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IV Clonidine Premedication in Laparoscopic Surgery

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INTRODUCTION

Patients comfort is a great concern in 21st century. Minimal access surgical procedures produce less trauma with potential advantage of reduced post operative pain compared to open procedures, shorter hospital stays, more rapid return to normal activities and is cost effective than conventional 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 revolutionalized 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. The operation table is tilted to 15 degree reverse trendelenburg for upper abdominal surgery like cholecystectomy. Techniques for pneumoperitoneum creation include insufflations after insertion of veress needle at infraumbilical region. [1]

It is important that anaesthetic approaches are developed to ensure that these techniques are safe and associated with minimal complications and rapid recovery. 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 insufflations.[3]

There is increase in mean arterial pressures (MAP), heart rate (HR) and increased systemic vascular resistance (SVR) and pulmonary vascular resistance (SVR).[2]

Intraabdominal pressure (lAP) should be maintained at 6 to 12 mm Hg which should not be allowed to exceed 15 mm Hg. After PNO necessary changes in ventilator settings like tidal volume and respiratory rate should be done to maintain nomocapnia.[2]

Both mechanical and neurohumoral factors contribute to hemodynamic instability, decreased cardiac output (CO), increased mean arterial pressure (MAP), heart rate (HR), right atrial pressure (RAP), pulmonary capillary wedge pressure(PCWP).[2]

Clonidine, an alpha 2-agonist, has a half-life around 8 to 12 hours has been shown to reduce peripheral sympathetic discharge, reduces intraoperative anaesthetic requirement, reduces postoperative pain and analgesic requirement in clinical use. These characteristics suggest that clonidine may be useful in the anesthetic management of patients undergoing laparoscopic cholecystectomy.[3]

Various pharmacological agents were chosen to prevent hemodynamic changes associated with Pneumoperitonium. The increase in systemic vascular resistance can be corrected by using vasodilating agents nitroglycerine, nicardipine and anesthetic agents such as isoflurane. Use of alpha-2 adrenergic agonists such as clonidine or dexmedetomidine and beta-b1ocking agents significantly reduces haemodynamic changes and anesthetic requirements.[36,61]

Clonidine inhibits the release of vasopressin and catecholamines, and modulates the haemodynamic changes induced by Pneumoperitonium, and reduces post operative analgesic requirement. [10,12,16,24,47,62,63]

Until recently only a few studies have focused on IV clonidine premedication for haemodynamic changes, post operative sedation and post operative analgesia in laparoscopic surgery, hence in this study we investigated the effect of clonidine in the dose of 2 mcg/kg iv premedication 20 mins before induction.

AIMS

To study the efficacy of IV clonidine two mcg/kg in reducing the haemodyriamic changes during laparoscopic sugeries.

OBJECTIVES

- To study the effect of clonidine in reducing Post operative pain in laparoscopic surgeries.
- To study the sedative effects of clonidine in postoperative period

REVIEW OF LITERATURE

Historical perspective of laparoscopy4

At the turn of the 20th Century, George Kelling of Dresden used a cystoscope to observe the abdominal organs of dogs and the first report of using this procedure in man was by the Swedish physician Hans Christian Jacobaeus in 1910 who coined it the term "laparoscopy". The early procedures were however entirely diagnostic, because the exposure obtained and the instruments available did not allow operative intervention.

In 1924, Richard Zollikofer of Switzerland promoted the use of CO_2 as the insufflating gas for pneumoperitoneum rather than filtered air or nitrogen.

Later Janos Veress of Hungary developed a spring loaded insufflation needle for the safe introduction of gas into the abdomen, which is used till today.

It was Raoul Palmer in Paris in 1944 who stressed the importance of monitoring intra-abdominal pressure. However it was another 20 years before Kurt Semm in Kiel, Germany, developed an automatic insufflation device that monitored intra-abdominal pressure and gas flow.

However, since laparoscopy was considered a "blind" procedure with an inherent risk of injury to intraperitoneal structures, acceptance was slow. throughout Europe and North America. It was the widespread introduction of videoscopic technologies in the 1980s that changed the face of surgery.

In 1985, Erich Muhe of Germany described his technique of laparoscopic cholecystectomy using the galloscope, it was in 1986 that a computer chip TV camera was developed and attached to the laparoscope. It was in 1987 that the complete removal of a diseased gall bladder in a patient was performed by Phillipe Mouret in Lyon, France.

Air was the first gas to be used since it was cheap and easily available. Later oxygen was also used for a long time. However both these gases have a potential for gas embolism because they have a poor Ostwald's blood gas solubility coefficient (0.006, 0.013) and are inflammable too.

In the 1970s, nitrous oxide (N_2o) emerged as the gas preferred bygynaecologists, however it supports combustion, if mixed with methane (from the bowel).

Pneumoperitoneum

CO_2 is the insufflation gas of choice as it is non-combustible and can be used safely and it has a high diffusion coefficient, highly soluble in blood, readily absorbed by the peritoneal membrane and is a normal metabolic end product rapidly cleared by the lung. Other alternative gases like helium, argon and Xenon are inert but expensive and have a very low blood gas solubility [0.00018] and therefore has high chances of gas embolism if accidental injection in a blood vessel results. [4]It is relatively inert, permitting the use of electro coagulation and because of its high blood gas solubility and pulmonary excretion reduces risk of embolism.[5]

Therapeutic Role of Clonidine in Anesthesia during Laparoscopic Surgeries Haemodynamic Stability

Joris JL,et al (1993)performed A study reported that laparoscopy for cholecystectomy in head-up position results in significant hemodynamic changes in healthy patients, particularly at the induction of pneumoperitoneum. Induction of anesthesia decreased significantly MAP and (CI). Tilting the patient to the head-up position reduced cardiac pre-load and caused further reduction of CI. Peritoneal insufflation resulted in a significant increase of MAP, a significant reduction of CI, and a significant increase in SVR and PVR. The combined effect of anesthesia, head-up tilt, and peritoneal insufflation produced a 50% decrease in CI. Administration of increasing concentrations of isoflurane, via its vasodilatory activity, may partially blunt these hemodynamic changes.[7]

Singh S , et al (2011) studied that clonidine has antihypertensive properties. Fifty patients were divided to receive oral clonidine 150 mcg (n=25) and placebo (n=25) in patients undergoing LC and compared the haemodynamic parameters, isoflurane use, pain, sedation postoperative request of analgesia. Clonidine group of patient showed improved hemodynamic stability, reduced intraoperative anesthetic requirement and post operative analgesia. [8]

Passi et al (2009)conducted A study on 50 adult ASA I and II patients undergoing LC reported that, premedication with oral clonidine before scheduled surgery provides stable hemodynamics and protection against stress response triggered by PNO. In the clonidine group (group A) who received tab. clonidine 150 mcg orally, the HR remained closed to the baseline values and had more stable MAP upon insufflation. Rise in blood pressure was observed in the control group B (premedicated with Tab. vitamin B complex orally). HR increased in response to PNO in the control group and remained elevated throughout the surgery. Pre operatively, HR and MAP were lower in the group A as compared to the group B. The study concluded that, premedication with oral clonidine potentiates parasympathetic nervous system and blunts the stress response to surgical stimuli and reduces the requirement of narcotic and anesthetic agents. Clonidine also increases cardiac baroreflex sensitivity to increase in SBP and thus stabilizes blood pressure and clonidine decreased preoperative anxiety levels .The incidence of postoperative nausea ,vomiting and other adverse effects were less in clonidine group in comparison with placebo group. [9]

Das M et al (2007) performed a prospective, randomized, single-blind, comparative study in 60 adult patients to investigate the clinical efficacy of oral clonidine premedication in prevention of hemodynamic response associated with undergoing LC they were randomly allotted to two groups ,the clonidine group c (n=30) premedicated with oral clonidine 150 mg and group p (n=30) received ranitidine 150 mg, 90 mm prior to induction of anesthesia. Oral clonidine premedication helped to provide perioperative hemodynamic stability [10]

O Leary E et al (1996) In a study authors assessed the potential for myocardial ischemia during laparoscopic cholecystectomy among 16 otherwise healthy patients. Acute ST segment changes in the ECG occurred in only two patients. These episodes were independent of creation of pneumoperitoneum and changes in position. Acute intraoperative increases in MAP and four-fold increase in plasma concentrations of renin and aldosterone were noted during insufflation of carbon dioxide and reverse trendelenburg positioning. There was a linear correlation between changes in plasma renin and aldosterone concentrations and MAP. Cortisol, HGH, adrenaline and noradrenaline concentrations increased after deflation of the pneumoperitoneum. They concluded that increased IAP and reverse trendelenburg positioning may reduce cardiac output and renal blood flow.[11]

De Kock M et al (1998) showed that, the administration of clonidine 4 mcg/kg during induction in 20 patients for orthotopic liver transplantation significantly reduced the intraoperative requirements of IV fluids and blood products (albumin and packed red blood cell) without compromising circulatory stability. Heart rate was significantly slower in patients of the clonidine group. After reperfusion, patients in the control group showed significantly lower diastolic arterial BP, required more vasopressor / inotropic support, and were more acidotic than patients in the clonidine group.[12]

Malek J et al (1999) conducted a study to confirm the incidence of adverse haemodynamic effects authors tried to suppress them by premedication with clonidine. Twenty one patients were given 0.15 mg clonidine in an I.V. infusion 15 minutes before operation and 0.15 mg clonidine by the IM route 60 to 90 min. before operation in 21 patients. Standard anaesthesia was administered. A highly significant drop in the incidence of hypertension was recorded during operation for systolic pressure ($p < 0.00$ 1) after both ways of administration, as well as of diastolic pressure ($p < 0.0l$ for IV and $p < 0.05$ for IM premedication). They recommended premedication with IV clonidine as a routine procedure before laparoscopic cholecystectomies. [13]

Yotsui T et al (2001) performed a study on twenty adult patients were allocated randomly to the clonidine group(n= 10) or the controle group (n 10) .The controle and clonidine groups recived placebo on clonidine 4 mcg/kg orally 2 hr before the induction of anaesthesia and concluded that, clonidine premedication 4 mcg/kg orally prevents sympathetic hyperactivity but does not suppress hypothalamo-pituitary-adrenocortical endocrinological responses in patients undergoing LC. Systolic and diastolic blood pressures were lower in the clonidine group than in the control group immediately after endotracheal intubation and extubation ($p < 0.05$). Patients in the clonidine group showed lower plasma concentrations of noradrenaline 2 hour after the beginning of the operation than patients in the control group ($p < O.Ol$). However, the plasma concentrations of the other hormones did not differ between groups.[14]

Abi Jaode F et al (1993) conducted a study to assess the efficacy of clonidine in achieving perioperative hemodynamic stability in 24 patients with left ventricular ejection fraction >0.5undergoing CABG performed under high-dose alfentanil anesthesia. Intraoperative hemodynamic profile analyses showed a continuous increase in SVR and MAP in the clonidine group from the time of skin incision until the onset of bypass, whereas the cardiac output profiles remained similar in the clonidine and placebo groups. The number of additional alfentanil boluses was similar. Isoflurane requirements were not significantly different. [15]

Taittonen MT et al (2009) compared the perioperative metabolic and haemodynamic effects of two alpha 2-agonists, clonidine and the more Selective dexmedetomidine, in 30 ASA I patients undergoing plastic surgical procedures under general anaesthesia. Patients were premedicated with clonidine 4mcg/kg (n=l0), dexmedetomidine 2.5 mcg/kg (n=10) or saline (n=l0). They concluded that both clonidine 4 mcg/kg and dexmedetomidine 2.5 mcg/kg decreased perioperative oxygen consumption effectively with a similar hemodynamic profile. The reduction in heart rate, systolic and diastolic arterial pressures were similar in the clonidine and dexmedetomidine groups compared with placebo. [16]

Boussofara M et al (2001) conducted a study to compare the effect of oral clonidine 3mcg /kg versus oral hydroxyzine 1 mg /kg on the hemodynamic and catecholamine responses to microlaryngoscopy in 35 ASA II and III patients, MAP was significantly lower in clonidine group, whereas there was no difference in heart rate and plasma catecholamine levels between the two groups. [17]

F avaherfroosh et al (2009) performed a study on 86 patients of which 43 patients, who received oral clonidine 0.2 mg and control group 43 patients who received placebo found that MAP after intubation did not change in 35 (81.4%) of clonidine group compared to 26 (60.5%) in control group. Mean blood pressure on intubation decreased in five (11.5%) in clonidine group as compared to three (7%) in control group (p<0.02). Heart rate was reduced in five (11.5%) study group, while only two (4.7%) in control group (p=0.001). The study concluded that, clonidine had statistically significant effect in reducing the incidence of both nausea and vomiting and has a favorable outcome on post operative pain score and it is an orally effective, inexpensive, readily available drug with low side effects and can be routinely used in laparoscopic surgery. [18]

Clonidine during laryngoscopy

Marshi SM et al (2009) performed a study to determine effects of clonidine on laryngoscopy in seventy five patients of ASA I and II of both sexes of 18 to 45 years, patients were randomly allocated into three groups of 25 each that is Group I (0.2 mg clonidine), Group II (Placebo) and Group III (900 mg Gabapentin) orally 120 min before operation. HR, SBP, DBP, MAP were recorded before induction, before laryngoscopy and at 1, 3, 5, 10 minutes after intubation. Highest HR noted was (101 .16±16.4) in placebo group and lowest HR (69.1 2±9.89)beats/min was noted in clonidine group , 10 mm after laryngoscopy. SBP (148.88±14) in placebo group and lowest in gabapentin group (99.7±14) and DBP (98.76±11) in placebo group lowest in gabapentin and clonidine group after 10 min of laryngosccopy. [19]

Talebi H et al (2010) assessed efficacy of oral clonidine on pulse rate, blood pressure, stress response to laryngoscopy and tracheal intubation in a double blinded fashion including 274 ASA I and II subjects of 18 to 45 year age scheduled for elective surgery. They were randomly allocated to receive oral clonidine 0.2 mg or placebo as a premedication 90-120 min before surgery. HR, SBP were recorded before, immediately and after every 5 mm after intubation until 20 minutes. The clonidine group showed superiority over placebo group. A significant difference was observed in both heart rate and SBP ,which is significantly higher in control group at three subsequent measurements following intubation. [20]

Raval DL et al (2002) assessed the effects of oral clonidine premedication on laryngoscopy and endotracheal intubation in 100 ASA grade I and II patients of 18 to 65 years of age with oral diazepam and placebo. Patients were divided into three groups namely Group C (oral clonidine 4 mcg/kg), Group D (diazepam 0.2 mg/kg) and placebo (Oral antacid) 90 minutes prior to induction of anesthesia. Clonidine produced marked anxiolysis and better sedation compared to placebo but less sedation and same level of anxiolysis compared to diazeparn. Clonidine provided extra advantage over diazepam and placebo by blunting hemodynamic responses during laryngoscopy and endotracheal intubation and also by its antisialoggogue effect. [21]

Deepshikha C Tripathi et al (2011).[22] conducted randomized ,double blind controlled study was conducted study on 90 adults of ASA physical status I and II scheduled for LC under general anaesthesia. Patients were divided in to one of the three group (n =30) ,group I received normal saline l00ml, while group II and III received 1mcg/kg and 2mcg /kg of clonidine respectively iv 100 ml normal saline . They concluded that 2mcg/kg iv , 30 min before induction is safe in producing the hemodynamic stress response during LC.

Nandkishore Karla et al (2011) .[23]conducted a randomized in to 4 groups of 30 each . Group k patient received 50 ml normal saline over a period 15 min after induction and PNO, group m patients received 50 mg/kg of mgso4 in normal saline (total volume 50 ml) over same time duration Similarly group c1 patients recived 1mcg/kg clonidine and group c2 1.5mcg/kg clonidine respectively in normal saline (total volume 50 ml) and concluded that.Although mgso4 50 mcg/kg produces hemodynamic stability comparable to clonidine 1 mcg/kg,clonidine in doses of 1.5 mcg/kg blunts the hemodynamic response to PNO more effectively.

Influence of Clonidine on Anaesthetic Requirements

Ghignone M et al (1987) assessed the effect of oral clonidine premedication in thirty patients. Clonidine 5 mcg/kg P0 provided stable hemodynamics and reduced isoflurane requirement up to 40% less compared to placebo group who received diazepam 0.15 mg/kg. [24]

Lee J et al (1999) conducted study on 41 patients who had received clonidine 3 mcg/kg IV or placebo at induction of isoflurane and nitrous oxide in oxygen anesthesia and had also received Metoprolol to achieve a systolic arterial pressure of 80 mm Hg found that, the requirements for metoprolol were significantly less in the clonidine group (p<0.00035), with no significant difference in MAP over time. The study concluded that, clonidine is an IV hypotensive agent worthy of consideration and giving clonidine by the IV route after induction causes a more immediate effect than oral administration and is under the direct clinical supervision of an anesthetist, able to respond to any adverse effects. [25]

Leslie K et al (1992) performed a study to investigate the influence of IV clonidine on thiopental dose requirements when used for induction of anesthesia and associated hemodynamic effects on 60 ASA physical status I or II patients. The patients were randomly given normal saline solution (control group); clonidine (2.5 mcg/kg) iv; or clonidine (5 mcg/kg) iv .Test drug administered before induction of anesthesia with iv thiopentone. Significant decreases in thiopental dose were observed in both groups receiving clonidine compared with the control group, but there was no significant difference between clonidine groups. Clonidine, in both doses, produced more sedation than control, and the 2.5 mcg/kg dose produced less sedation than the larger dose. Mean arterial blood pressure was lower in the clonidine groups. There were no significant differences in heart rate among the three groups. Authors concluded that if IV clonidine is to be used as an adjunct to general anesthesia, appropriate adjustments to the dosage of intravenous thiopental will be required.[26]

Clonidine and pain

Ghafari MH et al (2009) conducted a study to assess effects of clonidine and gabapentin on postoperative pain and morphine consumption after abdominal hysterectomy, patients were randomized to receive either oral placebo or gabapentin 300 mg or clonidine 100 mcg at night before surgery and one hour preoperatively. Total morphine consumption and VAS scores were lower in clonidine and gabapentin group. [27]

Hidalgo MP et al (2005) conducted a study to assess the effects of small doses of oral clonidine in perioperative out comes among 61 patients undergoing abdominal hysterectomy of ASA grade I and II. Patients were randomly assigned to receive either oral clonidine 100 mcg or placebo before and 24 hour

after surgery. The use of clonidine resulted in anxiolysis and analgesia throughout 72 hour of after surgery. The clonidine patients required small ropivacaine doses during surgery and a clinically anxiolytic effect was found in patients who received oral clonidine in the perioperative period. [28]

Bonnet F et al (1989) conducted a study and pain was assessed postoperatively by VAS score in 40 ASA I, II patients were allocated randomly to two groups .The extradural clonidine (EC)(n =20) and extradural saline (ES) (n=20). Extradural clonidine (EC) 2 mcg/kg in isotonic saline was given in 20 patients and extradural saline (ES) group received same volume saline. EC group mean (SD) pain relief was 68.2 (24.1%) Of initial VAS score and 14.7 (25.2%) in ES group. The post operative analgesic effect was prolonged in EC group for 210 ± 87 mm and 47±27 mm in ES group.[29]

Cigarini et al (1995) performed a study on two groups of pregnant healthy women and patients were allocated randomly to receive either 10 ml 0.125% bupivacaine plain solution (group B; n=10) or with 75 mcg cloidine (group B+C; n=12) . VAS score measured over 30 mm after each epidural injection . They concluded that 75 mcg of epidural clonidine increased the duration of epidural bupivacaine analgesia in labour with no adverse effects to mother or neonate. [30]

Rosting S et al (1991) conducted a study on twenty ASA physical status II or III patients recovering from abdominal surgery were allocated randomly to recive either epidural fentanyl (100 mcg in 10 ml isotonic saline ;EF group)or epidural fentanyl(same dose) plus clonidine (150 mcg; EF+C group) in isotonic saline. Reported that ,epidural clonidine appears to prolong epidural fentanyl analgesia without affecting its plasma concentration. [31]

Ghodki PS et al (2010) performed a study on sixty ASA grade I/II patients scheduled for elective short laparoscopic procedures under spinal anesthesia were divided into two groups of 30 each. The first group (group C) received 3.5 ml of hyperbaric bupivacaine with 30 mcg of clonidine. The second group (group B) received plain bupivacaine 3.5 ml. The study concluded that, bupivacaine along with clonidine in low doses provides good sedation and analgesia in intraoperative and postoperative period and at the same time abolishes shoulder tip pain during laparoscopic procedures. In addition, no significant changes in hemodynamics occur with the low dose of clonidine used. [32]

Eisenach JC et al (1989) conducted a study on ninety patients to find out appropriate dose of epidurally administered clonidine for intractable cancer pain reported that, epidural clonidine (range, 100-900 mcg in 100 mcg increments) was effective in treating cancer pain in patients tolerant to opioids. [33]

PHYSIOLOGY OF LAPAROSCOPIC SURGERY

Minimal1y invasive surgical procedures aim to minimize the trauma of the interventional process but still achieve a satisfactory therapeutic result. Tissue trauma is significantly less than that with conventional open procedures, offering the advantages of reduced post-operative pain, shorter hospital stay, more rapid return to normal activities and significant cost savings. Laparoscopic cholecystectomy is now a routinely performed procedure and has replaced conventional open cholecystectomy as the procedure of choice for symptomatic cholelithiasis. Public expectation and developments in instrumentation have fuelled this change. The physiological effects of intraperitoneal carbon dioxide insuffiation combined with variations in patient positioning can have a major impact on cardiorespiratory function, particularly in elderly patients with comorbidities. [34]

PHYSIOLOGICAL CHANGES
Cardiovascular changes

The cardiopulmonary changes occurring during laparoscopy are complex and depend on the interaction of the patient's preexisting cardiopulmonary status, the anesthetic technique used (ventilatory technique and

anesthetic agents used), and several surgical factors including intra-abdominal pressure (IAP), CO_2 absorption, patient position and duration of the surgical procedure along with neurohumoral responses[35]

Insufflation of CO_2 increasing IAP higher than 10 mm hg induces significant alterations of hemodynamics which are characterized by decrease in cardiac output, increase in arterial pressures and elevation of systemic and pulmonary vascular resistances. The decrease in cardiac output is proportional to IAP. A decrease in venous return is observed after transient increase in venous return at low IAP <10mm Hg. [36]

Caval compression, pooling of blood, and increase in venous resistance is observed by increased IAP. Decline in venous return parallels decrease in cardiac output reflected as decrease in LVEDV. Cardiac filling pressures also rise during peritoneal insufflations. Reflex increase in vagal tone result from sudden stretching of peritoneum results in bradycardia, cardiac arrhythmia and asystole. [36]

Pulmonary Changes

The head down position facilitates the development of atelectasis. Decrease in FRC, TLV, pulmonary compliance manifests in steep head down position which are more marked in elderly, obese and debilitated patients.PNO decreases thoracopulmonary compliance by 30-50%.[36]

Reduction in FRC and development of atelectasis due to elevation of diaphragm and changes in ventilation and perfusion results from increased airway pressure. [36]

Gastrointestinal Effects

Trochar insertion can damage viscera, particularly distended stomach, probably caused by manual ventilation during intubation. Therefore nasogastric aspiration should always be done prior to trochar insertion. Increased incidence of nausea and vomiting has been associated with the laparoscopic surgery, so regular antiemetic drugs may be considered. Though increased IAP may be considered to increase the chances of regurgitation but it also increases the barrier pressure thus preventing chances of regurgitation. [35]

Effects on Other Systems

Pneumoperitoneum, changes in patient position, reductions in cardiac output, and systemic CO_2 absorption influence splanchnic, renal, and cerebral blood flow during minimal access procedures. Numerous regional circulatory changes also occur during laparoscopy including increased cerebral blood flow and intracranial pressure, decreased total hepatic blood flow, reduced bowel circulation resulting in decreased gastric intramucosal pH (suggesting reduced GUT perfusion), reduction in renal blood flow and urine output (because of increase in renal vascular resistance, reduction in glomerular filtration gradient and decrease in cardiac output), and decreased femoral vein blood flow which may increase the risk of deep vein thrombosis. CO_2 PNO causes a hemodynamic stress response and decreases urine output because of an activated reninangiotensin-aldosterone system (RAAS) Massive elevation in IAP produces lactic acidosis, probably by severely lowering cardiac output and by impairing hepatic clearance of blood lactate. [35]

Neurohumoral Response

Potential mediators of the increased SVR observed during PNO include vasopressin and catecholamines. Hypercapnia and pneumoperitoneum are likely to cause stimulation of the sympathetic nervous system and catecholamine release. [35]

A study concluded that by correcting relative dehydration and preventing the pooling of blood, cardiac index decreased less than 20% during pneumoperitoneum as compared with the baseline awake level. The head-up positioning accounts for many of the adverse effects in hemodynamics during laparoscopic cholecystectomy. With the passive head-up tilt in awake and anesthetized patients, the cardiac index (CI), stroke index (SI), central venous pressure (CVP), and pulmonary capillary wedge pressure (PCWP)

decreased, and systemic vascular resistance increased. With the patient under anesthesia, SI decreased, but CI did not change significantly as a result of the compensatory increase in heart rate. Carbon dioxide (CO_2) insufflation at the start of laparoscopy produced increases in CVP and PCWP as well as mean systemic and mean pulmonary arterial pressures without changes in CI or SI. Toward the end of the laparoscopy, CI decreased by 15%. The hemodynamic values returned to nearly prelaparoscopic levels after deflation of the gas, and CI was elevated during the recovery period, whereas systemic vascular resistance was decreased in comparison with the baseline. [37]

Another study found that changes in cardiovascular function due to the insufflation are characterized by an immediate decrease in cardiac index and an increase in MAP and SVR. In the next few minutes there is partial restoration of cardiac index and resistance but blood pressure and heart rate do not change. The pattern is the result of the interaction between increased abdominal pressure, neurohumoral responses and absorbed CO_2. [38]

Another study concluded that, pulmonary function changes are characterized by reduced compliance without large alterations in PaO_2, but tissue oxygenation can be adversely affected due to reduced O_2 delivery. A major difficulty in maintaining normocarbia is due to the abdominal distention reducing pulmonary compliance and to CO_2 absorption. End tidal CO_2 tension is not a reliable index of $PaCO_2$, particularly in ASA III, IV patients. The pattern of lung function following laparoscopic cholecystectomy is characterized by a transient reduction in lung volumes and capacities with a restrictive breathing pattern and the loss of the abdominal contribution to breathing. Atelectasis also occurs. These changes are qualitatively similar to but of a lesser magnitude than those following "open" abdominal operations. [38]

A study reported that, CO_2 insufflation in laparoscopic surgery affected cardiopulmonary function significantly in end-tidal pressure of CO_2 ($ETCO_2$), peak airway pressure and MAP but could not find significant difference in the heart rate and body temperature. Arterial blood gas (ABG) analysis demonstrated higher $PaCO_2$ and lower pH during laparoscopic procedure than during open procedure. There was a rapid rise in $PaCO_2$ over the first 15 to 20 minutes followed by a second phase of only gradual change. The $ETCO_2$ returned to baseline within 10 minutes after completion of the laparoscopy. End-systolic and end-diastolic diameters of the left ventricle, contractility, and performance parameters of the heart did not change significantly with transesophageal echocardiography in laparoscopic cholescystectomy cases. First stage CO_2 insufflation caused decrease in cardiac output and affected the cardiovascular system. The effect of intraperitoneal pressure increment and reversed Trendelenberg position of the patient affected the decrease of cardiac output due to a decrease in the blood flow back to the heart. After this stage, blood pressure did not have significant changes. It was found that extraperitoneal CO_2 insufflation had lesser effect on MAP than intraperitoneal CO_2 insufflation. [39]

PATIENT POSITIONING

Patients are often placed in the Trendelenberg position for laparoscopic gynaecologic procedures while laparoscopic cholecystectomy usually change to steep reverse Trendelenberg, with left lateral tilt to facilitate retraction of the gallbladder fundus and to minimize the diaphragmatic dysfunction associated with the induced pneumoperitoneum. Trendelenberg position is commonly requested during insertion of Verres needle and cannula. Patient tilt should be reduced as much as possible (should not exceed 15 to 20 °) and must be slow and progressive to avoid sudden hemodynamic and respiratory changes. With Trendelenberg position and pneumoperitoneum, cardiac output fall by 60% and there are no changes in heart rate. Though preload is increased, MAP remains unchanged or decreases. Moderate fall in stroke volume occurs. Stroke index and cardiac index fall by 42%. Total peripheral resistance increases. These seemingly paradoxical

responses may be explained by carotid and aortic baroreceptor-mediated reflexes. The reverse Trendelenberg position decreases preload, cardiac output. [35]

Venous congestion of head and neck may compromise cerebral perfusion and produce intracerebral and intraocular hypertension. Anesthetic agents may blunt these effects. There is also an increase in left ventricular end-systolic wall stress and decreased left ventricular end-diastolic area but left ventricular ejection fraction was maintained during a study by trans-esophageal echocardiography.[35]

In head up position for upper abdominal surgery, there is improved pulmonary function at expense of decreased cardiac function. Nerve compression is a potential complication during the head down position. Overextension of the arm must be avoided. Shoulder braces should be used with great caution and must not impinge on the brachial plexus. Lower limb neuropathies have been reported after laparoscopy. Prolonged lithotomy position, as required for some operative procedures, can result in lower extremity compartment syndrome. [35]

ANAESTHESIA AND LAPAROSCOPY

An optimal anesthetic technique should provide excellent intraoperative conditions while ensuring rapid recovery, low incidence of adverse effects, and early return to daily activities. Anaesthetic approaches to laparoscopic surgery include infiltration of local anaesthetic with an intravenous sedative, epidural or spinal anesthesia, or general anaesthesia. General anesthesia with muscle paralysis and tracheal intubation with positive pressure ventilation remains the preferred technique for most laparoscopic procedures for many reasons; [35]

Increased risk of regurgitation from increased intra abdominal pressure during insufflation;

- The necessity for controlled ventilation to prevent hypercapnia;
- The relatively high peak inspiratory pressures required because of the pneumoperitoneum;
- The need for neuromuscular blockade during surgery to allow lower insufflation pressures, provide better visualization, and prevent unexpected patient movement; and
- The placement of nasogastric tube and gastric decompression to minimize the risk of visceral perforation during trocar introduction and optimize visualization.

Ventilatory settings have to be adjusted according to respiratory and hemodynamic response of the patient. Large tidal volumes (12 to 15 mL/kg) prevent progressive atelactasis and hypoxemia and allows for more effective alveolar ventilation and CO_2 elimination. However this may cause excessive increase in intrathoracic pressure and thus deleterious cardiovascular effects that will result in an increased alveolar dead space.[35]

Isoflurane is the volatile anesthetic agent of choice because it is less arrhythmogenic and causes less myocardial depression .Nitrous oxide (N_2O) is widely used in anesthesia because of its amnesic and analgesic properties and its ability to reduce the requirements of expensive inhaled and intravenous anesthetic drugs. However, the use of N_2O during laparoscopic procedures remains controversial because of concerns regarding its ability to diffuse into the bowel lumen, causing distention and impaired surgical access. Use of N_2O has also been reported to increase the incidence of postoperative nausea and vomiting (PONV). However, omitting N_2O from the anesthesia regimen may be an option in patients at risk or when there are surgical difficulties.[35]

MONITORING DURING LAPAROSCOPY

Routine intraoperative monitors include ECG, pulse oximetry, blood pressure, pulse rate, and $EtCO_2$ (End Tidal carbon dioxide) are essential. Anesthetic gases concentration and patient's temperature can be monitored depending upon the availability. $EtCO_2$ is most commonly used as a non-invasive substitute for

$PaCO_2$ in evaluating the adequacy of ventilation during laparoscopic surgery. However, $EtCO_2$ may differ considerably from $PaCO_2$ because of ventilation-perfusion (V/Q) mismatching, and erroneous clinical decisions may be reached if the two values are assumed to be equal, to change proportionally, or even to change in the same direction. $EtCO_2$ monitor is also useful for early detection of gas embolus. For hemodynamically unstable or compromised patient and patients with cardio-respiratory chronic diseases and obese patients, careful monitoring of cardiovascular and blood gases are indicated. Radial artery cannulation for continuous blood pressure recording and frequent ABG analysis should be considered in patients with preoperative cardiorespiratory disease and in situations where intra-operative hypoxemia, high airway pressures, or elevated $EtCO_2$ are encountered. There is a need for a urinary bladder catheter and nasogastric tubes to decompress the viscera and thus avoid injury to intra-abdominal contents during trocar insertion.[35]

COMPLICATIONS OF LAPAROSCOPY PROCEDURE

Awareness of the potential complications associated with laparoscopic procedures should allow early detection and treatment, and improve patient care and safety. The complications associated with laparoscopy include those related to surgical instrumentation, creation of the pneumoperitoneum, and patient's positioning.

Intraoperative Complications[35]

Complications from surgical instrumentation

- Misplacement of veress needle
- Uncontrolled hemorrhage

Cardiovascular complications

- Cardiac dysrrhythmias
- Myocardial dysfunction
- Cardiac tamponade
- Venous gas Embolism.

Pulmonary complications

- Hypoxemia, Hypercarbia
- Hypoventilation
- Pneumothorax
- Pneumomediastinum

Subcutaneous emphysema

- Significant hypercarbia
- Respiratory Acidosis
- Hypothermia
- Postoperative Complications

Impaired postoperative ventilation from residual anesthetics and/or neuromuscular blockade may result in significant hypercapnia. In patients with significant respiratory dysfunction and restricted CO_2 clearance, positive pressure ventilation may be required in the postoperative period until the patient can eliminate the CO_2 load with resumption of spontaneous respiration. Increased IAP during pneumoperitoneum has been reported to cause venous stasis that can increase the potential for deep vein thrombosis and pulmonary embolism.[35]

Post operative nausea and vomiting (PONV)

PONV is a common complication regardless of the anaesthetic technique used. However, the risks of PONV associated with Total Intravenous anesthesia (that is, propofol-based anesthetic) appear to be lower than that

associated with inhalation anesthesia. Combinations of antiemetics administered prophylatically are more effective than either antiemetic administered alone, particularly in high- risk patients. [35]

PAIN

Pain after laparoscopic surgical procedures may be quite severe, particularly in the early postoperative period. There is more visceral pain after laparoscopic procedures compared with parietal (that is, abdominal wall) pain after open abdominal procedures. Shoulder pain secondary to diaphragmatic irritation is a frequent occurrence after laparoscopy and there is a strong correlation between the severity of shoulder pain and the volume of residual subdiaphragmatic gas. Every attempt should be made to remove as much CO_2 as possible at the end of the procedure. Stretching of the intra-abdominal cavity from higher insufflations pressures significantly increases the severity of pain.[35]

Physiological review

Visual Analog Scale (VAS) is currently, the most commonly used method; first described by AITKEN is 1966. The subject makes a mark on a 10 cms line - horizontal or vertical, one end of which is marked as "No pain" and the other as "The worst pain one can imagine". The position of the mark on the line measures how much pain the subject experiences.

Alpha-2 adrenoceptor agonists have analgesic properties when given parenterally, epidurally or intrathecally. Stimulation of alpha-2 adrenoceptors in the substantia gelatinosa of the dorsal horn of the spinal cord by specific agonists inhibits the firing of nociceptive neurons stimulated by peripheral A and C fibres.[40]

Use of analgesics before pain stimulus (preventive analgesia) obstructs development of neuroplastic changes in central nervous system and reduces pain.[41]

PHARMACOLOGY
CLONIDINE
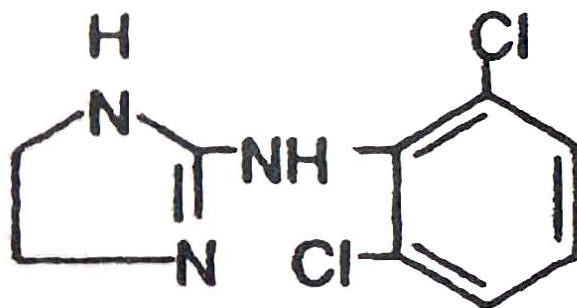
Figure 3. Chemical structure of clonicline

Clonidine decreases peripheral norepinephrine release by stimulation of prejunctional inhibitory alpha-2 adrenoceptors and by inhibition of neural transmission in different brainstem areas, such as the nucleus tractus solitarius and lateral reticular nucleus in the ventrolateral medulla. Hypnotic-sedative, analgesic and anxiolytic actions of clonidine may be modulated via the alpha 2A adrenoceptor subtype.[42] It is a partial agonist with an alpha-2a to alpha-1 selectivity ratio of 39. The alpha-2a-to-imidazoline selectivity ratio is 16.[43] Clonidine is an imidazoline and is the alpha-2 adrenoceptor agonist currently available for use in anesthetic practice.

Pharmacokinetics

Intravenous Clonidine

In a study, authors studied IV clonidine for postoperative analgesia in patients who had undergone spinal fusion surgeries during postoperative period with IV infusion in a dose of 5 mcg /kg and found that plasma clonidine concentration reached 1.5 to 2 ng/ml.At plasma concentration of 1.5 to 2 ng/ml maximum hypotensive and sedative effects have been recognized. It was found that, at 5mcg/kg, rapid control of pain was obtained at first hour. After the loading dose of 5 mcg/kg of clonidine continuous administration of 0.3 mcg/kg/hr of clonidine maintained plasma concentration close to this level in satisfactory range for analgesia and continuous analgesia was thus obtained. The plasma drug concentration reaches plateau at three half lives when administered by continuous infusion and average elimination half life of clonidine is 12 hours. To avoid the plasma levels of clonidine more than 2 ng/ml continuous administration of clonidine should be stopped or decreased at end of 12 hour. [44]

Clonidine 150 mcg IV was found to effectively diminish shivering when compared with droperidol or saline. Surgical patients recovering from spinal fusion were given clonidine by continuous infusion (5 mcg/kg loading dose over period of one hour followed by 0.3 mg/kg/hr for 12 hour. In patients recovering from active surgery perioperative administration of clonidine 7 mcg/kg/2hr resulted in fewer postoperative hypertensive episodes and maintained concentrations of norepinephrine, epinephrine and vasopressin levels at much lower values.[45]

Clonidine is lipid soluble and so has both rapid and complete absorption after oral administration, reaching a peak plasma level in 60 to 90 minutes. Time release transdermal patches are also available; two days of administration are required before therapeutic plasma concentrations are achieved. Because of its high lipid solubility clonidine crosses the blood-brain barrier and disappears rapidly from the cerebrospinal fluid (CSF). The elimination half-life after epidural injection of clonidine 150 mcg is 30 minutes. It is 20% bound to plasma proteins and the volume of distribution is 1.7 to 2.5 l/Kg. Clonidine is less than 50% metabolized in the liver to inactive metabolites, the remaining drug being excreted unchanged in the kidney; about 20% is excreted in the feces. The elimination half-life is of the order of 6 to 23 hour and is prolonged if renal impairment exists; the clearance is 1.9 to 4.3 ml/min/kg. [46]

Preparation and Route of Administration

- Available as 100 / 250 / 300 mcg tablets for oral administration
- Transdermal patch releasing 100/200/300 mcg over 24 hour and

Injectable solution containing 150 mcg/ml for intravenous, intramuscular, local and regional use. The adult oral dose is 100 to 600 mcg administered 8 hourly; the corresponding intravenous dose is 150 to 300 mcg, a dose of 150 mcg has been used epidurally.[46]

Central alpha-2 adrenoceptor agonists attenuate sympatho adrenal activation and provide greater perioperative stability. Selective and nonselective alpha-2 adrenoceptor agonists are;

Nonselective Alpha-2 Adrenoceptor Agonists	selective Alpha-2 Adrenoceptor Agonists
Noradrenaline Adrenaline	Dexmedetomidine Mivazerol clonidine alpha methyldopa

Pharmacodynamics

Central Nervous System Effects

When adrenaline has been administered intracerebroventricularly, so that the blood-brain barrier is avoided, sedation ranging from sleep to surgical anesthesia has been described. The use of clonidine as an antihypertensive has been limited by its sedative effects, but offers advantages in anesthetic practice. When clonidine was given in a sufficient dose to produce sleep, the EEG showed an increase in stage 1 and 2 sleep and decrease in rapid eye movement sleep. Alpha-2 ainedrenoceptor agonists and benzodiazepines produce comparable anxiolysis. Clonidine at high doses can be anxiogenic owing to alpha-1.[46]

Renal System Effects

Activation of alpha- 1 receptors in the kidney results in a redistribution of blood from the cortical to medullary areas due to an increase in renal vascular resistance. Stimulation of alpha-2 adrenoceptors has a number of effects that promote diuresis and natriuresis. They decrease the secretion of vasopressin and antagonise its action on renal tubules. Alpha-2 adrenoceptors are also thought to inhibit the release of renin and increase the release of atrial natriuretic factor.[46]

Neuroendocrine System Effects

The alpha-2 adrenoceptor agonists have a number of neuroendocrine effects, mainly related to their inhibition of sympathetic outflow and the decrease in plasma levels of circulating catecholamines. Stimulation of alpha-2 adrenoceptors located on the beta cells of the islets of Langerhans can temporarily cause direct inhibition of insulin release; clinical hyperglycemia has not proved to be a problem. Alpha-2 receptor agonists also increase the release of growth hormone and inhibit adipose tissue lipolysis. Clonidine can inhibit the secretion of adrenocorticotropic hormone (ACTH) and cortisol during surgery.[46]

Effects on Platelets

Selective alpha-2 adrenoceptor agonists, as well as adrenaline, are known to stimulate platelet aggregation by stimulating alpha-2c receptors on platelets. High concentrations of alpha-2 adrenoceptor agonists are required to cause platelet aggregation, as low concentrations of these drugs decrease plasma adrenaline concentration; the net effect may be a reduction in platelet aggregation. Alpha-2 receptor stimulation also results in the release of nitric oxide, a potent inhibitor of platelet aggregation. Clonidine does not promote platelet aggregation; it also blocks adrenaline-induced platelet aggregation.[46]

In a study authors compared the effects of clonidine 4.5 mg/kg or saline on hemodynamies, neuroendocrine response, and renal parameters in 30 healthy patients undergoing laparoscopic cholecsteetomy. They found that the heart rate, arterial blood pressures, and plasma renin activity were lower during and after PNO in patients with clonidine. There were no differences in urine output, urine oxygen tension (reflecting medullary perfusion), or antidiuretic hormone between the groups. They concluded that clonidine enabled stable hemodynamics and prevented activation of RAAS seen as unchanged plasma renin activity and that clonidine may be beneficial during laparoscopy in patients with hypertension, cardiovascular, and/or renal diseases.[47]

In a study, authors concluded that vasopressin and catecholamines probably mediate increase in systemic vascular resistance observed during CO_2 PNO. Clonidine before PNO reduces catecholamine release and attenuates hemodynamic changes during laparoscopy. They conducted two studies, each in 20 healthy patients scheduled for elective laparoscopic cholecystectomy. In the first study, serial measurements of hemodynamics and plasma concentrations of cortisol, catecholamines, vasopressin, renin, endothelin and prostaglandins were measured during laparoscopy and after exsufflation. In the second study, patients were randomly premedicated with 8 mcg/kg clonidine infused over one hour or placebo before PNO. Hemodynamics and plasma levels of cortisol, catecholamines and vasopressin were measured during PNO

and after exsufflation. They found that peritoneal insufflation resulted in a significant reduction of cardiac output and increases in MAP and systemic and pulmonary vascular resistances. Laparoscopy resulted in progressive and significant increases in plasma concentrations of cortisol, epinephrine, norepinephrine and renin. Vasopressin plasma concentrations markedly increased immediately after the beginning of PNO. The profile of vasopressin release paralleled the time course of changes in systemic vascular resistance. Prostaglandins and endothelin did not change significantly. Clonidine significantly reduced MAP, heart rate and the increase in systemic vascular resistance. Clonidine also significantly reduced catecholamine concentrations but did not alter vasopressin and cortisol plasma concentrations.[48]

Cardiovascular System Effects

There are both alpha-1 and alpha-2 postjunctional receptors in the arterial and venous vasculature where they both mediate vasoconstriction.[49] The alpha-1 and alpha-2 adrenoceptors differ in their location and their utilization of calcium. In the arterial vasculature, the alpha-1 adrenoceptors are junctional and the alpha-2 adrenoceptors are extra-junctional, while the reverse is true of the venous vasculature. Alpha-1 adrenoceptor stimulation produces vasoconstriction by utilizing intracellular calcium while the alpha-2-adrenoceptor-mediated vasoconstriction uses extracellular calcium.[50] This makes the alpha-2 adrenoceptor agonist's pressor response more sensitive to calcium antagonists.

Clonidine lowers the 'set point' around which arterial blood pressure is regulated. It also increases the gain of the baroreceptor system, resulting in lower heart rates for a given increase in blood pressure, and broadens the range of heart rate responses to changes in blood pressure.[51]There are no known directly mediated alpha-2 adrenoceptor effects on the myocardium. Alpha-2 adrenoceptor reduction in sympathetic tone and increase in parasympathetic tone results in a reduced heart rate, systemic metabolism, myocardial contractility and systemic vascular resistance thereby decreasing the myocardial oxygen requirements. This is may be why clonidine has been successful in the treatment of angina pectoris.[52]

Respiratory System Effects

Alpha-2 adrenoceptors have a minimal effect on ventilation. In humans, clonidine in doses up to 300 mcg seems to cause a small reduction in resting minute ventilation and an increase in expired carbon dioxide . The locus coeruleus is involved in arousal reactions; suppression of its activity by alpha-2 adrenoceptor agonists can result in a state similar to sleep with mild respiratory depression. There is no significant effect on hypercapnic or hypoxic ventilatory drive with alpha-2 adrenoceptor stimulation. The combination of alpha-2 adrenoceptor agonists with opioids does not lead to further ventilatory depression.[53]

Gastrointestinal System Effects

It has been postulated that gastric cholinergic prejunctional alpha-2 adrenoceptors inhibit gastric secretions during stress. Clonidine causes activation of alpha-2 adrenoceptors to inhibit water secretion and increases net absorption in the large bowel; and hence can be used to treat diarrhoea. Stimulation of alpha-2 adrenoceptors is known to reduce salivary secretions and may lead to a dry mouth.[54]

MATERIAL & METHOD

The present study was conducted in the Department of Anesthesiology, M.G.M Medical College and Hospital Aurangabad during the period of June 2011 to December2013.

Study design

Two year randomized controlled trial.

Source of Data

Patients undergoing laparoscopic cholesystectomy at M.G.M Medical College and Hospital Aurangabad

Study Period

Two year from June 2011 to December 2013.

Sample Size

A total of 80 patients divided into two groups using computer randomization.

Sampling procedure

Using results of previous studies and pilot study and using the formula 40 patients are selected in each group based on the following calculation.

Sample Size (n) $= \dfrac{2 \text{ X } (Z\alpha + Z\beta)^2 (S1^2 + S^2)}{(X_1 - X_2)^2}$

α error   =   0.05

β error =   0.1

Power =   90%

S.D^1 = 7.21 = 7

S.D^2 = 5.07 = 5

Difference of mean of mean BP 14mm of Hg

$2 \times (1.96 + 1.282)^2 (7^2 + 5^2)$

Sample Size (n) $= (14)^2$

= 1555.48/196

=8

However it was decided that to do 40 cases in each group.

= 40 patients were selected in each group.

1. Selection criteria.

Inclusion criteria

1. Patients of ASA gr I and II.
2. Patients of age >20 to<60 years.
3. Patients for laparoscopic cholecystectomy.

Exclusion criteria

1. Age<20 &>60 years.
2. Pregnant patient
3. Patient with hypertension, hypotension, ischemic heart disuse, aortic stenosis, left ventricular failure and atrioventricular conduction block.
4. Patient taking clondine, methyldopa, mao inhibitors and beta blockers

Randomization

- Patients were randomly allocated into one of the two groups by computer generated randomization that is
- Group I -n=40; receiving 2 mcg/kg clonidine IV in 100 ml normal saline over 20 min.
- Group II- n=40 receiving l00 ml normal saline over 20 min administered as premedication (20 min before induction)
- Preparation of drugs was made by anesthesiologist not involved in study.

Procedure

Prior to the commencement of study ethical clearance was obtained from Institutional Ethics Committee. Based on the selection criteria patient undergoing LC at M.G.M. Medical College and Hospital Aurangabad were screened for eligibility and a written informed consent was obtained from the selected patients. Patients

were randomly allocated into two groups namely group I and group II. Prior to surgery thorough history was taken and clinical examination was done for all patients and findings were recorded on predesigned and pretested proforma (AnnexIl).

The written informed consent was obtained from all the patients before including them in the study. Pre anesthetic evaluation done and CBC, LFT, Urine Analysis, ECG, Blood Group will be noted.. Patient randomly allocated into two groups namely group I and group II. All patients advised Tab. Alprazolam 0.5mg and Tablet, Omeprazole 20mg orally on night before Surgery. Further, Nil by mouth (NBM) status confirmed. Monitors like, ECG, NIBP, Pulseoximetry applied. Intravenous line (IV) will be secured with appropriate IV cannula and 500 ml crystalloids started. Heart rate, NIBP and saturation were monitored before and during the surgery. Drugs given intravenously as slow infusion to patients 20 minutes before inductuion in operative room. Group I had received clonidine 2 mcg/Kg diluted to 100 ml normal saline IV and Group II received normal saline 100 ml IV infused over 20 minutes. After premedication with glycopyrolate 0.005 mg/Kg and fentanyl 2mcg/Kg, Patients then induced with thiopentone 5 mg/kg until loss of eye lash reflex, and succinylcholine 1.5mg/kg. Further they intubated with appropriate sized cuffed endotracheal tube and maintained on inj. Vecuronium0.lmg/kg iv bolus followed by incremental dose of 0.02mg/kg (IV)., nitrous oxide and oxygen (66:33), isoflurane 0.6%-1 .5%. Controlled Mechanical ventilation will be applied to maintain $ETCO_2$ between 30-4OmmHg. After pneumoperitoneum if there was increase in MAP more than 20% of basal MAP, isoflurane concentration increased accordingly as a rescue agent. Repeat dose of Inj Fentanyl 0.5mcg/kg given every 1 hour. Intrabdominal pressure not be allowed to exceed 15 mmHg throughout the surgical procedure. Heart rate < 60 beats/min managed by inj. Atropine 0.6mg (IV). Mean arterial blood pressure < 60 mmHg managed with fluid challenge and inj. Mephentermine 6 mg bolus (IV). MAP, HR noted at P1(Baseline), P2(laryngoscopy), P3(After pneumoperitoneum) P4(15 minutes after PNO), P5(30 minutes after PNO), P6 (Exsufflation) P7 (Post operatively 15 minutes), P8 (post operatively 30 minutes) and End tidal carbon di-oxide [$ETCO_2$], SPO_2 noted at intervals. After surgery patients reversed with glycopyrolate 0.005 mg/Kg and neostigmine 0.05 mg/kg and extubated. Patients shifted to recovery. Duration of surgery and duration of carboperitoneum was noted. In recovery room patient monitored for degree of sedation by sedation scale. (1) awake a agitated (2) awake and comfortable (3) Asleep but arousable (4) Asleep with sluggish response to persistent call touch. (5) No response to call or touch. Pain intensity was assessed by using 10cm VAS. 0 denoting pain and 10 denoting intolerable pain. Sedation and VAS Score were recorded at every 30 min for 90 min in post recovery room. Postoperative requirement of injection Diclofenac (1.5 mg/kg) was noted.

Statistical Analysis

Demographic data, HR and mean arterial pressure [MAP] were tabulated as Mean ± SD and analyzed by student't' test

Non parametric variables like pain expressed as median tabulated as per VAS score duration of analgesia, sedation score and requirement of Isoflurane concentration analyzed by student 'T' test. Diclofenac injection was standardized as rescue analgesic.

RESULT

The present prospective randomized controlled trial of eighty patients aged between 20 to 60 years of ASA grade I AND II undergoing LC were studied to evaluate the intraoperative hemodynamic effects, sedation score anaesthetic requirements.Patients were devidedin two groups of foutry each namely group I(clonidine 2mcg/kg in normal saline and group II (normal saline100 ml).The data recorded on predisgned and pretested proforma and master chart was prepared.The analysis was done as follows

Table 1: Age-Distribution:

Age-Group	Group I		Group II	
	No.	Percentage	No.	Percentage
18-30	07	17.5%	07	17.5%
31-45	18	45%	15	37.5%
46-60	15	37.5%	18	15%
Total	40	100%	40	100%
Mean±SD	41.93±10.82		44.05±11.10	
t-value	0.867			
p-value	P=0.389 NS			
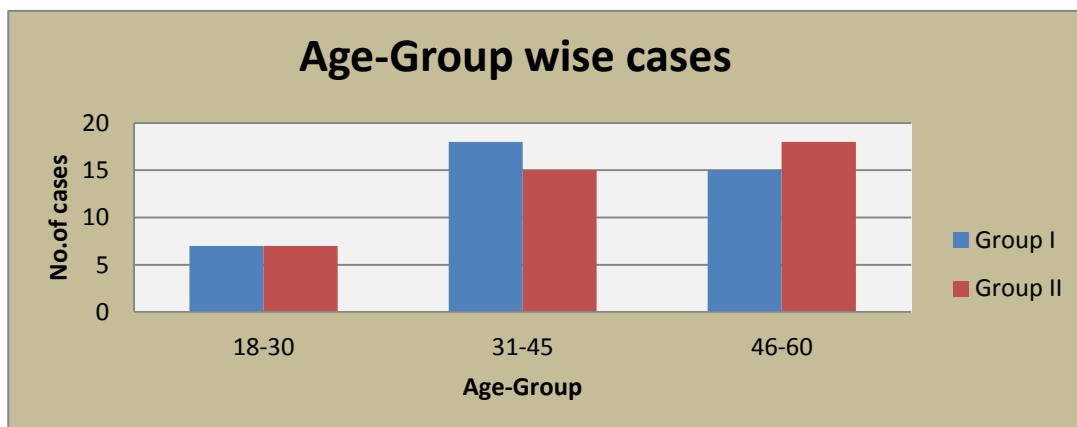
In this study most of the patient (group I 45% and group II 37.5%) in both the group were aged between 31 to 45 years. The mean age in group I was 41.93+_10.82 years and group II it was 44.05 +_11.10 years, suggesting both the groups had comparable demographic characteristics

Table 2: Gender-Distribution:

Gender	Group I		Group II	
	No.	Percentage	No.	Percentage
Male	16	40%	15	37.5%
Female	24	60%	25	62.5%
Total	40	100%	40	100%
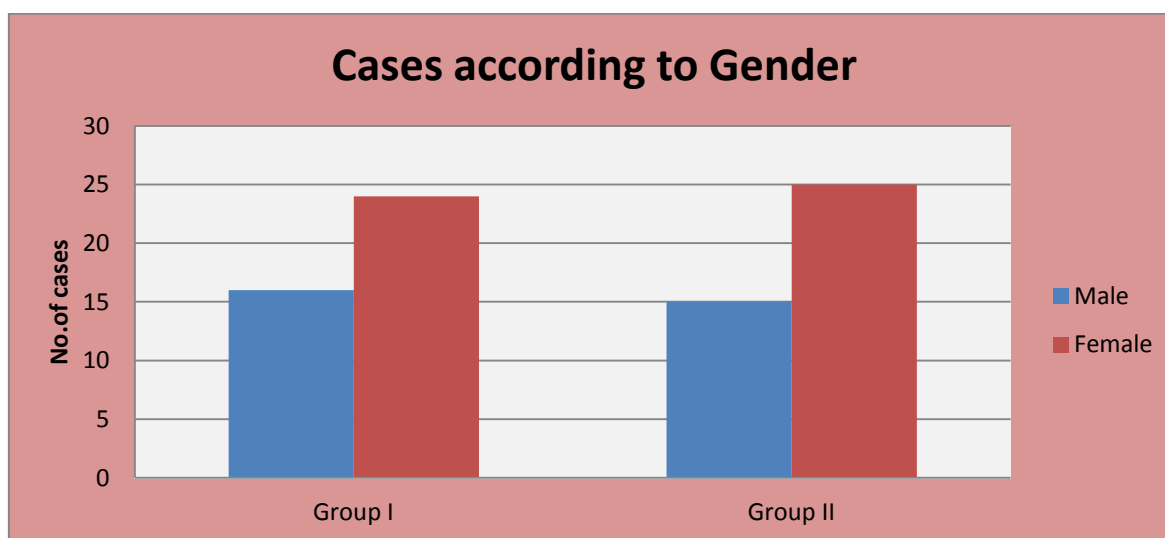
In this study in group I 40% were males and 60% were females,in group II male 37.5% and female 62.5%

Table 3: comparison of weight in Group I & Group II

| Variable	Group I Mean±SD	Group II Mean±SD	t-value	P-value
Weight	62.82±7.94	61.50±10.53	0.636	P=0.527 NS

The mean weight in group I was 62.82+_7.94kgs and in group II it was 61.50+_10.53 kgs suggesting mean weight in both groups were comparable.

Table 4: Comparison of HR (Heart Rate) in Group I and Group II : at P1, P2, P3,P4,P5,P6,P7&P8:

	Group	Mean ± SD	t-value	P-value
P1	Group I	81.55± 2.41		P=0.347
	Group II	83.67±13.99	0.948	NS
P2	Group I	85.35±1.90	4.51	P=0.000
	Group II	103.70±25.78		S
P3	Group I	79.50±2.16	3.87	P=0.000
	Group II	90.17±17.29		S
P4	Group I	75.75±1.52	6.51	P=0.000
	Group II	89.60±13.35		S
P5	Group I	73.25±2.38	6.74	P=0.000
	Group II	90.10±15.64		S
P6	Group I	74.95±3.67	4.60	P=0.000
	Group II	81.57±8,32		S
P7	Group I	78.80±2.17	6.13	P=0.000
	Group II	88.02±9.26		S
P8	Group I	80.85±1.50	2.06	P=0.040 S
	Group II	97.40±7.96		

Ingroup I,the mean baseline heart rate was 81.55+_2.41per min and group II the mean heart rate was 83.67+_13.99 per min (p=0.347) which is non significant.However there is significant difference in heart rate in both group atP2(p=0.000), P3(p=0.000), P4(p=0.000),P5(p=0.000),P6(p=0.000), P7(p=0.000),P8 (p=0.040) level.
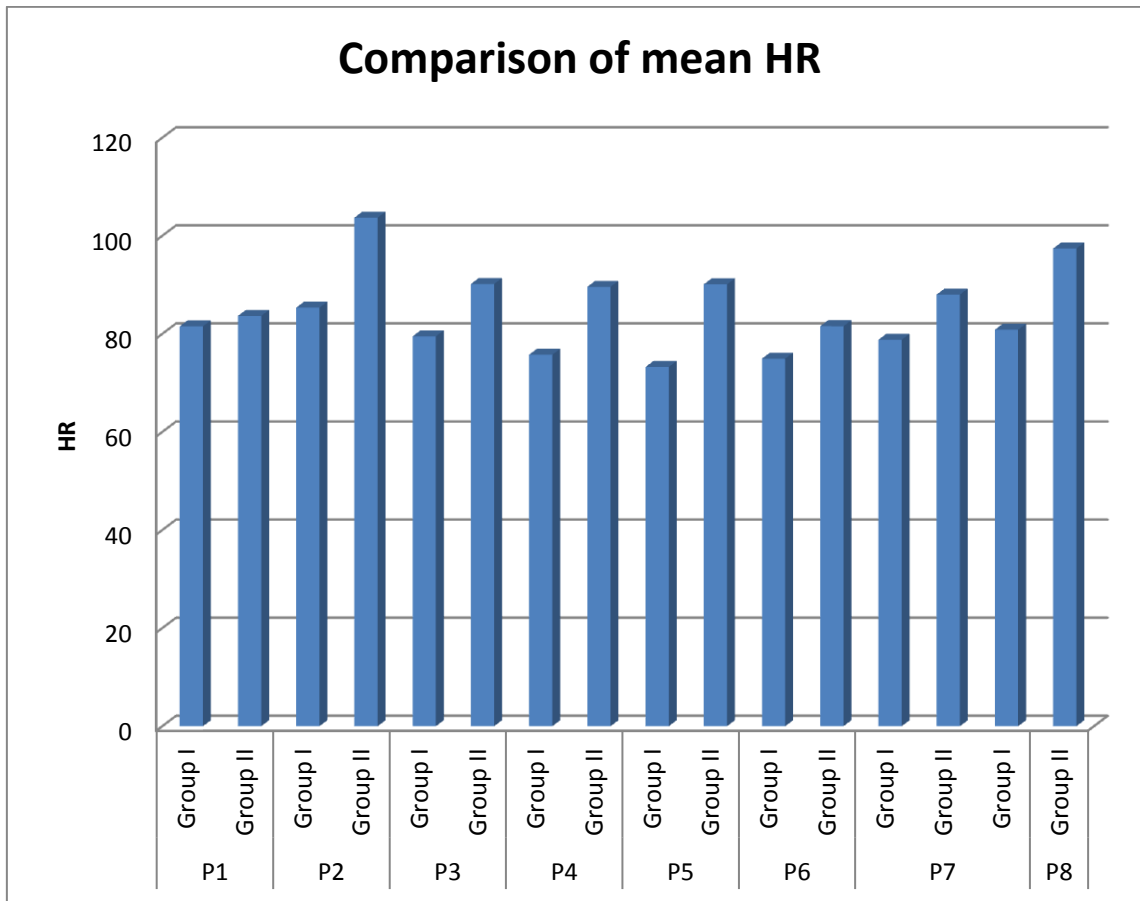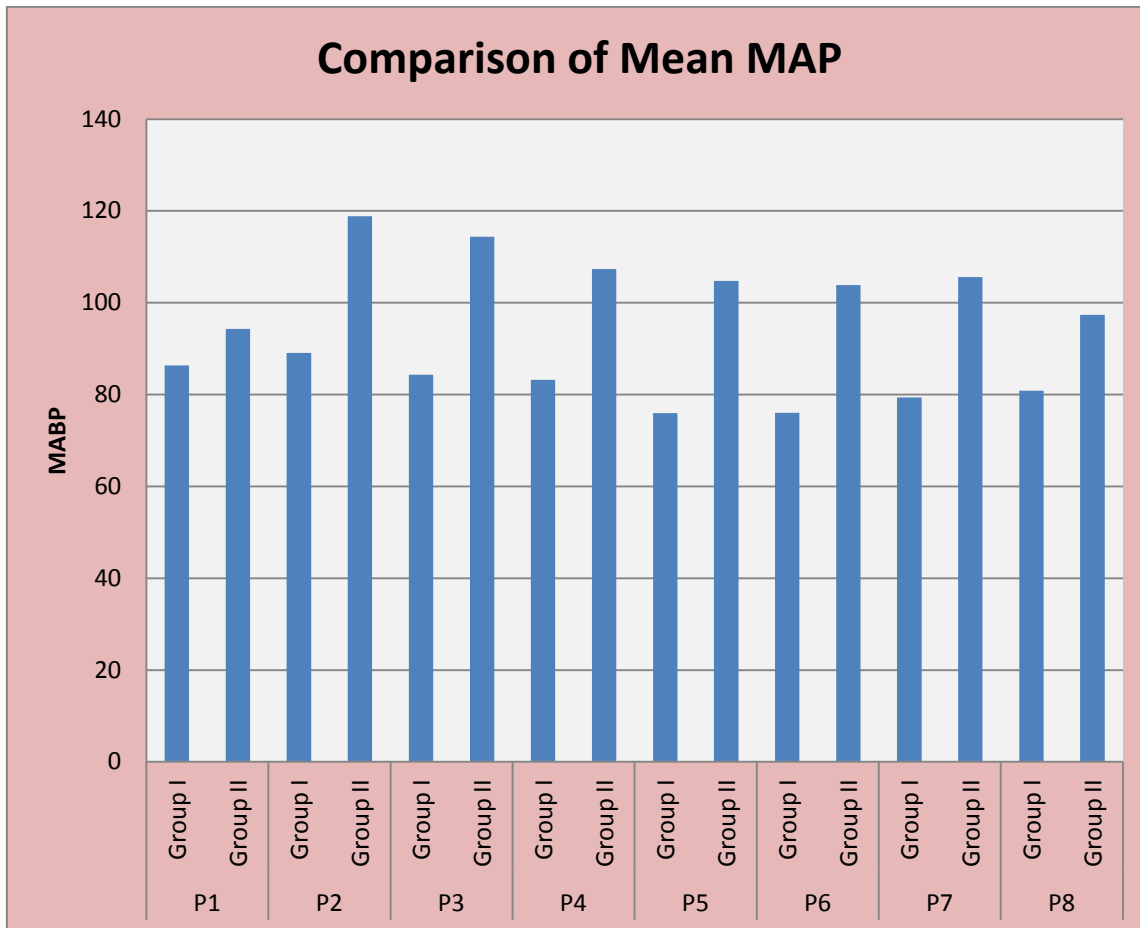
The figure shows intraoperative heart tate changes of clonidine group I of patients isoflurane (0.6 to 0.9%) are at lower level compared to normal saline group II with isoflurane 1 to 1.6% at various periods of procedure.

Table 7: Comparison of MAP in Group I and Group II : at P1, P2, P3,P4,P5,P6,&P7:

	Group	Mean ± SD	t-value	P-value
P1	Group I	86.35±2.88		P=0.000
	Group II	94.29±9.73	4.94	S
P2	Group I	89.06±1.90	9.35	P=0.000
	Group II	118.85±19.99		S
P3	Group I	84.35±1.83	21.59	P=0.000
	Group II	114.35±8.68		S
P4	Group I	83.22±0.95	18.63	P=0.000
	Group II	107.32±8.12		S
P5	Group I	75.96±1.70	19.04	P=0.000
	Group II	104.75±9.42		S
P6	Group I	76.04±2.59	19.45	P=0.000
	Group II	103.87±8.57		S
P7	Group I	79.36±1.78	16.49	P=0.000
	Group II	105.60±9.90		S
P8	Group I	80.85±1.50	12.96	P=0.040
				S
	Group II	97.40±7.96		

There is significant difference in MAP in both group at P2(p=0.000), P3(p=0.000), P4(p=0.000),P5(p=0.000),P6(p=0.000), P7(p=0.000),P8 (p=0.040) level.

The figure shows inrtraoperative MAP changes of clonidine group I of patients with isoflurane (0.6 % to 0.9%)are at lower level compared to normal saline group II with isoflurane 1 % to 1.6% at various periods of procedure

Table 10: Comparison of Post operative VAS score in Group I and Group II : :at 30 min.,60 & 90 min.

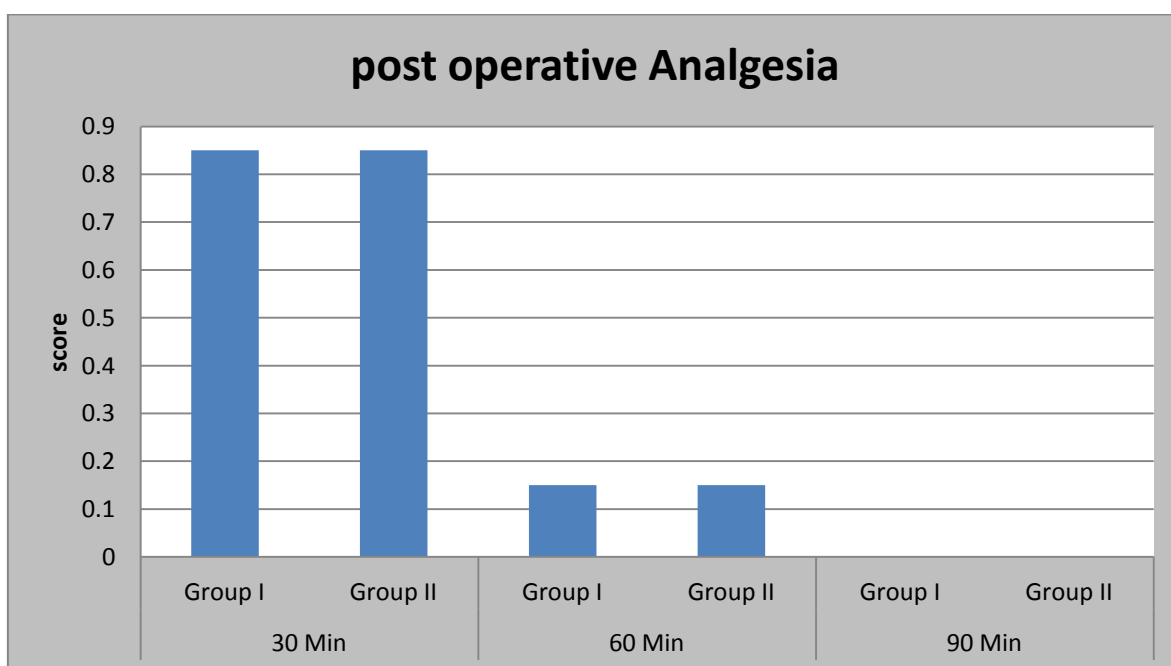|	*Group*	*Mean ± SD*	*t-value*	*P-value*
30m	*Group I*	8.45±0.78	0.143	*P=0.887*
	Group II	8.42±0.78		*NS*
60m	*Group I*	1.57±3.46	0.000	*P=1.000*
	Group II	1.57±3.46		*NS*
90m	*Group I*	0.00±0.0	000	*P=1.000*
	Group II	0.00±0.0		*NS*

There is no significant changes in both group at 30 mins(p=0.887),60 mins (p=1.000) in VAS score
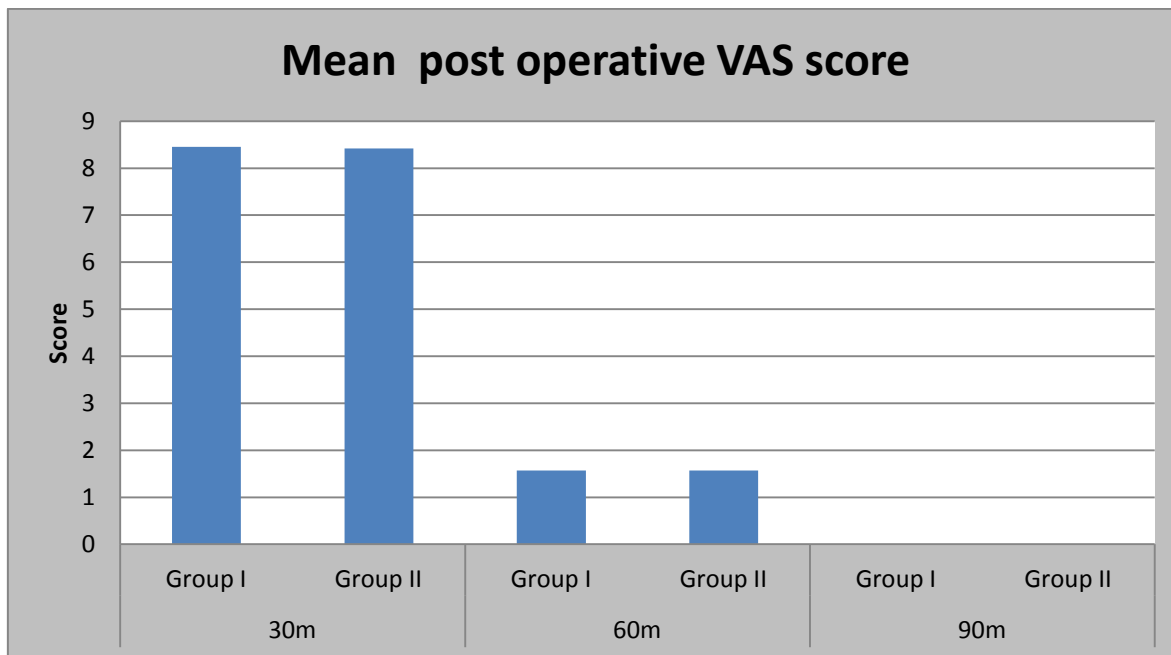
Table 11: Comparison of Post operative analgesia requirement duration in Group I and Group II : : at 30 min.,60 & 90 min.

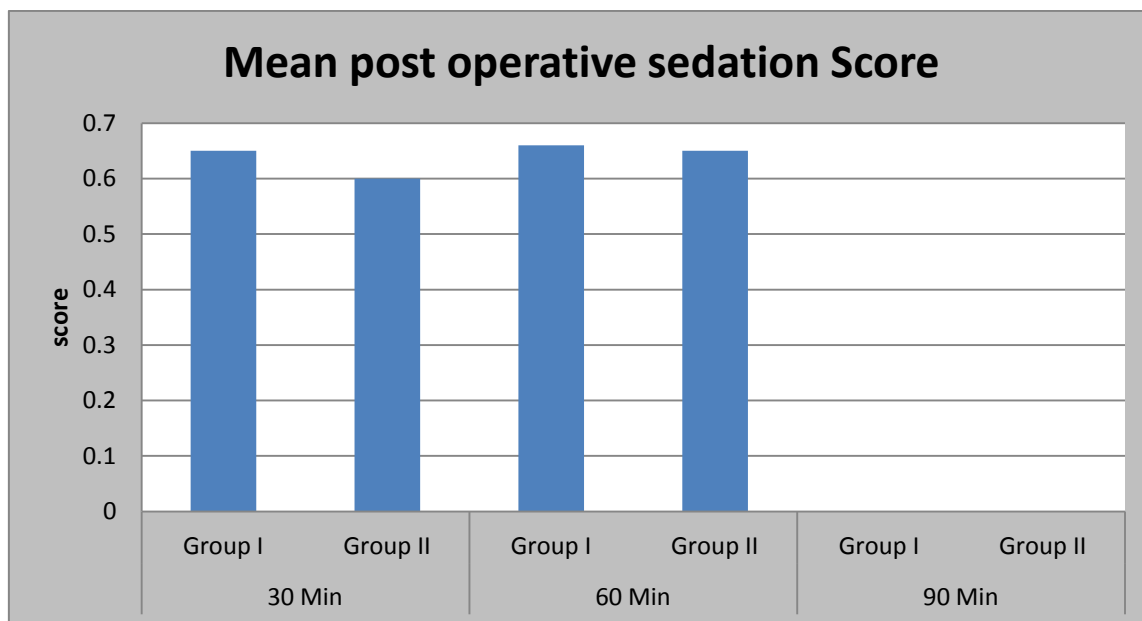|	Group	Mean ± SD	t-value	P-value
30 Min	Group I	0.85±0.36	0.00	P=1.000
	Group II	0.85±0.36		NS
60 Min	Group I	0.15±0.36	0.00	P=1.00
	Group II	0.15±0.36		NS
90 Min	Group I	0.00±0.0		
	Group II	0.00±0.0		

There is no significant changes in both groups on post operative analgesia requirement duration(30 mins p=1.000 and 60 mins p=1.000)

Table 12: Comparison of Post operative SEDATION score in Group I and Group II : :at 30 Min, 60 Min. & 60 Min.

| SEDATION	Group	Mean ± SD	t-value	P-value
30 Min	Group I	0.65±0.44	0.457	P=0.649 NS
	Group II	0.60±0.49		
60 Min	Group I	0.66±0.47	0.234	P=0.616 NS
	Group II	0.65±0.48		
90 Min	Group I	0.0±0.0		P=0.000 S
	Group II	0.0±0.0		

There is no significant changes in both groups on post operative sedation score at different intervals (30 mins p=0.649 and 60 mins p=0.616)

Table 13: Comparison of   isoflurane requirement in Group I and Group II :

	Group	Mean ± SD	t-value	P-value
isoflurane	Group I	0.82±0.09	10.92	P=0.000
	Group II	1.25±0.23		S

The reqirement of isoflurane is reduced in group I (mean sd 0.82+_0.09)as compared to group II (1.25+_0.23) which is significant(p=0.000)
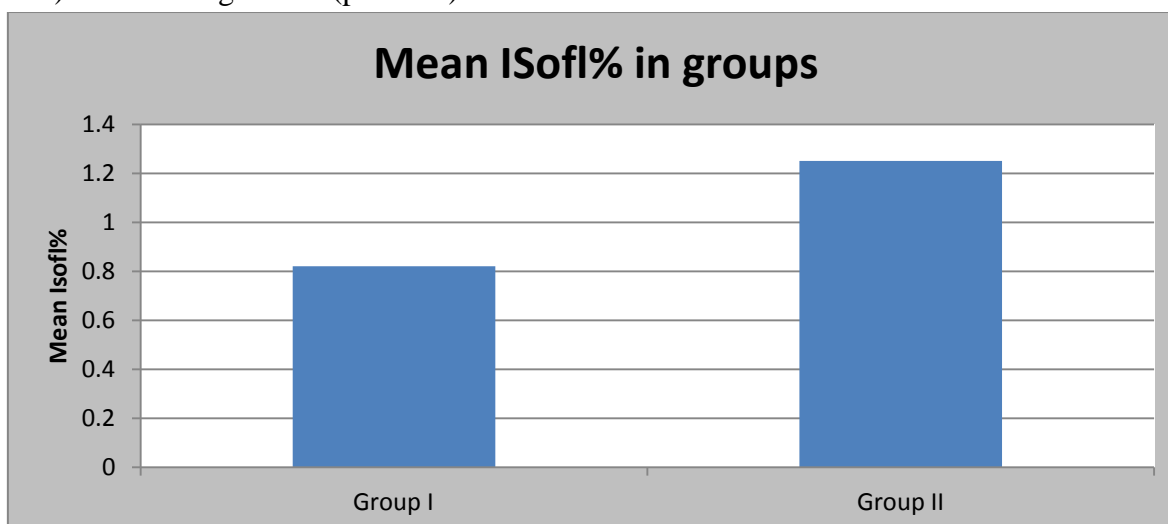
DISCUSSION

Laparoscopic cholecystectomy has rapidly become the procedure of choice for routine gallbladder removal and has become the most common major abdominal procedure performed in Western countries.[55]

LC decreases morbidity and shortens hospital stay from 1 week to less than 24 hours, and returns the patient to full activity within 1 week compared to 1 month after open cholecystectomy (OC).[56,57]

Laproscopic cholecystectomy (LC) requires production of pneumoperitoneum and thus routinely requires general anesthesia with intubation. The hallmark of laparoscopy is creation of carbon dioxide (CO_2) pneumoperitoneum and change in the patients position from Trendelenberg to reverse Trendelenberg. It also results in stress hormone responses (cortisol, epinephrine and nor-epinephrine) especially when CO_2 pneumoperitoneum is used concomitantly.[8]

Pneumoperitoneum results in caval compression and increase in venous resistance.[36]

Peritoneal carbon dioxide insufflations necessary for laparoscopic Cholecystectomy 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.[2]

Clonidine is an alpha 2 adrenoreceptor agonist. It exerts central sympatholytic effect and has a half life of 9-12 h. Clonidine decreases peripheral norepinephrine release by stimulation of prejunctional inhibitory alpha-2 adrenoceptors and by inhibition of neural transmission in different brainstem areas, such as the nucleus tractus solitarius and lateral reticular nucleus in the ventrolateral medulla. [42]

These characteristics suggest that clonidine may be useful in the anesthetic management of patients undergoing laparoscopic surgeries. Accordingly, this study was designed to evaluate the effects of intravenous clonidine on reduction of perioperative stress response, maintaining hemodynamic stability, decreases intraoperative anesthetic requirement and on modulation of postoperative pain in 80 patients undergoing LC at M.G.M. Medical college and Hospital Aurangabad, I n our study ,clonidine 2 mcg/kg was used as a premedication, it is pharmacokinetics ov iv clonidine explained by a study [44] showing plasma levels 1.5 to 2 ng/ml after loading dose of 5mcg/kg of clonidine which results in to sedation and hypotensive effects. In order to avoid such effects of clonidine 2mcg/kg as a pre medication over a period of 20 min slowly, which did not result in any adverse hemodynamic changes like hypotension and bradycardia.

In this study 37.5 % were males and 62.5% were females in group I and II. Most of the patients (Group I 45% and group II 37.5%) in both the groups were aged between 31 to 45 years. The mean age in group I was 41.93 ± 10.82 years and in group II it was 44.05 ± 11.10 years suggesting both the groups had comparable demographic characteristics.

The mean weight in group I was 62.82 ± 7.94 Kg and in group II it was 61.50 ± 10.53 Kg suggesting mean weight in both groups were comparable. Present study results clearly showed intraoperative MAP changes were significantly lower in clonidine group 1(C) that is { P2(89.06±1.90) mmHg, P3 (84.35 ±1.83)mm Hg , P4 (83.22±0.95) mm Hg and P5(75.96±1.70) mm Hg with (isoflurane 0.6 to 0.9%) and at P6 (76.04±2.59)mm Hg,P7 (79 .36 ±1.78)mm Hg,P8 (80.85±1.50) mm Hg} p = <0.000 compared to group II(n) at all intervals where in consumption of isoflurane was [1 -1 .6%]. Thus MAP remained under satisfactory control.

Also intraoperative heart rate changes were found to be significantly lower in clonidine group that is {P2 (85.35±1.90) bpm, P3 (79.50 ±2.16) bpm, P4 (75.75±1.52) bpm and P5 (73.25±2.38) bpm with (isoflurane 0.6 to 0.9%) and at P6 (74.95±3.67) bpm, P7 (78.80±2.17) bpm, P8 (80.85±1.50) bpm} p<0.000 compared to normal saline group II group at all intervals with consumption of isoflurane {1 to 1 .6%}. Thus heart rate remained under satisfactory control.

MEAN ARTERIAL PRESSURE

Singh S et al (2011) [8]observed that rise in MAP in placebo group compared to clonidine group (clonidine 150 mcg orally) at T2 (laryngoscopy; 100.04 ± 12.16 mm Hg vs 85.84 ± 10.12; p=0.330), at T3 (after PNO; 89.20 ± 11.50 mm Hg vs 78,28 $\pm$ 13.69; p=0.008), T4 (at 15 minute after PNO; 88.00 ± 14.17 mm Hg vs 79.76 ± 10.74; p=0.020), T5 (at 30 minute after PNO; 83.80 ± 12.70 mm Hg vs 79.28 ± 9.50; p=0.02l). These results were comparable with the our study in group (N) vs group(C) that is, at P2 (laryngoscopy; 118.85 ± 19.91 mm Hg vs 89.06 ± 1.90; p=0.000), at P3 (after PNO; 114.35 ± 8.68 mm Hg vs 84.35 ± 1.83; p=0.000), P4 (at 15 minute after PNO; 107.32 ± 8.12 mmHg vs 83.22+ 0.95; p=0.000), T5 (at 30 minute after PNO; 104.75 ± 9.42 mm Hg vs 75.96 ± 1.70; p=0.000).

Passi Yet al (2009) [9] studied the effects of oral clonidine (150 mcg) premedication in LC and they concluded that decrease in MAP in clonidine group compared to placebo group T2 (laryngoscopy 88 ± 9 mmHg vs 97 ± 14mmHg;p<0.005) T4 (15 min after PNO 92 ± 8 mmHg vs1o6$\pm$5 mm Hg; p<0.005) T5 (30 min after PNO 92 ± 9 mmHg vs 106 ± 5 mmHg;p<0.005)T6(exsufflation 94 ± 7mmHg vs 103 ± 6mmHg,p<0.005.In our study also mean blood pressure was significantly rasised in group II (N) vs group I (C) i.e ,at P2 (laryngoscopy 118.85 ± 19.91vs 89.06 ± 1.90 mmHg;p=0.000) p4 (15 min after PNO 107.35 ± 8.68 mmHg vs83.22$\pm$0.95 mmHg;p<0.005) p5 (30 min after PNO 104.75 ± 9.42 mmHg vs 75.96 ± 1.70 mmHg;p<0.005)p6(exsufflation 103.87 ± 8.57mmHg vs 76.04 ± 2.59 mmHg,p<0.005).Which is comparable to our study.

Das M et al (2007) conducted a study.[10]and reported significant rise in MAP in Group P (placebo) as compared to Group C (clonidine 150 mcg oral) after intubation (113.56 ± 16.33 mm Hg vs 93.70 ± 7.33; p<0.001), after PNO at 15 minutes as (114.13 ± 16.57mm Hg vs 93.83 ± 8.10; p=0.001), at 30 minutes ($108.60 + 15.11$ mm Hg vs 93.64 ± 8.40; p=0.033). In our study similar significant decrease in MAP was noted in group I (clonidine) as compared group II (N) at intubation (89.06 ± 1.90 mm Hg vs 118.85 ± 19.99mmHg; p=0.000), after PNO at 15 minutes (83.22 ± 0.95 mm Hg vs 107.32 ± 8.12mmHg; p=0.000) and at 30 minutes (75.96 ± 1.70mm Hg vs 104.75 ± 9.42mmHg; p=0.000).

Deepshikha C Tripathi et al(2011) .[22] performed a study to find out the effect of two different doses of intravenous clonidine premedication on hemodynamic stress response during laparoscopic cholecystectomy and concluded that in group I (placebo) there was significant increase in haemodynamic variables during intubation, pneumoperitoneum and extubation (p<0.001).In group II(clonidine 1mcg/kg) attenuated haemodynamic stress response to pneumoperitoneum (p<0.05) but not that associated with intubation and extubation.In group III(clonidine 2mcg/kg) prevented hemodynamic stress response to pneumoperitoneum and that associated with intubation and extubation In our study also we found the same results as like above group III in which clonidine 2mcg/kg given.

Bernard JM et al(1991) conducted a study[44]and found that significant rise in average MAP was observed in control group compared clonidine (4mcg/kg I.V at two stages)group at (15 minutes after PNO; 100mm Hg vs. 79mm Hg) and at(30 minutes; 88mm Hg vs. 79 mm Hg)(p<0.00l). In our study also mean MAP significantly raised in group II(N) vs. group I(C) that is at15 minutes after PNO; 107.31 ± 8.12mm Hg vs. 83.22 ± 0.95mm Hg) and at(30 minutes; 104.75 ± 9.42mm Hg vs. 75.96 ± 1.70mm Hg): (p=0.000)..

HEART RATE

Singh S et al.[8] also reported that, rise in HR in placebo group compared to clonidine group at T2 (laryngoscopy; 100.04 ± 12.16 bpm vs. 85.84 ± 10.12bpm; p0.03), T4(at 15 minute after PNO; 88 ± 14.17 bpm vs. 79.36 ± 10.74 bpm; p=0.02), T5 (at 30 minute after PNO; 83.80 ± 12.76 bpm vs. 79.28 ± 9.50 bpm; p=0.16) and these results were comparable with the our study group II(N) vs group I (C) that is, at P2 (laryngoscopy; 103.70 ± 25.78 bpm vs. 85.35 ± 1.90 bpm; p=0.000), at P4 (at 15 minute after PNO; $89.60 \pm$

13.35 bpm vs. 75.75 ± 1.52 bpm; p=0.000), P5 (at 30 minute after PNO; 90.10 ± 15.64 bpm vs. 73.25 ± 2.38 bpm;p=0.000)

Passi Yet al (2009) [9] studied the effects of oral clonidine (150 mcg) premedication in LC and they concluded that decrease in HR in clonidine group compared to placebo group T2 (laryngoscopy 92±12 bpm vs 107±14bpm;p<0.005) T4 (15 min after PNO 93±9bpm vs110±16bpm;p<0.005) T5 (30 min after PNO 92±8 bpm vs 111±17 bpm;p<0.005)T6(exsufflation 96±12bpm vs 110±14bpm,p<0.005.In our study also mean blood pressure was significantly rasised in group II (N) vs group I (C) i.e ,at P2 (laryngoscopy; 103.70± 25.78 bpm vs. 85.35 ± 1.90 bpm; p=0.000), at P3 (after PNO; 90.17 + 17.29 bpm vs. 79.50 ± 2.16 bpm; p=0.00), P4 (at 15 minute after PNO; 89.60 ± 13.35 bpm vs. 75.75 ± 1.52 bpm; p=0.000), P5 (at 30 minute after PNO; 90.10 ± 15.64 bpm vs. 73.25 ± 2.38 bpm;p=0.000)P6(exsufflation 81.57±8.52 vs 74.95±3.67).

Das M et al (2007) [10] also reported significant rise in HR in Group P as compared to Group C after intubation (107.76 ± 14.06 bpm vs. 87.26 ± 11.34 bpm; p=0.006), after PNO at 15 minutes as (96.06± 21.81 bpmvs. 75.76 ± 10.07 bpm; p0.008), at 30 minutes (94.76 ± 19.79 bpm vs. 75.70 ± 10.20 bpm; p=0.004) which were comparable to the our study that is, group(N) vs. group (C) at P2 (laryngoscopy; 103.70± 25.78 bpm vs. 85.35 ± 1.90 bpm; p=0.000), at P3 (after PNO; 90.17 + 17.29 bpm vs. 79.50 ± 2.16 bpm; p=0.000), P4 (at 15 minute after PNO; 89.60 ± 13.35 bpm vs. 75.75 ± 1.52 bpm; p=0.000), P5 (at 30 minute after PNO; 90.10 ± 15.64 bpm vs. 73.25 ± 2.38 bpm;p=0.000)

Nand K etal(2011) [23] performed a study to evaluate the effects of i.v. adminstred sclone and mgso4 on hemodynamic response during LC and concluded tht on comparing heart rate of the patient in groupK(50ml NS) with group M(50mg/kg Mgs04 i.v.) and C1(clonidine 1mcg/kg). No significant difference was found. However HR in group K patient was significantly higher as compared to group C2(clonidine 1.5mcg/kg) at P20(P<0.01), P30(P<0.05) in group M as compared to group C2, no significant difference was found at any time interval. HR was significantly higher at P30(P<0.05), P40(P<0.05). This results were compared to our study. /the group (N) vs Group(C) at 15 min after PNO(P=0.000) and at 30 min after PNO (P=0.000).

Bernard JM et al(1991) [44] conducted a study and found that rise in average HR was observed in control group compared clonidine group(5 mg/kg iv) , at(15 minutes after PNO; 82bpm vs. 70 bpm) and at (30 minutes; 83 bpm vs. 78 bpm): p<0.001). In our study also mean HR was significantly raised in group II(N) vs. group I(C) that is, at P4 (at 15 minute after PNO; 89.60 ± 13.35 bpm vs. 75.75 ± 1.52 bpm; p=0.000), P5 (at 30 minute after PNO; 90.10 ± 15.64 bpm vs. 73.25 ± 2.38 bpm; p=0.000).

Marashi MS et al (2009) [19] performed a study in which patients were premedicated with 0.2 mg clonidine orally, 900 mg gabapentin orally 120 mm before operation. Patients showed highest rates of ,HR in placebo group and 1 min after intubation. That lowest rate of HR in 10 min after laryngoscopy was in clonidine group. The clonidine group showed significant superiority than placebo in prevention of increase in HR over the intubation. [20] In our study also we found that significant increase in HR (103.70 ± 25.78bpm) in group II(N) vs. (85.35 ±l.9obpm) in group I(C).

Raval DL et al (2002) [21] conducted a study in which patients were premedicated with clonidine 4mcg/kg orally,diazepam 0.2 mg 1kg orally and antacid orally placebo group and concluded that the rise in HR during larygoscopy and intubation from basal value was statistically highly significant in diazepam group and placebo group (p<0.0l) but it was not significant in clonidine group (p>0.05). In our study we found the same result like in group I (C) there is significant decrease in HR as compared to group II(N) p=0.000. Clonidine provided extra advantage over diazepam and placebo by blunting hemodynamic responses during laryngoscopy and endotracheal intubation.

Talebi H et al (2010) [20] conducted a study in which HR, were recorded before, immediately and every 5 min after intubation until 20 min. The clonidine (100 mcg) group showed superiority over placebo group. A

significant difference was observed in HR in control group at three subsequent measurements following intubation. In our study also we found same results, in group I (c) , at laryngoscopy MAP and HR (89.06 ± 1.90 mm Hg and 85.35±1.90 1mm) were significantly high compared to group 11(n) (118.85±19.99 mm Hg and 103.70 ± 25.78 1Mm) p=<0.000. The results clearly showed that Group I patients showed greater hemodynamic stability than Group II patients.

SEDATION SCORE

Singh S et al (2011) [8] conducted a study in which patients were premedicated with clonidine 150 mcg orally and found that there was no statistically signifient difference between clonidine and placebo groups in sedation scores recorded at 30 min intervals till 2 h post operatively. . In our study post operative sedation score in both groups at fist 30 mins (p=0.64.9),60mins (p=0.6l6) These findings suggest that, no statistically significantly differences were observed between both group for sedation so clonidine 2mcg/kg iv premedication did not produced sedation post operatively. Which is comparable to our study.

Raval DL et al (2002) [21] conducted a study in which patients were premedicated with clonidine 4mcg/kg orally,diazepam 0.2 mg /kg orally and antacid orally placebo group produced marked anxiolysis and better sedation compared to placebo but less sedation and same level of anxiolysis compared to diazepam(p=0.05).22 In our study post operative sedation score in both groups at fist 30 mins (p=0.64.9),60 mins (p=0.6l6) These findings suggest that, no statistically significantly differences were observed between both group for sedation so clonidine 2mcg/kg iv premedication did not produced sedation post operatively.

Tameatsu M et al (1995) . [58]performed a study   and found that recovery time in clonidine (5 mcg/kg orally) were a 150 min and in controle group 120 min they suggested that clonidine may be useful in iv sedation with midazolam. In our study post operative sedation score in both groups at fist 30 min (p=0.64.9),60 mins (p=0.6l6) These findings suggest that, no statistically significantly differences were observed between both group for sedation so clonidine 2mcg/kg iv premedication did not produced sedation post operatively.

V Sidda Reddy et al (2013) [59] performed a study to evaluate the effect if iv dexmeditomidine (0.5mcg/kg)premedication   with clonidine (1mcg/kg) and placebo in spinal block patients undergoing surgery under bupivaccaine intra thical block .they concluded that the maximum ramsay sedation score was greater in the dexmeditomidine group than other clonidine and placebo group (P<0.0001). In our study post operative sedation score in both groups at fist 30 mins (p=0.64.9),60mins (p=0.6l6) These findings suggest that, no statistically significantly differences were observed between both group for sedation so clonidine 2mcg/kg iv premedication did not produced sedation post operatively.

J E Hall et al (2001) [60]conducted a study and found that ,all three doses of clonidine produced a significant sedation compared with placebo groups. There was increasing sedation with increasing dose but the bispectral index was unable to differentiate between 1 and 2 mcg/kg/hr. After 60 min infusion bispectral index had decreased by 6,17,21 and 62 %in placebo and clonidine three groups(1,2,4 mcg/kg /hr) respectively. At 90 min recovery from clonidine 1mcg/kg/hr the bispectral index had returned to base line concentration but 90 min after 2 and 4 mcg/kg/hr infusions there were still significant concentration based on bispectral index. Only slight different results from the VAS sedation test were noted; a 23,57,60 and 84% reduction in score recorded at the 6o min infusion time for the four groups respectively, this test did not provide a statistically significant difference between placebo and clonidine 2 and 4 mcg/kg/hr and similar recovery profile to bispectral index. In our study post operative sedation score in both groups at fist 30 mins (p=0.64.9),60 mins (p=0.6l6) These findings suggest that, no statistically significantly differences were observed between both group for sedation so clonidine 2mcg/kg iv premedication did not produced sedation post operatively.

ISOFLURANE

Sung CS et al (2000) .[3]showed that clonidine 150 mcg given 60 -90 min before surgery provided stable hemodynamics reduced isoflurane requirement up to 30 % compared to placebo group and in our study isoflurane requirement statistically significant reduction in isoflurane in group I(C) as compared to group II (N) p<0.00l .

Singh S et al (2011) [8]conducted a study in which patients were premedicated with clonidine 150 mcg orally and found that in perioperative period isoflurane concentration required for maintaining acceptable haemodynamics was reduced in clonidine group and placebo groups than placebo groups. in our study isoflurane requirement statistically s significant reduction in isoflurane in group I(C) as compared to group II (N) p<0.00l .

Ghigone M et al(l987) conducted A study.[24] to assess the effect of clonidine premedication in thirty patients, clonidine 5 mcg/kg po provided stable hemodynamics and reduced isoflurane requirement (0.61 ± 0.20 vs 1.03 ± 0.16% p<0.0l) compared to placebo group who received diazepam 0.15 mg/kg. In our study requirement of isoflurane was reduced to in group I (C) compared to group II (N) (0.82 ± 0.09vs 1.25 ± 0.23; p<0.000).

VAS AND REQUIREMENT OF ANALGESIA

Alpha-2 adrenoceptor agonists have analgesic properties when given parenterally, epidurally or intrathecally. Stimulation of alpha-2 adrenoceptors in the substantia gelatinosa of the dorsal horn of the spinal cord by intrathecal noradrenaline or specific agonists inhibits the firing of nociceptive neurones stimulated by peripheral A delta and C fibres. Antinociception produced by alpha-2 adrenoceptor agonists may be due in part to acetyicholine release in the spinal cord as it has been suggested that the spinal cord is the major site of analgesic action of alpha-.2 adrenoceptor agonists.[40]

In the our study VAS scores were not significant changed in both group in the first 30 min(p=0.887),60 minutes(p=l .000) and 90 minutes (p=l .000) These findings suggest that, no statistically significant differences were observed between both groups(C) and (N) for duration of post operative analgesia so clonidine 2mcg/kg iv premedication require analgesic for first 30 min to 60 min postoperatively.

Sung CS et al (2000) performed a study.[3] in which patients were premedicated with clonidine 150 mcg orally displayed greater hemodynamic stability perioperatively with VAS scores statistically significant and the postoperative analgesic requirement was significantly less (1.5±1.3 vs. 2.2±1.3) dose and the time for the first dose of analgesic was prolonged (411±565 vs. 264±441 mm) in clonidine group p<0.005 where as in our study statistically there is no significant changes in requirement of analgesia in group I (C) vs group II (N) at 30 min (0.85±0.36 vs. 0.85 ± 036) p=1.000 and at 60 min 0.15±0.36 vs. 0.15 ± 0.36) p=l.00 . In our study, in VAS scores there were no significant changes in group I (C) vs. group II(N) at 30 min (8.45±0.78 vs. 8.42± 0.78) p=0.887 and 60 min1.57±3.46 vs. 1.57± 3.46)(p=1.000). Which is not comparable to our study.

Singh S et al (2011) [8]conducted a study in which patients were premedicated with clonidine 150 mcg orally and found that there was no statistically significant difference between clonidine and placebo groups in VAS scores recorded at 3o min interval till 2 h postoperatively. In our study in VAS scores there were no significant changes in group I (C) vs. group II(N) at 30 min (8.45±0.78 vs. 8.42± 0.78) p=0.887 and 60 min1.57±3.46 vs. 1.57± 3.46)(p=1.000). Which is comparable to our study.

Das M et al (2007) [10] found that intensity of pain was less in clonidine group (150mcg orally) compared to placebo group (VAS 1.9 ±1.688 vs 5.214±2.114) .In our study in VAS scores there were no significant changes in group I (C) vs. group II(N) at 30 min (8.45±0.78 vs. 8.42± 0.78) p=o.887 and 60 min1.57±3.46 vs. 1.57± 3.46)(p=1.000). Which is comparable to our study.

Bernard and co-workers. [44]reported the analgesic effects of an intravenous infusion of clonidine after major spinal surgery. They administered either clonidine 5 mg/kg during the first hour followed by 0.3 mg/kg/hr for 11 h or placebo. A visualanalogue scale assessed pain. Intramuscular morphine was used to supplement analgesia if the pain scores were above 50%. In the clonidine group, pain onset was delayed, total morphine requirements were decreased significantly and pain scores reduced compared with placebo. .In our study there were no significant changes in VAS score in group I (C) vs. group II(N) at 30 min (8.45±0.78 vs. 8.42± 0.78) p=0.887 and 60 min1.57±3.46 vs. 1.57± 3.46)(p=1.000). which is not comparable to our study.

Bonnet F et al (1989) A study .[29]to assess the effects of oral clonidine l00mcg 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) .In our study In VAS scores there were no significant changes in group I (C) vs. group II(N) at 30 min (8.45±0.78 vs. 8.42± 0.78) p=0.887 and 60 min 1.57±3.46 vs. 1.57 ±3.46) p=l.000 which is not comparable to our study.

Overall the present study showed that, the administration of IV clonidine 2 mcg/Kg given as a premedication in patients undergoing LC resulted in improved perioperative haemodynamic stability, reduction in intraoperative anaesthetic requirement.Increase in sedation not found. Reduction in post operative pain and requirement of analgesic not found. Further studies on large sample would confirm these results.

CONCLUSION

From the results of present study following conclusions may be drawn with use of clonidine given as 2 mcg/kg IV premedication in laparoscopic cholecystectomy surgery .

1. Mean arterial blood pressure is maintained with clonidine as it gives more hemodamic stability .
2. Maintains heart rate during PNO .
3. Not produces sedation.
4. Reduces intraoperative anesthetic requirement
5. Not reduces VAS scores and not prolongs the requirement of first postoperative analgesic

SUMMARY

Hemodynamic instability has been reported in association with laparoscopic surgery in humans. Pneumoperitoneum and Laryngoscopy causes stress response with wide variations in hemodynamic. Alpha- receptor agonists are reported to have suppressed these changes in various studies. Systemic alpha2 adrenergic agonist (clonidine) administration alters the hemodynamic changes associated with pneumoperitoneum and suppresses plasma catecholamine responses. Stimulation of alpha 2 receptors in substantia gelatinosa of spinal cord by alpha 2 adrenergic agonists inhibits firing of nociceptive neurons. Use of analgesics before pain stimulus obstructs development of neuroplastic changes in central nervous system and reduces pain. Patients were divided into two groups of 40 each that is group I (C)-iv clonidine 2 mcg/kg in 100 ml NS 20 min before induction and group II (N) 100ml ,20 mins before induction All the patients were given tablet Alprazolam 0.5 mg previous night of surgery. Intravenous line was secured with appropriate IV cannula and 500 ml crystalloids was started. Heart rate, non invasive blood pressure and oxygen saturation were monitored before and throughout the procedure The study drugs were prepared by anesthesiologist not involved in the study. They were induced and intubated with appropriate endotracheal tube and maintained on oxygen, nitrous oxide and isoflurane. After creation of pneumoperitoneum if there was increase in blood pressure more than 20% of basal BP, isoflurane concentration will be increased accordingly as a rescue agent. MAP, HR were recorded Study results

clearly showed intraoperative MAP and HR changes were significantly at the lower level in clonidine groupI (c) p<0.000 at all intervals of procedure with consumption of isoflurane 0.6 -0.9 % compared to control group II(n)at all intervals with consumption of isoflurane [1 -1.6%]. VAS scores were not significant lower in both group postoperatively and requirement of first postoperative analgesic was not significant changed in both groups Hence clonidine given as 2 mcg/kg IV premedication 20 min bfore inductionmaintains HR . The mean arterial blood pressure was maintained with clonidine as it gives more hemodynamic stability, reduces intraoperative anesthetic requirement. No significant changes in VAS scores,sedstion score and the requirement of first postoperative analgesia.

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ANNEXURE I CONSENT

<div align="center">

संमति पत्र   दिनांक

</div>

मी -- वय -----------वर्षे

राहणार --- माझ्या

स्वेच्छेने प्रकल्पामध्ये सहभागी होण्यास संमती देत आहे. INTRAVENOUS CLONIDINE PRE MEDICATION

FOR LAPAROSCOPICSURGERY------------------------

माझ्यावर प्रस्तुतच्या प्रकल्पामध्ये सहभागी होण्यासाठी कोणाचाही दबाव नाही.

१. प्रस्तुतच्या प्रकल्पात येणा-या तपासण्या व औषधोपचार घेण्यास मी तयार आहे.

२. प्रस्तुतच्या प्रकल्पाची सर्वसाधरण माहिती मला समजेल अशा भाषेत मी वाचली आहे. व मला समजावुन सागंण्यात आले

   आहे. मला प्रस्तुतच्या प्रकल्पाच्या होण्या-या संभाव्य धोक्याची माहिती सांगण्यात आलेली आहे. व मी वाचलेली आहे.

३. मी या प्रकल्पामधुन कधिही बाहेर पडु शकते/शकतो यांची मला माहिती आहे.

४. या प्रकल्पात निघणारे निष्कर्श केवल शासकीय कारणांसाठी वापरली जाते. व प्रकाशित केले जाते याची मला कल्पना

   आहे. तसेच माझी ओळख कायदेशी बाबींव्यतीरिक्त इतर वेळेस गुप ठेवली जाईल.

५. मला मराठी वाचता येते व मराठी वाचुन दाखविलेले समजते.

दिनांक   सहभागी व्यक्तिची सही

साक्षीदार

१.

२.   प्रमुख संशोधकांची सही

ANNEXURE II - PROFOMA

STUDY: "INTRAVENOUS CLONIDINE PREMEDICATION FOR LAPAROSCOPIC SURGERY"

Patient Name : I.P. No :

Age : Weight :

Date of Operation : Gender:

Address : Anaesthesiologist :

Diagnosis: Proposed Surgery :

Preoperative physical status: ASA Grade I II

Observations

ECG	EtCo2

Time P1   P2   P3   P4   P5   P6   P7   P8

MABP (mm Hg)

HR (bpm)

                                            Group I   Group II

 Intraoperative requirement of isoflurane (in %)

  vas

30 min

60 min

9o min

Analgesia required at

Sedation scale

30 min

60 min

90 min

ANNEXURE III- PHOTOGRAPH

Photograph 1. Clonidine hydrochloride

ANNEXURE IV-LIST OF ABBREVIATIONS USED

BP   -   Blood pressure

CI   -   Cardiac index
CO   -   Cardiac output
CO_2 -   Carbon dioxide
DBP   -   Diastolic blood pressure
$EtCO_2$ - End tidal carbon dioxide

FRC   -   Functional residual capacity
HR   -   Heart rate
IAP   -   Intra abdominal pressure
IV   -   Intravenous
LC   -   Laparoscopic cholecystectomy
LVEDV   -   Left ventricular end diastolic volume

MAP   -   Mean arterial pressure
mcg   -   Microgram
mg   -   Milligram
ml   -   Millilitre
N_2O -   Nitrous oxide

NS   -   Normal saline
O_2 -   Oxygen
PAOP -   Pulmonary artery occlusion pressure

PCWP -   Pulmonary capillary wedge pressure
PNO   -   Pneumoperitoneum
PONV   -   Post operative nausea and vomiting
PV   -   Pulmonary vascular resistance

RAP   -   Right atrial pressure
SBP   -   Systolic blood pressure

SD   -   Standard deviation
SVR   -   Systemic vascular resistance
TLV   -   Total lung volume
                    VAS   -   Visual analogue scale