ORIGINAL ARTICLE

EFFECT OF PRE-EMPTIVE CLONIDINE ON INTRAOPERATIVE ISOFLURANE REQUIREMENT, HEMODYNAMIC STABILITY AND POST OPERATIVE ANALGESIA IN PATIENTS UNDERGOING LAPAROSCOPIC CHOLECYSTECTOMY

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ABSTRACT: BACKGROUND AND OBJECTIVES: Haemodynamic instability has been reported in association with laparoscopic surgery in humans. Pneumoperitoneum and Laryngoscopy causes stress response with wide variations in haemodynamics. The present study was conducted to evaluate the effects of IV clonidine on reduction of perioperative stress response, maintaining hemodynamic stability, reduction of intraoperative anaesthetic requirement and on modulation of postoperative pain. **METHODS:** In the present prospective randomized controlled trial of forty patients aged between 18 to 60 years of ASA I and II undergoing laparoscopic cholesystectomy. Patients were divided into two groups of twenty each that is, Group I (Normal saline) and Group II (Clonidine 6 mcg/kg in normal saline). The study drugs were prepared by anaesthesiologist not involved in the study. **RESULTS:** Sex, age and weight and were comparable in both the groups. Study results clearly showed intraoperative MAP and HR changes were significantly at the lower level in clonidine group ($p<0.05$) at all intervals of procedure and also at laryngoscopy with consumption of isoflurane 0.2 -0.4% compared to control group at all intervals with consumption of isoflurane [1-1.5%]. VAS scores were significantly lower in clonidine group 24 hour postoperatively and requirement of first postoperative analgesic was prolonged up to 8 hour postoperatively. **CONCLUSION AND INTERPRETATION:** Clonidine given as 6 mcg/kg IV in two stages that is, at pre-induction and just before PNO maintains HR during PNO but one should be watchful for bradycardia. The mean arterial blood pressure was maintained with clonidine as it gives more haemodynamic stability, reduces intraoperative anaesthetic requirement and VAS scores and prolongs the requirement of first postoperative analgesic.

KEYWORDS: Clonidine; Hemodynamic stability; Laparoscopic surgeries; Perioperative stress response.

INTRODUCTION: Minimal access surgical procedures produce significant less trauma than conventional open procedures with potential advantage of reduced post-operative pain, shorter hospital stays, more rapid return to normal activities and cost effective compared to open procedures.

Extensive endoscopic procedures are now performed in all patients with various co-morbidities. The development of minimally invasive surgery (MIS) has not only revolutionized surgery but this process has also influenced the practice of anaesthesiology.[1]

Laparoscopic operative techniques involve insufflation of carbon dioxide ($CO_{2)}$. Gases like helium, air can also be used Intraabdominal pressure should be maintained at 6 to 12 mm Hg which should not be allowed to exceed 15 mm Hg. The important physiological changes associated with laparoscopy are due to pneumoperitoneum (PNO) and positioning.[2]

During the laparoscopic cholecystectomy there is reduced venous return, left ventricular end diastolic (LVED) pressure is reduced, intrathoracic pressure is increased, right atrial and pulmonary artery occlusion pressure (PAOP) increased during CO2 insufflations.[3] There is increase in mean arterial pressures, heart rate and increased systemic and pulmonary vascular resistance.[2]

Both mechanical and neurohumoral factors stimulates a series of hormonal and metabolic changes that constitute stress response.[2]

Clonidine is centrally acting selective partial α2 adrenergic agonist (α2: α1-220:1). Clonidine acts acutely by stimulating α2 adrenoceptors thereby decreasing non-adrenergic release from sympathetic nerve terminates and consequently decreasing sympathetic rate. The analgesic effects are mediated by activation of α2 adrenoreceptors in dorsal horn of spinal cord. The IV dose is 0.15 to 0.3 mg, has a half-life around 8 to 12 hours. The drug acts in 10 minutes and lasts for three to seven hours.[3]

Post-operative pain after laparoscopic surgical procedures may be quiet severe, particularly in early post-operative period either from incision or visceral manipulation and peritoneal inflammation, presence of gas in abdomen, release of inflammatory mediators contribute to pain after laparoscopic cholecystectomy.[3]

Hence the present study was conducted to evaluate the effects of IV clonidine on reduction of perioperative stress response, maintaining hemodynamic stability, reduction of intraoperative anaesthetic requirement and on modulation of postoperative pain.

METHODOLOGY: This randomized controlled trial was conducted on 40 patient's under-going laparoscopic cholecystectomy. Patients were randomly allocated in to two groups Group I and Group II that is 20 patients in each group. Patients undergoing laparoscopic cholecystectomy between age 15 to 60 years and weight between 40 to 60 Kg, ASA grade I and II were included in the study. Patients with cardiovascular pathology, diabetes, hypertension, ischaemic heart disease, valvular heart disease, left ventricular hypertrophy, arrhythmia, treatment with beta blocker, methyldopa angiotensin converting enzyme inhibitors, renal or hepatic dysfunction, were excluded from the study.

The study was approved and ethical clearance was obtained from Human Ethics Committee. After a thorough preanaesthetic evaluation and over-night fasting patients were pre-loaded with an intravenous infusion of 10 ml/kg of Ringers lactate solution after obtaining IV access on the forearm with 18 Gauge I V cannula.

Investigations like, complete blood count, urine routine and microscopy, blood urea nitrogen, serum creatinine, fasting and post prandial blood sugar, X-ray Chest PA view, electrocardiography (ECG) and bleeding and clotting time were done. Drugs were given intravenously as slow infusion to patients 30 minutes before surgery in pre-operative room.

Group I received saline 10 ml and Group II received clonidine (3 µg/Kg) 300 mcg diluted to 10 ml NS given as 0.1 ml/kg.

After premedication with glycopyrrolate 0.005 mg/Kg and fentanyl 0.15 mcg/Kg. Patients were then induced with thiopentone 5 mg/Kg and vecuronium 0.1 mg/Kg. Further they were intubated with appropriate sized cuffed endotracheal tube and maintained on nitrous oxide and oxygen (66:33), isoflurane 0.5%, -1%. Just before creation of pneumoperitoneum same dose of clonidine 3 µg/Kg 300 mcg diluted to 10 ml NS given as 0.1 ml /kg (over 10 min) was infused to group II and 10ml saline to group I. After pneumoperitoneum if there was increase in BP more than 20% of basal BP, isoflurane concentration was increased accordingly as a rescue agent. Any > 20% fall in BP was treated with ephedrine 3 to 6 mg. SBP, DBP, MAP, HR were noted at T1 (Baseline), T2 (laryngoscopy), T3 (After pneumoperitoneum), T4 (15 minutes), T5 (30 minutes), T6 (Exsufflation), T7 (Post operatively 5 minutes), T8 (30 minutes) and End tidal carbon di-oxide [$ETCO_2$], SPO_2 were noted at all intervals.

After surgery patients were reversed with glycopyrrolate 0.005 mg/Kg and Neo stigmine 0.05 mg/Kg and patients were shifted to recovery. Intensity of pain was noted by Visual Analogue scale (VAS) for every five minutes for 15 minutes, every 15 minutes for two hours, every second hourly for 12 hours, fourth hourly for 24 hours. Postoperative requirement of injection Diclofenac (1.5 mg/kg) was noted.

Demographic data were analyzed by Analysis of Variance Test [ANOVA]. Parametric variables like systolic BP, diastolic BP and mean arterial pressure [MAP] and heart rate were tabulated as Mean ± SD and analyzed by student 't' test. Non parametric variables like pain expressed as median tabulated as per VAS score and analyzed by Mann Whitney U test. VAS score up to 3/10 was standardized as satisfactory analgesia. Diclofenac injection was standardized as rescue analgesic.

RESULTS: In this study 65% were males and 35% were females in group I and II with male to female ratio of 1.85:1. Most of the patients (Group I 65% and group II 85%) in both the groups were aged between 46 to 60 years. The mean age in group I was 46.80 ± 3.55 years and in group II it was 49.75 ± 4.19 years suggesting both the groups had comparable demographic characteristics.

The mean height in group I was 159.45 ± 2.35 Cms and in group II it was 160.05 ± 3.17 Cms. The mean weight in group I was 59.70 ± 3.10 Kgs and in group II it was 62.75 ± 3.97 Kgs suggesting mean weight and height in both groups were comparable. In both the groups 70% of patients had ASA status I and 30% had II.

Intraoperative MAP changes of clonidine groups of patients with consumption of isoflurane (0.2 to 0.4%) were at lower level $p<0.001$ compared to placebo groups with isoflurane 1.0 to 1.5% at various periods of procedure with (Table 1).

The intraoperative heart rate changes of clonidine groups of patients with consumption isoflurane (0.2 to 0.4%) were at lower level with $p<0.001$ compared to placebo groups with isoflurane 1.0 to 1.5% at various periods of procedure (Table 2).

Isoflurane concentration in clonidine group (0.2 to 0.4%) was significantly lower than in placebo group with isoflurane concentration (1.0 to 1.5%) to maintain hemodynamic stability (Graph 1).

The VAS scores were significantly lower in Clonidine group ($p<0.001$) without the use of analgesic for the first 7 to 8 hours whereas in control group with the use of analgesic VAS scores are higher (Graph 2).

Requirement of first dose of analgesic was prolonged in clonidine group for up to first 8 hrs postoperatively ($p<0.001$). Diclofenac sodium was used as rescue analgesic in both the groups.

DISCUSSION: No other operation has been so profoundly affected by the advent of laparoscopy as cholecystectomy. In fact, the converse may be more accurate; laparoscopic cholecystectomy (LC) has been instrumental in ushering in the laparoscopic era.[4]

Peritoneal carbondioxide insufflations necessary for laparoscopic Cholecystectomy results in stress response, induces major hemodynamic changes in healthy patients. These significant disturbances characterized by increase in MAP, SVR, PVR and a decrease of CI. CI significantly decreases as much as 50% of the preoperative value five minutes after CO_2 insufflation. The paradoxical increase in RAP and PCWP after insufflations is explained by increase intrathoracic pressure.[5,6]

Alpha-2 adrenoceptor agonists have analgesic properties when given parenterally, epidurally or intrathecally.[7]

Clonidine is an α–2 adrenoreceptor agonist. It exerts central sympatholytic effect and has a half-life of 9-12 h. Premedication with clonidine blunts the stress response to surgical stimuli and the narcotic and anaesthetic doses are also reduced. Clonidine activates postsynaptic alpha 2 receptors in dorsal horn of spinal cord producing analgesia.[8]

Demographic data were comparable in both the groups .Present study results clearly showed intraoperative MAP changes were significantly lower in clonidine group that is $p <0.001$** compared to control group at all intervals . Thus MAP remained under satisfactory control.

Also intraoperative heart rate changes were found to be significantly lower in clonidine group at all intervals of procedure that is $p<0.001$ compared to placebo group at all intervals. Thus heart rate remained under satisfactory control.

Similar effects of clonidine were reported by Shivinder Singh et al,[9] Mrinmoy Das et al,[10] Laisalmi et al,[11] Joris J et al.[12] Shivinder Singh[9] et al and Mrinmoy Das et al[10] showed Clonidine 150 mcg improved hemodynamic stability in patients undergoing laparoscopic Cholecystectomy.

Laisalmi[11] et al showed clonidine 4.5 mcg /kg maintained arterial blood pressure, heart rate and plasma rennin activity during and after pneumoperitoneum. Joris J L et al[12] showed clonidine 8 mcg /kg infused over 1 hr before PNO decreased catecholamine release and maintained hemodynamic stability.

In the present study, clonidine 3 mcg/kg was used in two stages, one at pre induction and same dose repeated just before pneumoperitoneum as it is pharmacokinetics of IV clonidine explained by a study[13] showing plasma levels 1.5 to 2 ng/ml after loading dose of 5 mcg/kg of clonidine which results in sedation and hypotensive effects. In order to avoid such effects of IV

clonidine 3 mcg/kg at pre induction was used as slow infusion in this study and same dose repeated just before pneumoperitoneum. In total 6 mcg/kg of IV clonidine was used as slow infusion which did not result in any adverse hemodynamic changes like hypotension and bradycardia.

In this study, at laryngoscopy, MAP and HR (97.43 ± 1.9 mm Hg and 101±2.0 /min) were significantly high compared to group II (91.06±1.19 mm Hg and 84.9±1.88 /Min) p <0.001.

In a study patients were pre medicated with 0.2 mg clonidine, placebo and gabapentin 900 mg. At laryngoscopy, lowest HR found in clonidine group and lowest BP found in clonidine and gabapentin group.[14] In a study HR, SBP were recorded before, immediately and every 5 min after intubation until 20 min. The clonidine (100 mcg) group showed superiority over placebo group in maintaining hemodynamic stability.[15]

In this study intra operative anaesthetic requirement was decreased in clonidine group as compared to placebo group (0.27 ± 0.13 vs 1.45 ± 0.07; p<0.001 **) and reduced 75 % of the isoflurane requirement.

A study done to assess the effect of clonidine premedication 5 mcg/kg provided stable hemodynamics and reduced isoflurane requirement up to 40% (0.61 ± 0.20 vs 1.03 ± 0.16% p<0.01) compared to placebo group.[16]

In the present study VAS scores were significantly lower in clonidine group in the first 24 hours, up to 2hrs (p<0.001), 2 hourly for 12 hour (p=0.002), 4 hourly for 24 hour (p=0.387).

Up to 12 hr postoperatively VAS scores were significantly lower (p<0.001) without the use of analgesic for the first eight hours compared to control group with the use of diclofenac sodium as analgesic.

A study to assess the effects of clonidine 100mcg on postoperative pain and morphine consumption after abdominal hysterectomy showed that, total morphine consumption and VAS scores were lower in clonidine group up to 48 hr compared to control group and morphine consumption was less in clonidine group 20 ± 1.28 Vs 26.9 ± 2.8 (p<0.05) comparable to our study VAS scores were significantly lower in group II with (p<0.001) up to 12 hr and (p=0.002) up to 24 hr and the time for first postoperative analgesic was prolonged up to 480 min postoperatively (p<0.001).[17]

Ghafari Md et al studied effects of clonidine 100mcg ,showed total morphine consumption and VAS scores were lower in clonidine group up to 48 hr compared to control group and morphine consumption was less in clonidine group 20 ± 1.28 Vs 26.9 ± 2.8 (p<0.05).[18]

Overall the present study showed that, the administration of IV clonidine 6 **µ**g/Kg in patients undergoing Laparoscopic cholecystectomy resulted in improved perioperative haemodynamic stability and reduction in post-operative pain and requirement of analgesic. Further studies on large sample would confirm these results.

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Time interval	Group I (n=20)	Group II (n=20)	'p' value
T1	89.47 ± 1.34	88.53 ± 2.11	0.211 NS
T2	97.43 ± 1.90	91.07 ± 1.19	< 0.001 HS
T3	101.22 ± 2.22	84.37 ± 1.77	< 0.001 HS
T4	103.30 ± 1.91	83.30 ± 1.13	< 0.001 HS
T5	101.07 ± 1.53	76.00 ± 1.60	< 0.001 HS
T6	98.65 ± 1.47	76.23 ± 2.92	< 0.001 HS
T7	100.57 ± 1.64	79.05 ± 1.98	< 0.001 HS
T8	101.47 ± 4.70	80.52 ± 1.68	< 0.001 HS

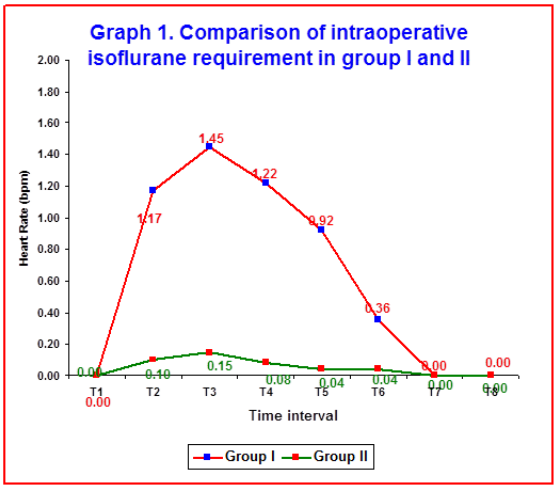
Table 1: Comparison of intraoperative MAP changes in group I and II

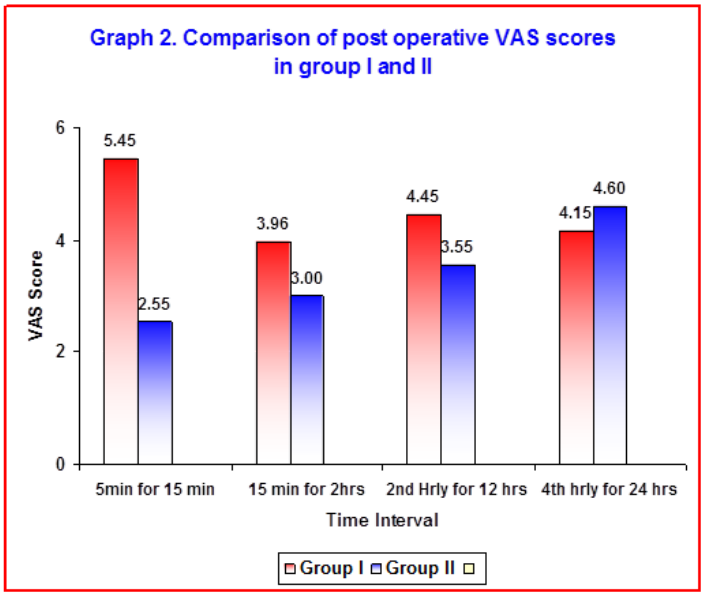
NS – Not Significant, HS – Highly Significant.

Time interval	Group I (n=20)	Group II (n=20)	'p' value
T1	81.00 ± 1.89	81.80 ± 2.14	0.218 NS
T2	94.95 ± 2.24	84.90 ± 1.89	< 0.001 HS
T3	91.90 ± 2.00	79.20 ± 2.09	< 0.001 HS
T4	98.20 ± 3.05	75.80 ± 1.58	< 0.001 HS
T5	91.35 ± 2.08	72.90 ± 2.38	< 0.001 HS
T6	87.40 ± 2.16	74.60 ± 3.38	< 0.001 HS
T7	92.20 ± 2.91	79.20 ± 1.64	< 0.001 HS
T8	89.70 ± 2.08	79.50 ± 2.14	< 0.001 HS

Table 2: Comparison of intraoperative heart rate changes in group I and II

NS – Not Significant, HS –Highly Significant.





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