Research Article

Effect of intravenous clonidine premedication in patients undergoing laparoscopic cholecystectomy

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ABSTRACT

Background: Pneumoperitoneum to facilitate laparoscopic surgery produces hemodynamic changes that can be harmful for the elderly as well as patients with cardiovascular compromise. Clonidine is an alpha- 2 agonist that can attenuate these changes.

Methods: This study of 100 patients was a single blind prospective randomized controlled study. Patients were randomly divided into two groups of 50 each. The clonidine group received 2 microgm/kg iv clonidine in 10 ml normal saline 15 minutes prior to induction. The placebo group received only normal saline. Hemodynamic parameters and incidence of vomiting and shivering were noted.

Results: Data was analysed by Pearson's chi-square test. Clonidine significantly attenuated the rise in heart rate, and the blood pressure. The incidence of postoperative nausea and vomiting was less in the clonidine group. It also reduced shivering.

Conclusions: 2 microgm/kg of clonidine iv can be reasonably recommended as a premedicant for laparoscopic procedures in otherwise healthy patients. However further study is required to test its efficacy in patients with compromised cardiovascular function.

Keywords: Alpha 2 agonists, Hemodynamic attenuation, Laparoscopic surgery

INTRODUCTION

Laparoscopic surgery, also called minimally invasive surgery (MIS), bandaid surgery, or keyhole surgery is a modern surgical technique in which operations in the abdomen are performed through small incisions (usually 0.05-1.5cm) as compared to larger incisions needed in traditional surgical procedures. There are a number of advantages with laparoscopic surgery versus an open procedure. These include reduced pain due to smaller incisions and shorter recovery time. The abdomen is usually insufflated with carbon dioxide gas. Carbon dioxide is used because it is common to the human body and can be absorbed by tissue and removed by the respiratory system. It is also non-flammable, which is important because electrosurgical devices are commonly used in laparoscopic procedures.

Laparoscopic cholecystectomy has revolutionized gall bladder surgeries and it has now become the "gold standard" for the treatment of cholelithiasis.

However, the pneumoperitoneum (PNO) required for laparoscopy results in pathophysiologic changes.[1] More particularly, changes in cardiovascular function occur during laparoscopy. These are characterized by an increase in arterial pressure and systemic and pulmonary vascular resistances (SVR and PVR) early after the beginning of intra-abdominal insufflation, with no significant changes in heart rate (HR). A 10% to 30%

decrease in cardiac output has also been reported in most studies.[1-3]

Both mechanical and neurohumoral factors contribute to these haemodynamic changes.[2,4] Several mediators have been proposed: catecholamines prostaglandins, renin and vasopressin.[5-11]

Alpha 2-adrenergic agonists have been shown to improve haemodynamic stability during gynaecologic laparoscopy.[12,13] Clonidine is a selective α-2 adrenergic receptor agonist, which is known to produce sedation, analgesia and haemodynamic stability. It modulates haemodynamic changes during anaesthesia induction, both during and after surgery, improves myocardial perfusion during surgery, and decreases requirements for volatile anaesthetics and opioids during surgery.[14] Aim of the study was to investigate whether a single dose of intravenous Clonidine (2 µg/kg) as a premedication blunts the haemodynamic response to laparoscopy in patients undergoing laparoscopic cholecystectomy.

Objectives of the study were to evaluate the efficiency of Clonidine in preventing increased

- Heart rate response to pneumoperitoneum.
- Systolic blood pressure response to pneumoperitoneum.
- Diastolic blood pressure response to pneumoperitoneum.
- Mean arterial pressure response to pneumoperitoneum.
- And to note the incidence of post-operative nausea-vomiting and shivering in both the groups.

METHODS

The study was a single blind prospective randomized controlled study of 100 cases. Cases were divided into two groups (50 each) as,

Group 'C': In this group 2 µg/kg of Inj. Clonidine mixed in 10 ml of normal saline was administered intravenously for a period of 10 minutes about 15 minutes prior to surgery.

Group 'P': In this group only 10ml of normal saline was administered intravenously over a period of 10 minutes about 15 minutes prior to surgery.

The drug/placebo was given to the patient by investigator according to random number table but the observer taking the readings was blind about the drug/placebo given.

Inclusion criteria

- Patient undergoing laparoscopic cholecystectomy.
- ASA grade I and II.

- Age between 18 to 60 years.

Exclusion criteria

- Patient's refusal.
- ASA grade III and IV.
- Age less than 18 years and more than 60 years.
- Patient known to have allergy to Clonidine.
- Pregnant women and lactating mothers.
- Morbid obesity.
- Patients with acute cholecystitis.
- Patients having cardiorespiratory disease and those taking medications for it.

Study procedure: Institutional ethics committee approval was obtained. Preoperative evaluation of the patients was done as per departmental protocol. Patients were allocated randomly to two predetermined groups. The patients were kept nil by mouth for the last 10-12 hours prior to surgery. On the day of surgery, informed written consent was taken. Preoperative vitals were recorded in the form of baseline pulse and blood pressure (BP). Venous cannulation was done. All patients were premedicated with ranitidine 50mg IV, metoclopramide 10mg I.V. and with either clonidine 2µg/kg or normal saline (placebo), 15 minutes prior to surgery. All patients received 500ml of lactated ringer's solution prior to induction. Propofol 2 mg/kg was used as induction agent and atracurium 0.8 mg/kg as muscle relaxant. Dexamethasone 4 gm was given I.V. during induction. Patients were intubated with appropriate sized PVC endotracheal tube.

Fentanyl 1mcg/kg was used as analgesic for the surgery intraoperatively and tramadol 1mg/kg post operatively in every patient. Diclofenac suppository 100mg was inserted in all patients. Every patient was given ondansetron 4 mg along with Neostigmine 0.05mg/kg with glycopyrrolate 0.008 mg/kg for reversal. Anaesthesia was maintained by Nitrous oxide in oxygen 50:50 with isoflurane as the inhalational agent (MAC 1). The end-tidal carbon dioxide ($EtCO_2$) level was maintained between 30-40 mmHg by controlling the minute ventilation. Intra-abdominal pressure was maintained below 12 mmHg. Increase in mean arterial pressure more than 20% from the baseline at any point intraoperatively, was treated with nitro-glycerine infusion. Monitoring was done by cardio scope (HR) pulse oximetry (SPO_2), non-invasive blood pressure (NIBP), end tidal CO_2 ($EtCO_2$). Heart rate, systolic and diastolic BP and $EtCO_2$ was recorded pre-operatively, at intubation, at 5, 10, 30 and 60 minutes post-insufflation and at extubation.

Statistical analysis: Demographic data was analysed by Pearson's chi-square test. Change in the heart rate, systolic BP and diastolic BP was analysed using unpaired t-test. P-value less than 0.05 was considered significant.

RESULTS

Statistical analysis revealed that clonidine significantly attenuated the hemodynamic changes due to pneumoperitoneum. Increase in heart rate was significantly higher in placebo group and the difference was maximal at 45 to 60 minutes post insufflation. The attenuation of hypertension by clonidine was more marked in the systolic pressure as compared to diastolic pressure.

Table 1: Comparison of changes in mean heart rate between two groups analyzed by unpaired t-test

Event	Mean hour	Mean hour	Mean hour	Significance
	Clonidine	Placebo	P value	
Preop	81.08±14.01	77.08±9.73	0.1006	Not signicant
Intubation	82.88±9.22	88.34±8.47	0.0027	Significant
Insufflation	78.48±11.02	83.06±7.89	0.0188	Significant
5 min	80.68±11.81	85.40±6.74	0.0158	Significant
10 min	81.78±11.15	87.04±7.12	0.0059	Significant
15 min	81.34±13.16	87.90±7.83	0.0031	Significant
30 min	80.38±11.87	87.74±7.16	0.0002	Significant
45 min	79.76±11.75	88.22±6.89	2.85134e-05	High significant
60 min	79.06±10.16	87.80±7.00	2.42086e-06	High significant
Extubation	87.52±10.76	94.34±8.63	0.0007	Significant

p-value <0.05 is considered highly significant. There was significant increase in heart rate over a period of time in placebo group which approached a highly significant level 45 minutes post insufflation.

Table 2: Comparison of changes in mean systolic blood pressure between two groups.

Event	Mean sys bp	Mean sys bp	Mean sys bp	Significance
	Clonidine	Placebo	P-value	
Preop	134.34±14.31	131.24±9.28	0.2018	Not significant
Intubation	128.78±16.81	134.74±8.27	0.0267	Significant
Insufflation	128.52±16.61	139.72±9.77	8.24704e-05	Highly significant
5 min	137.04±16.88	145.22±9.41	0.0035	Significant
10 min	135.96±13.07	147.92±8.81	5.4141e-07	Highly significant
15 min	135.06±12.87	146.78±5.56	4.99288e-08	Highly significant
30 min	133.58±12.12	146.04±6.69	6.27284e-09	Highly significant
45 min	133.30±9.96	145.60±6.44	6.61519e-11	Highly significant
60 min	133.10±9.44	143.88±5.45	3.33891e-10	Highly significant
Extubation	136.28±11.16	148.16±5.62	1.18705e-09	Highly significant

Analyzed by unpaired t test, p value<0.05 is significant. The rise in mean systolic blood pressure was highly significant after insufflation upto extubation in placebo group the pressor response to pneumoperitoneum was higher than that due to intubation.

Table 3: Comparison of changes in diastolic blood pressure between two groups.

Event	Mean dbp	Mean-dbp	Mean-dbp	Significance
	Clonidine	Placebo	P value	
Pre op	84.34±6.78	82.82±5.63	0.2254	Not significant
Intubation	83.04±9.66	87.00±7.77	0.0261	Significant
Insufflation	85.46±12.47	89.40±6.22	0.0484	Significant
5 min	89.00±10.17	92.54±6.20	0.0382	Significant
10 min	90.26±10.01	93.94±6.15	0.0291	Significant
15 min	90.34±9.59	93.64±5.15	0.0345	Significant
30 min	88.12±8.63	93.12±4.66	0.0005	Significant
45 min	88.10±7.64	92.64±4.91	0.0006	Significant
60 min	86.56±7.89	91.38±4.34	0.0002	Significant
Extubation	88.04±8.76	94.02±4.27	3.45284e-05	High significant

Analyzed by unpaired t test, p value<0.05 is significant. The rise in diastolic pressure was significantly higher at intubation, after pneumoperitoneum and at extubation in the placebo group.

In fact, clonidine produced a slight fall in mean arterial pressure during intubation and insufflation. In our study, 14 patients (28%) in the placebo group had nausea and /or vomiting while only 3 (6%) in clonidine group had such an episode in the postoperative period.

None of the patients who received clonidine premedication had shivering in the postoperative period as compared to 6 (12%) in the placebo.

Table 4: Comparison of changes in mean arterial pressure between two groups.

Event	MAP Clonidine	MAP Placebo	MAP P value	Significance
Pre op	101.01±8.68	98.96±6.68	0.1896	Not significant
Intubation	98.29±11.60	102.91±7.35	0.0192	Significant
Insufflation	99.81±13.14	106.17±7.11	0.0033	Significant
5 min	105.01±11.80	110.10±6.73	0.0095	Significant
10 min	105.49±10.39	111.93±6.70	0.0004	Significant
15 min	105.25±9.97	111.35±4.83	0.0002	Significant
30 min	103.27±9.17	110.76±4.73	1.4731e-06	High significant
45 min	103.17±7.58	110.29±5.02	2.5372e-07	High significant
60 min	102.07±7.67	108.88±4.08	2.5674e-07	High significant
Extubation	104.12±9.01	112.07±4.33	1.7671e-07	High significant

Analyzed by unpaired t test, p value < 0.05 is significant. There was a slight decrease in mean arterial pressure during intubation and insufflation. the difference in MAP between the two groups was significant till extubation.

Table 5: Incidence of PONV and shivering in the two groups.

Groups	PONV no of patients	Shivering no of patients
clonidine group	3 (6%)	0 (0%)
placebo	14 (28%)	6 (12%)

The incidence of PONV was higher in placebo group. The incidence of shivering was higher in placebo group

DISCUSSION

Pneumoperitoneum during laparoscopy produces significant haemodynamic changes, which can be detrimental especially in elderly and haemodynamically compromised patients. Several studies have been conducted to evaluate the efficacy of Clonidine in laparoscopic surgery.

We conducted a single blind prospective randomized controlled study in 100 healthy (ASA I and II) adult patients to evaluate the effect of intravenous Clonidine as premedication to attenuate the haemodynamic stress response associated with pneumoperitoneum.

Demographic parameters: All the patients were comparable with respect to the demographic parameters: age, sex and weight.

Haemodynamic parameters: Clonidine, an imidazoline derivative is a selective α-2 adrenergic agonist. It is a potent antihypertensive drug. It produces a fall in the heart rate and blood pressure associated with decreased systemic vascular resistance and cardiac output.

In our study, Clonidine 2 µg/kg was administered intravenously, 15 minutes prior to surgery. Dose of Clonidine varied from 1.5 to 3 µg/kg in different studies. Aho et al. observed that a small oral dose of clonidine decreased the incidence of perioperative myocardial ischemic episodes without affecting haemodynamic stability.[12] They used 3 µg/kg and 4.5 µg/kg clonidine for suppression of haemodynamic response to pneumoperitoneum. Rise in blood pressure and heart rate was less in both the groups, however 4.5 µg/kg clonidine produced greater fall in mean arterial pressure before induction of anaesthesia. So they recommended 3µg/kg of clonidine for perioperative haemodynamic stability.

In our study, following pneumoperitoneum with carbon dioxide, minute ventilation was adjusted so as to maintain normocapnia. Every effort was made to maintain intra-abdominal pressure (IAP) below 12 mmHg.

Ishizaki et al tried to evaluate the safe intra-abdominal pressure during laparoscopic surgery. They observed a significant fall in cardiac output at 16 mmHg of intra-abdominal pressure.[15]

Haemodynamic alterations were not observed at 12mmHg 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 assessed the ejection fraction (EF) of left ventricle by trans-esophageal echocardiography during pneumoperitoneum.[16] No significant change in ejection fraction was reported up to 15mmHg of intra-abdominal pressure. Considering all these facts intra-abdominal pressure was kept below 12 mmHg.

In our study, inspite of maintaining end tidal carbon-dioxide level between 30-40 mmHg and intra-abdominal pressure below 12mmHg, significant rise was observed in heart rate, systolic, diastolic and mean arterial blood pressure in the placebo group compared to the clonidine group. It was observed that,

- The rise in the heart rate was significantly lower in the clonidine group than the placebo group.
- The rise in the systolic blood pressure was significantly lower in the clonidine group than the placebo group.
- The rise in the diastolic blood pressure was significantly lower in the clonidine group than the placebo group.
- The rise in the mean arterial pressure was significantly lower in the clonidine group than the placebo group.

Joris JL et al, from Liège, Belgium studied haemodynamic changes induced by laparoscopy and their endocrine correlates and the effect of intravenous Clonidine in 20 healthy patients scheduled for elective laparoscopic cholecystectomy.[4] They found that Clonidine administered prior to pneumoperitoneum reduces catecholamine release and attenuates haemodynamic changes during laparoscopy.

Ray M et al. from Kolkatta, India compared the effect of intravenous clonidine (3µg/kg) with magnesium sulphate (30mg/kg) on anaesthesia consumption, haemodynamic changes and postoperative recovery in seventy five patients undergoing elective upper limb orthopaedic surgery.[17] They found that the requirement of propofol and fentanyl was significantly reduced in clonidine group. Postoperative recovery was slower in magnesium group compared with the Clonidine group. Perioperative use of both Clonidine and magnesium sulphate significantly reduced the consumption of propofol and fentanyl citrate. However, magnesium sulphate caused a delayed recovery.

Toshu Yotsui, Tokyo, Japan studied the effects of oral administration of clonidine on sympathetic and endocrinological responses in 20 patients undergoing elective laparoscopic cholecystectomy and found that systolic and diastolic blood pressure were lower in the clonidine group than in the control group immediately after endotracheal intubation and extubation. Patients in the clonidine group showed lower plasma concentrations of noradrenaline 2 hour after the beginning of the surgery than patients in the control group. They concluded that clonidine premedication prevents sympathetic hyperactivity but does not suppress hypothalamo-pituitary-adrenocortical responses in patients undergoing laparoscopic cholecystectomy.[18]

In our study, increase in mean arterial pressure more than 20% from the baseline at any point intraoperatively, was treated with nitro-glycerine infusion. Sixteen patients (32%) in placebo group received titrated nitro-glycerine infusion (0.5µg/kg/min) intraoperatively, whereas only five patients (10%) of clonidine group showed short duration increase in blood pressure which responded well to single nitro-glycerine bolus. Similar findings were reported by Aho et al and Joris et al.[4,12]

Incidence of post-operative shivering and nausea-vomiting

The incidence of shivering in the postoperative period was less in the patients who had clonidine premedication as compared to placebo. Shivering occurred in six patients (12%) in the placebo group compared to none in the clonidine group.

Buggy et al, in his study reported reduced postoperative shivering after general anaesthesia in 60 patients who were premedicated with clonidine.[19]

This finding corroborates the finding of Nicolaou et al, who concluded that clonidine inhibits cold thermoregulatory response due to an effect on central integration control and output from the thermoregulatory centres.[20] 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.

In our study, fourteen patients (28%) in the placebo group suffered from nausea and/or vomiting in the post-operative period, while only three patients (6%) who received clonidine premedication had any such episode.

Clonidine increases gastrointestinal motility by decreasing sympathetic outflow and increasing parasympathetic outflow from the central nervous system. Although many workers have reported the antiemetic property of clonidine, the mechanism by which it acts is not clear.

The findings of our study are in agreement with the findings of various above mentioned investigators in that clonidine is an effective premedicant to reduce the haemodynamic fluctuations associated with laparoscopic surgery. It also reduces the incidence of post-operative shivering and nausea-vomiting.

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