COMPARATIVE STUDY OF ITRAVENOUS NITROGLYCERINE AND CLONIDINE ON HAEMODYNAMIC STABILITY IN LAPROSCOPIC CHOLECYSTECTOMY.

P.K. Omar, S. K. Katiyar,Vineeta Gupta.

1. Assistant Professor Department of Anesthesiology, Rama Medical College Hospital & Research Centre, Kanpur.
2. Associate Professor Department. of surgery, Rama Medical College Hospital & Research Centre, Kanpur.

CORRESPONDING AUTHOR:
Dr. S. K. Katiyar M. S.,
FIAGES 675, Singhpur,
Kanpur- 208017.
E-mail: drskkatiyar59@rediffmail.com

ABSTRACT: Clonidine has been shown to reduce perioperative haemodynamic instability. The aim of the study was to investigate the clinical efficiency of intravenous clonidine premedication with nitroglycerine infusion in prevention of haemodynamic response associated with pneumoperitoneum.

Sixty adult patients of ASA physical status I& II, scheduled for elective laparoscopic cholecystectomy were recruited for a prospective randomized, double-blinded comparative study. They were randomly allocated to one of the two groups to receive either nitroglycerine infusion (Group I) or i.v. clonidine 2mg (Group II), before induction of anaesthesia. Significant rise in heart rate was observed following pneumoperitoneum in Group I as compared to Group II (99.23±14.02 Vs 81.26±8.40 bpm). Similarly, while systolic arterial pressure, diastolic arterial pressure and mean arterial pressure changes were insignificant in both the groups following pneumoperitoneum. Nitroglycerine drip was started in 2 patients in Group II to control intraoperative hypertension. Incidence of postoperative nausea-vomiting and shivering was less in GroupII.

To conclude, clonidine premedication provides better perioperative haemodynamic stability, hence it can be recommended as a routine premedication for laparoscopic cholecystectomy.

INTRODUCTION: Laparoscopic cholecystectomy has revolutionized gall bladder surgeries and it has now become the "gold standard" of cholelithiasis [1]. It offers many benefits than conventional cholecystectomy, and has been promoted as a "gentle surgery". The number of cases continue to increase because of its clinical advantages in decreasing perioperative complications, postoperative pain and postoperative hospitalization compared to the conventional open technique. However, this procedure is not risk free.

In fact it produces significant haemodynamic changes specially in elderly and haemodynamically compromised patients. Pneumoperitoneum affects several homeostatic systems leading to alteration in acid-base balance, cardiovascular, pulmonary physiology and stress response. The extent of cardiovascular changes associated with pneumoperitoneum includes an

increase in mean arterial pressure, decrease in cardiac output and increase in systemic vascular resistance which in turn compromise tissue perfusion.

Various pharmacological agents like nitroglycerine, β blocker, and opioids are used to provide hemodynamic stability during pneumoperitoneum [4], but they have their own disadvantages. Nitroglycerine was used to correct the reduction of cardiac output associated with increased pulmonary occlusion pressure and systemic vascular resistance.

Aho et al used $á_2$ adrenergic receptor agonist for prevention of haemodynamic responses associated with laparoscopic surgery. They found that dexmedetomidine effectively reduces the maximum heart rate response after intubation and pneumoperitoneum. Clonidine inhibits the release of catecholamine and vasopressin and thus modulates the haemodynamic changes induced by pneumoperitoneum. [3]

Clonidine, a α-2 adrenergic receptor agonist, has shown promising results for attenuation of hemodynamic response associated with laparoscopic surgery [4-8]. The present study was undertaken with the objective of evaluating the type and extent of hemodynamic changes during laparoscopic cholecystectomy and their modification by two different drugs i.e. intravenous nitroglycerine and intravenous clonidine.

Nitroglycerin is mainly used for the treatment and prevention of ischemic heart disease by dilating the coronary artery, systemic or focal veins with an ordinarily low dose which decreases preload and workload of the right ventricle and decreases the pulmonary artery pressure in addition to dilation of the pulmonary vessels. Nitroglycerin dose not induce remarkable changes in SVR at a low dose but induces a decrease in SVR by dilation of arterioles with a high dose. The usual dose of nitroglycerin is 0.5-2 μg/kg/min while the dose used in this study was a relatively low at 0.5 μg/kg/min, in consideration of the possibility that high dose nitroglycerin may induce severe hypotension in cases of hypovolemic states

OBJECTIVES OF STUDY: To study the influence of clonidine and nitroglycerine as intravenous infusion on the carbon dioxide pneumoperitoneum induced haemodynamic changes during laparoscopic surgeries

SOURCE OF DATA:- 60 patients undergoing elective laparoscopic surgeries under general anaesthesia in Rama medical college and Hospital Mandhana Kanpur, satisfying the inclusion criteria were randomized into two groups based on block randomization during the study period from October 2012 to March 2013.

INCLUSION CRITERIA:-

1. Patients belonging to ASA physical status 1 and 2.
2. Patients between 18-70 years.
3. Elective laparoscopic surgeries

EXCLUSION CRITERIA:-

1. Patients belonging to ASA physical status 3, 4 and 5.
2. Patients with Aortic Stenosis.
3. Patients with history of left ventricular failure.

4. Patients with Atrioventricular Conduction Block.
5. Patients taking Clonidine, Beta blocking drugs, MAO inhibitors.

MATERIALS AND METHODS: After institutional review board approval and informed written consent from the patients, this prospective, randomized, double-blind controlled clinical study was carried out in 60 patients of either sex, aged 18-70 years, of ASA physical status I and II, scheduled for laparoscopic cholecystectomy under general anesthesia from Oct 2012 to March 2013. Exclusion criteria were patients with anticipated difficult airway; body mass index (BMI) >25, history of cardiopulmonary diseases; psychiatric illness; and therapy with α-2 adrenergic agonists, β blocker, methyldopa, MAO inhibitors, tricyclic antidepressant, and benzodiazepines.

In the pre-anesthetic preparation room, monitoring for heart rate (HR), non-invasive systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP), peripheral oxygen saturation (SpO_2), and end-tidal CO_2 ($Et\ CO_2$) was instituted. Sedation was rated as per score shown in [Table 1].

Table 1

SCORE	LEVEL OF SEDATION
0	Awake and agitated
1	Awake and comfortable
2	Asleep and arousable
3	Asleep with sluggish response to verbal commands or touch
4	No response to verbal command or touch

Patients were randomly divided into two groups of 30 each. Group I received NITROGLYCERINE INFUSION@ 0.5mcg/kg/min from the time of intubation and group II, received, 2 µg/kg of clonidine in 100 ml of normal saline before induction of anaesthesia. The drug was given over 15 min intravenously along with glycopyrrolate 0.004 mg/kg and tramadol 1.5 mg/kg, 30 min before induction of anesthesia.

Induction of anesthesia was done with intravenous propofol followed by succinyl choline, 2 mg/kg to facilitate tracheal intubation; trachea was intubated with an appropriate sized cuffed, disposable endotracheal tube. Lungs were mechanically ventilated with O_2 - N_2O (30-70), isoflurane (1-2%), and vecuronium bromide 0.1 mg/kg bolus followed by 1 mg intermittently for neuromuscular blockade. Tidal volume and ventilator frequency were adjusted to maintain normocapnia ($EtCO_2$ 40 ± 4 mmHg). Pneumoperitoneum (PP) was created by insufflations of CO_2 and operation table was tilted to about 15 degree reversed trendelenberg. Intra-abdominal pressure was not allowed to exceed 15 mmHg. Throughout the study period, All the parameters selected (HR, SBP, DBP, MAP, and SpO_2) were recorded at specified timings. Any change in hemodynamic variables more than 20% on either side of baseline was considered significant. Any increase in MAP up to 20% from baseline was treated by increasing the concentration of isoflurane to a maximum 2%. Any increase in MAP more than 20% from baseline was treated with nitroglycerine infusion. Nitroglycerine infusion was adjusted to maintain the MAP within 20% of baseline. Time duration from creation of pneumoperitoneum to the release of pneumoperitoneum was taken as duration of pneumoperitoneum. At the end of surgery, neuromuscular blockade was

reversed with neostigmine 50 μg/kg and glycopyrrolate 10 μg/kg intravenously. After satisfying the extubation criteria, trachea was extubated and patients were transferred to post-anesthesia care unit (PACU). In PACU, HR, SBP, DBP, MAP, SpO_2, sedation score, and any incidence of complications/adverse event were monitored for next 1 h. Maintenance of MAP and SpO_2 within 20% of baseline and sedation score ≤ 2 was considered criteria for recovery. Sample size of minimum 29 per group was derived using Cohen's formula based on assumption of α error 0.05 and power of study 80% after permitting β error of 0.2 to detect a difference of at least in the quantitative variables between the groups. Mean and standard deviation were calculated for all the quantitative variables using graph-pad prism statistical software. An intra-group comparison was made using paired Student's t-test and comparison between two groups at a time (inter-group comparison) was done using the unpaired t-test. P <0.05 was considered statistically significant.

OBSERVATION: All patients (n=60) completed the study. Demographic parameters were comparable between groups (P >0.05) [Table 2]. Duration of pneumoperitoneum in all the patients was 80 min or less except one patient in group I in whom the pneumoperitoneum lasted for 90 min. As the monitored hemodynamic variables at 90-min time point were not available in other groups, this time point was excluded. Two patients out of 30 in group 2 required nitroglycerine infusion for more than 20% rise in MAP above baseline.

In group III, a decrease in HR, SBP, DBP and MAP from baseline was observed within 15 min of clonidine premedication (P <0.05), but at no time, this decrease was more than 20% from baseline. At tracheal intubation, HR and DBP increased (P >0.05), while SBP decreased (P >0.05) and MAP remained comparable to baseline. Within 40 min of pneumoperitoneum HR and within 20 min SBP, DBP, and MAP decreased (P <0.05) and remained so throughout the study period Hemodynamic variables at the time of extubation remained comparable to baseline. All the patients maintained MAP comparable to baseline with 1% isoflurane. No patient in group III required nitroglycerine infusion. SpO_2 remained stable and comparable to baseline in all the three groups.

Higher sedation score was observed in group II as compared to group I at specified timings (P <0.05) but it never approached 2 at any time and no sign of respiratory depression observed. No patient in any group demanded supplemental analgesic up to 1 h postoperatively. 30%, 20%, and 10% patients in group I had nausea, vomiting, and shivering respectively in the postoperative period while none had any complication in other two groups.

Table 2 Demographic Profile (Mean ± SD)

Demographic Profile	Group I	Group II	P Value	Significance
Age (years)	38.13±9.47	36.13±9.17	0.196	NS
Weight (Kg)	57.06±5.98	56.16±5.28	0.109	NS
Weight (Kg)	5 : 25	7:23	0.100	NS
ASA Grading	Grade I = 26 Grade II = 4	Grade I = 26 Grade II = 4		

Table 3: Preoperative vital parameters (Mean ± SD)

Vital Parameters	Group II	Group II	P Value	Significance
Pulse Rate (bpm)	79.1±7.81	81.1±9.61	0.357	NS
MAP (mm Hg)	94.7±7.22	92.5±8.62	0.151	NS
SpO2 (%)	96.4±1.27	96.4±1.17	0.1	NS
Sedation Score	1.23±0.43	1.33±0.20	0.065	NS

Table 4: Changes in pulse rate in two groups

Diastolic Blood Pressure (mm Hg)	Group I (Mean ± SD)	Group II (Mean ±SD)	P Value	Significance
Before Premedication	79.1±7.81	79.1±7.81	0.3540	NS
Before Induction	89.1±7.81	84.1±7.81	0.085	S
After Intubation	99.1±7.81	89.1±7.81	0.0069	HS
Before Pneumoperitoneum	101.89±7.81	92.1±7.81	0.051	HS
After Pneumoperitoneum(15 min)	96.1±7.81	85.1±7.81	0.007	HS
After Pneumoperitoneum(30 min)	97.1±7.81	83.1±7.81	0.0043	HS
After Release of Carbon Dioxide	81±7.81	81.1±7.81	0.01	NS
After Extubation	110.1±7.81	99.1±7.81	0.0040	HS

Table 5: Changes in systolic blood pressure in two groups

Diastolic Blood Pressure (mm Hg)	Group 1(Mean ±SD)	Group 2(Mean ± SD)	Group 3(Mean ± SD)	Significance
Before Premedication	119.1±7.81	112.1±7.81	0.345	NS
Before Induction	121.1±7.81	116.1±7.81	0.300	NS
After Intubation	126.1±7.81	121.1±7.81	0.091	NS
Before Pneumoperitoneum	122.1±7.81	115.1±7.81	0.003	HS
After Pneumoperitoneum(15 min)	120.1±7.81	117.1±7.81	0.097	NS
After Pneumoperitoneum(30 min)	118.1±7.81	115.1±7.81	0.30	NS
After Release of Carbon Dioxide	117.1±9.1	113.1±7.81	0.089	NS
After Extubation	122±7.81	120.1±7.81	0.078	NS

Table 6: Changes in mean arterial pressure in two groups

Diastolic Blood Pressure (mm Hg)	Group 1(Mean ± SD)	Group 2(Mean ± SD)	Group 3(Mean ±SD)	Significance
Before Premedication	89.1±7.81	91.1±7.81	0.342	NS
Before Induction	1001±7.81	94.1±7.81	0.030	HS
After Intubation	90.1±7.81	91.1±7.81	0.091	NS
Before Pneumoperitoneum	92.1±7.81	91.1±7.81	0.099	NS
After Pneumoperitoneum(15 min)	91.1±7.81	91.1±7.81	0.097	NS
After Pneumoperitoneum(30 min)	90.1±7.81	88±7.81	0.30	NS
After Release of Carbon Dioxide	85.1±9.1	90.1±7.81	0.089	NS
After Extubation	122±7.81	120.1±7.81	0.078	NS

Table 7: Changes in diastolic blood pressure in two groups

Diastolic Blood Pressure (mm Hg)	Group 1(Mean ±SD)	Group 2(Mean ±SD)	Group 3(Mean ± SD)	Significance
Before Premedication	81.1±7.81	79.1±7.81	0.342	NS
Before Induction	841±7.81	81.1±7.81	0.030	NS
After Intubation	84.1±7.81	83.1±7.81	0.091	NS
Before Pneumoperitoneum	83.1±7.81	80.1±7.81	0.099	NS
After Pneumoperitoneum(15 min)	82.1±7.81	81.1±7.81	0.097	NS
After Pneumoperitoneum(30 min)	80.1±7.81	78±7.81	0.30	NS
After Release of Carbon Dioxide	84.1±9.1	80.1±7.81	0.089	NS
After Extubation	86±7.81	80.1±7.81	0.078	NS

RESULTS: Three patients were withdrawn from the study because the proposed laparoscopic cholecystectomy surgery was converted to open cholecystectomy. Aside from these three patients, rest of the patients completed the analysis. Demographic profile and preoperative vital parameters were compared between the two groups of patients and no significant difference was found [Table 1]& [Table 2]. Mean intra-abdominal pressure was 13.1±1.47 mm Hg in Group I and Group II.. Normocapnia was maintained throughout the procedure. EtCO 2 varied from 31.13±3.45

to35.46±5.36 mmHg in Group I, Group II. Mean pulse rate varied from 81.43±11.21 to 113.17±13.33 bpm in Group I and Group II. Upon statistical comparison in two groups of patients, no significant variation was observed throughout the intra operative period including the baseline value. [Table3].Changes in the blood pressure when compared was found to be statistically insignificant. [Table 4], [Table5], [Table6]and [Table7].

Patients remained haemodynamically stable in both the groups. Incidence of nausea-vomiting, hypertension, shivering and shoulder pain were 35.70%, 35.70%, 10.7% and 14.3% in the Group I in Group II only 6.89% patients suffered from nausea vomiting. Sedation was common in Group II (33.33%). Other complications were not observed in Group II. None of the patient showed any evidence of ischaemia or arrhythmia intraoperatively.

DISCUSSION: Pneumoperitoneum during laparoscopy produces significant haemodynamic changes, which can be detrimental especially in elderly and haemodynamically compromised patients.[10]. Various techniques and pharmacological agents have been used to counteract these detrimental effects of pneumoperitoneum. This double blind prospective study was carried out in 60 adult patients, to compare the effect of nitroglycerine infusion and clonidine premedication in attenuating haemodynamic stress response associated with pneumoperitoneum. Clonidine, an imidazoline derivative is a selective $á_2$ adrenergic agonist. It is a potent antihypertensive drug. It produces a fall in the heart rate and blood pressure associated with decreased SVR and cardiac output. Dose of clonidine varied from 2 to 5 $\mu g.kg^{-1}$ in different studies. Higher dose of clonidine (5 $\mu g.kg^{-1}$) is usually required for potentiation of postoperative analgesia by intrathecal morphine.[11]. A small oral dose of clonidine decreased the incidence of perioperative myocardial ischemic episodes without affecting haemodynamic stability.[8] Aho et al[9] used 3 $\mu g.kg^{-1}$ and 4.5 $\mu g.kg^{-1}$ clonidine for suppression of haemodynamic response to pneumoperitoneum. Rise in blood pressure and heart rate was less in both the groups but 4.5

$\mu g.kg^{-1}$ clonidine produced greater fall in mean arterial pressure before induction. Joris et al[9] used very high dose of clonidine (8 $\mu g.kg^{-1}$) for reducing the level of catecholamine and vasopressin following pneumoperitoneum. Malek et al[12] used 150 µg of clonidine as i.v. infusion and intramuscularly while Sung et al[13] and Yu et al[14] used 150 µg of oral clonidine as premedication for maintenance of haemodynamic stability during pneumoperitoneum. Following pneumoperitoneum with carbon dioxide, patients were hyper ventilated to maintain normocapnia. Every effort was made to maintain intra abdominal pressure (IAP) below 14 mm Hg. Mean intra-abdominal pressure was 13.1±1.47 mm Hg in Group 1 and 12.7±1.15 mm Hg in Group II. Haemodynamic changes associated with pneumo peritoneum were first recognized in 1947.[15] Diamant et al[16] reported 35%decrease in cardiac output in dog with a raised intra abdominal pressure of 40 mm Hg. Ishizaki et al[17] tried to evaluate the safe intra-abdominal pressure during laparoscopic surgery. They observed significant fall in cardiac output at 16 mm Hg of intra-abdominal pressure. Haemodynamic alterations were not observed at 12 mm Hg of intra-abdominal pressure. Based on all these observations the current recommendation is to monitor intra-abdominal pressure and to keep it as low as possible. Cunningham et al[20] and Dorsay et al[21] assessed the ejection fraction (EF) of left ventricle by trans esophageal echocardiography during pneumoperitoneum. No significant change in ejection fraction was reported up to 15 mm Hg

of intra-abdominal pressure. Considering all these facts intra abdominal pressure was kept below 14 mm Hg.

In spite of maintaining normocapnia and keeping intra-abdominal pressure below 14 mm Hg significant rise in heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure was noticed in Group P. Rise in systolic, diastolic and mean arterial pressure was more than 20% from the baseline. Slight fall in systolic blood pressure, diastolic blood pressure and mean arterial pressure was noticed following premedication with clonidine. Following intubation and pneumoperitoneum, increase in arterial pressure was noticed but it never crossed the base line value. Hence clonidine premedication was able to achieve haemodynamic stability during pneumoperitoneum.

Similar findings were reported by Aho et al [8], Joris et al [9], Malek et al [12], Sung et al [13], Yu et al [14] and Laisalmi et al[20].

Aho et al [2] observed that 4.5 $\mu g.kg^{-1}$ of clonidine significantly decreased the mean arterial pressure before induction of anaesthesia. So they recommended 3 $\mu g.kg^{-1}$ of clonidine for perioperative haemodynamic stability. Joris et al [9] used higher dose of clonidine for reduction of catecholamine and vasopressin associated with pneumoperitoneum. Clonidine significantly reduced the concentration of catecholamine but not vasopressin and cortisol concentration. Similarly Sung et al [13] observed haemodynamic stability during pneumoperitoneum with 150 µg oral clonidine. Requirement of isoflurane was also less by 30% in the clonidine group. Yu et al [14]recommended the routine use of clonidine premedication in laparoscopic patients.

The adverse effects in the postoperative period were less in the patients who had clonidine premedication in comparison with nitroglycerine group. There was incidence of shivering in 10.70% patients in the group 1patients as compared to none in the clonidine group.

This finding corroborates the finding of Nicolaou et al, where they concluded that clonidine inhibits cold thermoregulatory response due to an effect on central integration control and output from the thermoregulatory centers. [21]. Thus he opined that clonidine can be used as an effective agent for inhibition of perioperative shivering which can adversely increase metabolic rate and cardiac work and may also disrupt surgical repair or result in wound dehiscence.

Thirty five percent of patients of the Group I suffered from nausea and / or vomiting, while only 6.89% of the patients receiving clonidine had any such episode. Clonidine increases gastrointestinal motility by decreasing sympathetic outflow and increasing parasympathetic out-flow from the central nervous system. Although many workers have reported the antiemetic property of clonidine, the mechanism by which it acts warrants further investigation.

CONCLUSION: Premedication with 2µg/kg of IV clonidine, has been found to be relatively safe as well as effective method that provides stable hemodynamics and protection against stress response triggered by pneumoperitoneum in patients undergoing laparoscopic cholecystectomy. Clonidine also affords an added advantage of reduction in postoperative complications such as nausea-vomiting and shivering.

Although nitroglycerine infusion at a rate of 0.5mcg/kg/min from the time of intubation also attenuates the haemodynamic changes associated with carbon-dioxide associated pneumoperitoneum but fail to have other beneficial effects as compared to clonidine

premedication.

Hence 2μg/kg of IV clonidine can reasonably be recommended as premedicant for all laparoscopic procedures in otherwise healthy patients. However further study is required to find out its efficacy in patient with compromised cardiovascular system.

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