($\bar{x}\pm\sigma$) | P |
|---|---|---|---|
| Baseline | 76.71±7.46 | 78.04±7.11 | 0.500 |
| 1min after intubation | 94.57±13.75 | 90.43±14.26 | 0.273 |
| 5 min after intubation | 93.39±11.48 | 107.96±13.81 | 0.000 |
| At skin incision | 88.93±12.76 | 111.50±12.21 | 0.000 |
| At pneumoperitoneum | 88.64±11.65 | 112.00±12.75 | 0.000 |
| 15 min after insufflation | 84.50±11.96 | 96.39±11.68 | 0.000 |
| 30 min after insufflation | 83.11±12.13 | 88.82±8.74 | 0.048 |
| 15 min after release of pneumoperitoneum | 76.11±12.21 | 84.21±13.91 | 0.024 |
| At the end of surgery | 78.93±7.97 | 81.75±9.52 | 0.234 |

**Table 3:** Comparison of MAP

| MAP | Group I (n=28) ($\bar{x}\pm\sigma$) | Group II (n=28) ($\bar{x}\pm\sigma$) | P |
|---|---|---|---|
| Baseline | 85.25±9.70 | 88.29±11.23 | 0.284 |
| 1 min after intubation | 90.54±11.51 | 103.82±10.68 | 0.000 |
| 5 min after intubation | 85.07±8.86 | 104.14±11.28 | 0.000 |
| At skin incision | 85.75±11.40 | 111.00±9.40 | 0.000 |
| At pneumoperitoneum | 89.43±14.28 | 116.14±13.23 | 0.000 |
| 15 min after insufflation | 93.64±14.09 | 109.21±16.98 | 0.000 |
| 30 min after insufflation | 88.82±7.36 | 92.86±9.33 | 0.078 |
| 15 min after release of pneumoperitoneum | 83.07±6.50 | 91.32±11.72 | 0.002 |
| At the end of surgery | 82.64±7.26 | 88.04±9.03 | 0.017 |

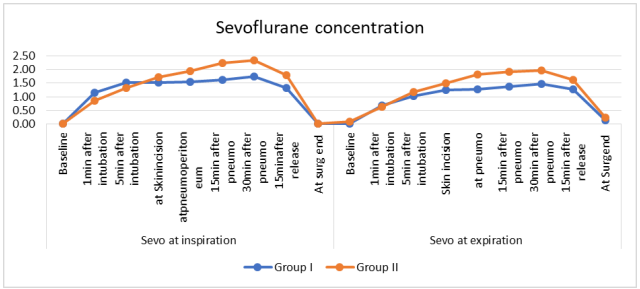


**Fig. 1:**

VAS score was lower in group I when compared with group II, being statistically significant at 30 min intervals till 2 hours postoperatively ($p < 0.05$). (Table 4)

Group I (Clonidine group) TAR was significantly prolonged (6.5 ± 1.6 hours) when compared with group II (1.9 ± 1.1 hours), $p < 0.05$. Clonidine group patients received only one dose of Tramadol and Metoclopramide during the first 24hour period. On the other hand, more patients in the Vitamin C group required two or more doses of Tramadol and Metoclopramide thus needing higher 24hr cumulative analgesic doses when compared to group I (Clonidine group). (Figure 2)

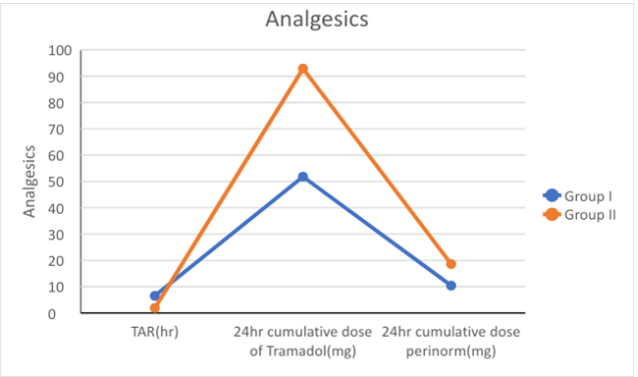


**Fig. 2:** Comparison of TAR and 24hr cumulative analgesic doses

**Table 4:** Comparison of Sedation and VAS score

| Sedation score | Group I (n=28) ($\bar{x}\pm\sigma$) | Group II (n=28) ($\bar{x}\pm\sigma$) | p |
|---|---|---|---|
| 30 min | 1.11±0.99 | 0.89±1.07 | 0.440 |
| 60 min | 0.43±0.63 | 0.46±0.88 | 0.862 |
| 90 min | 0.25±0.44 | 0.18±0.55 | 0.593 |
| 120 min | 0.07±0.26 | 0.04±0.19 | 0.561 |
| **VAS Score** | | | |
| 30 min | 0.00±0.00 | 0.79±1.34 | 0.003 |
| 60 min | 0.54±1.11 | 2.42±2.93 | 0.003 |
| 90 min | 0.67±0.92 | 3.00±2.30 | 0.000 |
| 120 min | 1.33±1.41 | 3.29±2.59 | 0.002 |

**Table 5:** Comparison of adverse effects

| Adverse events | Group I (n=28) ($\bar{x}\pm\sigma$) | Group II (n=28) ($\bar{x}\pm\sigma$) |
|---|---|---|
| Nausea | 5(17.9%) | 5(17.9%) |
| Vomiting | 3(10.7%) | 3(10.7%) |
| Bradycardia | 1(3.6%) | 1(3.6%) |
| Hypotension | 1(3.6%) | 0 |
| Bradypnea | 0 | 0 |

Although not statistically significant (P > 0.05), occurrence of Nausea and vomiting were comparable in both groups, but were less in group I during the first 30 minutes. Only one patient in the Clonidine group had hypotension which was not statistically significant. (Table 5)

## 4. Discussion

Our study confirms that low dose(100$\mu$g) oral Clonidine premedication attenuated hemodynamic response to laparoscopy and surgical stress like other previous studies.[17,18] In addition it also had a Sevoflurane sparing effect and reduced the total analgesic dose needed to control postoperative pain. Most of the studies in the literature using Clonidine as premedication on perioperative hemodynamic response were done on upper abdominal laparoscopic surgery with isoflurane as an inhalational agent for maintenance. We did our study on patients undergoing laparoscopic gynecological surgeries with Sevoflurane for maintenance, as hemodynamic responses in upper and lower abdominal surgeries differ.[19] Sevoflurane also provides hypnosis, amnesia, analgesia, akinesia, and autonomic blockade during surgical and procedural interventions which synergistically helps to reduce clonidine dose and its adverse effects.[20,21]

Surgical stress and changing patients position, especially after creation of pneumoperitoneum during laparoscopic abdominal surgeries, cause labile hemodynamics, which can be dangerous particularly in older patients with pre existing ischemic heart disease, hypertension, cardiac failure and hemodynamically unstable patients. This is because pneumoperitoneum causes sudden increase in plasma catecholamines, vasopressin levels and renin.[22] These hormones in-turn causes cardiovascular instability like abrupt increase of BP, SVR and HR. These detrimental effects of pneumoperitoneum are counteracted using various pharmacological agents.[4–10] "General anaesthesia (GA) with muscle paralysis, tracheal intubation and intermittent positive pressure ventilation is the most commonly preferred technique for laparoscopic surgeries".[23] GA includes laryngoscopy and endotracheal intubation as a standard technique. This causes sympathetic stimulation which also results in hemodynamic alterations[24] such as tachycardia, increase in BP, sometimes acute coronary syndromes, arrhythmias and cerebrovascular accidents.[25] The properties of ideal premedication are ease of administration, anti-anxiety, sedative, analgesic, reduction in anesthetic requirement, prevention of autonomic stress responses, anti-shivering, drying of airway secretions, antiemetic and reduction of gastric fluid volume with less side effects. Most of these properties are met by Clonidine. Accordingly this study was conducted in fifty-six adult females of ASA grade I and II, to evaluate the effects of oral Clonidine premedication in attenuating the hemodynamic stress response to intubation and laparoscopy, reduction of anesthetic requirements and postoperative pain associated with laparoscopic gynecological surgeries.

Clonidine, a partial selective $\alpha_2$ agonist is an imidazole derivative. Oral bioavailability of Clonidine is 70 to 90%, reaching its peak plasma concentration within 60-90 minutes of intake. Shivender Singh et al[14] and Deepshika et al[15] have used Clonidine 150$\mu$g per orally as premedication who have documented maintenance of stable hemodynamics intraoperatively and during pneumoperitoneum but associated with adverse effects. Considering above reasons in our study, Clonidine 100$\mu$g tablets were given 90 minutes prior to the scheduled laparoscopic procedure and demonstrated more stable

hemodynamics like lower increase in HR and MAP when compared to the placebo (Vitamin C) group during the pneumoperitoneum period as observed by Shivender Singh et al,[14] and Deepshika et al[15] in their study. However, in our study at the end of surgery there was no statistically significant difference in HR. This is probably due to release of pneumoperitoneum. "A decrease in sympathetic tone is by its action on preganglionic prejunctional $\alpha_2$ receptors which causes inhibition adenylyl cyclase resulting in reduced norepinephrine release and vagomimetic action of Clonidine at nucleus tractus solitarius (NTS) is responsible for decrease in HR and bradycardia. Clonidine related bradycardia is more commonly associated with Clonidine poisoning or overdose and rarely occurs after Clonidine administration in prescribed doses".[26] In our investigation, one patient from the Clonidine group and one patient from the Vitamin C group (placebo) developed bradycardia but they responded well to inj. atropine of 0.6 mg. Low incidence of bradycardia may be due to the use of low dose Clonidine. MAP also showed no statistical difference 30 minutes after creation of pneumoperitoneum. This may be because of use of higher concentration of Sevoflurane in the placebo group to maintain MAP.

S Inomata et al[27,28] and Shivender Singh et al[14] showed a decrease in MAC and inhalational agent requirements with Clonidine premedication which is consistent with our study. Sevoflurane concentration needed to maintain stable hemodynamics intraoperatively was significantly lower in Clonidine group. In a study Bernard et al[29] used oral Clonidine premedication with 3.5$\mu$g/kg followed by postoperative IV infusion showed improved hemodynamic profile associated with anesthesia cessation, demonstrating its anesthetic sparing effect.

C. B. Sridhar et al[30] demonstrated a decreased need for postoperative analgesia with Clonidine use. Similarly in our study, TAR was shown to be longer in the Clonidine group in comparison with the vitamin C group. During the postoperative 24hr period, Clonidine group patients mostly required no Tramadol and Metoclopramide or just only one dose but more patients in the vitamin C group needed two or more doses of Tramadol and Metoclopramide. Thus 24hours cumulative analgesic dose requirements of Tramadol and Metoclopramide were statistically significantly lower in Clonidine group than in Vitamin C group (ranging 51.8± 9.4mg for Tramadol and 10.4± 1.9mg for Metoclopramide in group I, 92.9± 26.2mg for Tramadol and 18.6± 5.2mg for Metoclopramide n group II), thus demonstrating Clonidine's significant beneficial effect. This is because of its synergistic analgesic action with opioids and antinociceptive properties.[31,32]

In laparoscopic surgeries the release of catecholamines will be greater due to pneumoperitoneum this will trigger postoperative nausea and vomiting.[33] "Clonidine increases motility of gastrointestinal tract and decreases gastric pH and secretion by reducing sympathetic tone and increasing parasympathetic outflow from the central nervous system, thus reducing incidence of postoperative nausea and vomiting".[34] In our study incidence of nausea and vomiting was almost similar in both the groups postoperatively which required injection metoclopramide 10mg IV, this may be due to ineffective antiemetic action of Clonidine at low doses or multifactorial associated with laparoscopic surgeries. Javaher Froosch et al[35] and Shivender Singh et al[14] showed decreased incidence of postoperative nausea and vomiting, probably this may be because of higher dose of Clonidine.

There was a statistically significant ($p < 0.05$) difference between the two groups in VAS score until two hours from the end of surgery as shown in Table 4, which means that group I (Clonidine group) patients had better pain relief when compared to group II (placebo group). Similar findings were seen in a study by Shivender Singh et al[14] and Marodkar K et al.[36] The analgesic effects of Clonidine is by both central and peripheral action. Centrally, it acts on $\alpha_2$ receptors in the substantia gelatinosa of dorsal horn of the spinal cord, where it increases release of acetylcholine (ACh) and suppress the release of substance P and glutamate. Peripherally, it blocks C-fibers and interact with inhibitory G-proteins. But, in a study comparing oral Clonidine premedication with oral diazepam in elderly patients for intraoccular surgery showed no statistical difference in the postoperative VAS scores for pain, number of analgesic requests and emesis.[37] Possibly this may be because of its comparison with a benzodiazepine.

Clonidine which is structurally similar to norepinephrine stimulates prejunctional $\alpha_2$ receptors that opens up K+ channels and $Ca_{2+}$ channels which in-turn reduces post synaptic transmission from pontine locus coeruleus which results in analgesia and sedation. In our study, there was no statistically significant ($p > 0.05$) difference in sedation score between the groups recorded at 30 min intervals till 2 hours postoperatively (Table 4), probably because in our study only 100$\mu$g of Clonidine was used. In other studies using a higher dose of Clonidine patients were found to be more sedated.[38,39] Clonidine also prevents Sevoflurane induced emergence agitation in children as shown by P J Kulka et al.[40]

In our study, only one patient in the Clonidine group had hypotension who required IV Mephentermine 6mg single dose and none of the patients in the Vitamin C group(placebo) had hypotension during the perioperative period, because we used low dose Clonidine (Table 5). "Y. Passi et al[41] and Altan et al[42] also had similar findings of bradycardia and hypotension at higher doses of Clonidine.[43]

We summarize, that administration of oral Clonidine premedication 100$\mu$g in patients undergoing laparoscopic gynecological surgeries under general anesthesia resulted in improved perioperative hemodynamic stability like stable

heart rate and blood pressure during induction, intubation and laparoscopy. Clonidine also causes dose dependent sedation, hence it can be used as an anesthetic adjuvant for reduction in the intraoperative Sevoflurane concentration and postoperative analgesic requirements with no significant side effects.

## 5. Limitations of the Study

Adequate depth of anesthesia was monitored only by clinical observations and not with BIS monitoring. Drugs like fentanyl and diclofenac were used in our study as analgesic are known to influence the hemodynamic change which was not evaluated. Cortisol levels were not measured to objectively know the stress response to intubation and pneumoperitoneum. Clonidine drug level assay was not done because our study included only ASA I and II patients.

## 6. Conflict of Interest

There are no conflicts of interest, and the study has no external funding.

## 7. Acknowledgement

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