"INTRAVENOUS CLONIDINE FOR PERIOPERATIVE HAEMODYNAMIC STABILITY DURING LAPARO-SCOPIC CHOLECYSTECTOMY – A ONE YEAR RANDOMISED CONTROLLED STUDY"

By

Dr. RASHMI PATIL
(REG.NO. BA0109004)

Dissertation

Submitted to the
KLE University, Belgaum, Karnataka

In Partial Fulfillment
of the requirements for the degree of

M. D.
in
ANAESTHESIOLOGY

Under the Guidance of

Dr. LATA KULKARNI MD, DA
Professor

DEPARTMENT OF ANAESTHESIOLOGY,
JAWAHARLAL NEHRU MEDICAL COLLEGE,
BELGAUM, KARNATAKA

MAY - 2012

KLE UNIVERSITY, BELGAUM, KARNATAKA

DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation entitled **"INTRAVENOUS CLONIDINE FOR PERIOPERATIVE HAEMODYNAMIC STABILITY DURING LAPARO-SCOPIC CHOLECYSTECTOMY – A ONE YEAR RANDOMISED CONTROLLED STUDY"** is a bonafide and genuine research work carried out by me under the guidance of **Dr. LATA KULKARNI** $_{MD, DA}$ Professor, Department of Anaesthesiology, Jawaharlal Nehru Medical College, Nehru Nagar, Belgaum-590010.

Date:

Place: **(Dr. RASHMI PATIL)**
REG. NO. BA0109004

KLE UNIVERSITY, BELGAUM, KARNATAKA

CERTIFICATE BY THE GUIDE

This is to certify that the dissertation entitled **"INTRAVENOUS CLONIDINE FOR PERIOPERATIVE HAEMODYNAMIC STABILITY DURING LAPARO-SCOPIC CHOLECYSTECTOMY – A ONE YEAR RANDOMISED CONTROLLED STUDY"** is a bonafide research work done by **Dr. RASHMI PATIL (REG. NO. BA0109004)** in partial fulfillment of the requirement for the degree of **M. D.** in **ANAESTHESIOLOGY.**

Date:

Place:

Dr. LATA KULKARNI **MD, DA**
Professor,
Department of Anaesthesiology,
J. N. Medical College,
Nehru Nagar, Belgaum – 10

KLE UNIVERSITY, BELGAUM, KARNATAKA

ENDORSEMENT BY THE HOD/PRINCIPAL/ HEAD OF THE INSTITUTION

This is to certify that the dissertation entitled **"INTRAVENOUS CLONIDINE FOR PERIOPERATIVE HAEMODYNAMIC STABILITY DURING LAPARO-SCOPIC CHOLECYSTECTOMY – A ONE YEAR RANDOMISED CONTROLLED STUDY"** is a bonafide research work done by **Dr. RASHMI PATIL (REG. NO. BA0109004)** under the guidance of **Dr. LATA KULKARNI** **MD, DA** Professor, Department of Anaesthesiology, Jawaharlal Nehru Medical College, Nehru Nagar, Belgaum-590010.

Dr. C. S. SANIKOP **MD,DA**
Professor and Head,
Department of Anaesthesiology,
J. N. Medical College,
Nehru Nagar, Belgaum – 10

Date:
Place: Belgaum

Dr. V. D. PATIL **MD,DCH**
Principal,
J. N. Medical College,
Nehru Nagar, Belgaum – 10

Date:
Place: Belgaum

KLE UNIVERSITY, BELGAUM, KARNATAKA

COPYRIGHT

DECLARATION BY THE CANDIDATE

I hereby declare that the KLE University, Belgaum, Karnataka shall have the rights to preserve, use and disseminate this dissertation in print or electronic format for academic / research purpose.

Date :

Place :

Dr. RASHMI PATIL
(REG. NO. BA0109004)

ACKNOWLEDGEMENT

First and foremost I would like to thank my guide **Dr. Lata Kulkarni** $_{MD,DA}$ Professor, Department of Anaesthesiology, for her constant guidance, valuable suggestions, unparalleled encouragement and co-operation provided to me throughout the course of study. It has been a great pleasure and privilege to work under her. Without her immense professional insight and guidance I could have not completed this study.

I avail this opportunity to thank **Dr. C. S. Sanikop** $_{MD,DA}$ Professor and Head, Department of Anaesthesiology, for his keen interest, unparalleled encouragement and co-operation during this study.

I am deeply indebted to **Dr. P. F. Kotur** $_{MD}$, Professor, Department of Anaesthesiology. His stature and knowledge has been highly inspirational all through my career as a post graduate.

I express my sincere gratitude to **Dr. V. D. Patil** $_{MD,DCH}$ Principal, J. N. Medical College, Belgaum, **Dr. M. V. Jali** $_{MD}$, Director and Chief Executive, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum for allowing me to utilize the facilities in above institution for the dissertation.

I express my deep sense of gratitude to, **Dr. S. N. Suresh** $_{MD, DA}$ Professor, **Dr. Basavaraja Modi** $_{M.D}$**,** Professor, **Dr. V. K. Dhulkhed** $_{MD}$ Professor, **Dr. M. G. Dhorigol** $_{MD}$ Professor, **Dr. Vandana Gogate**

MD, Associate Professor, **Dr. Rajesh Mane** MD., DNB, Associate Professor, **Dr. Vijay Umarani** MD, Associate Professor and, **Dr. Manjunath Patil** MD, **Dr. Kedareshvara K. S.** MD., **Dr. Ravi Bhatt** MD, **Dr. Pushpa J** MD, **Dr. Deepak C. J.** MD Assistant Professors and **Dr. Geetha A.** DA Tutor for their valuable suggestions during my study.

I also express my sincere gratitude to **Dr. G. C. Mirji** MD. Senior Consultant, **Dr. Anand Vagrali** MD Associate Professor, **Dr. Sharan Patil** MD Associate Professor, **Dr. Sriram Sabade,** DA,DNB Associate Professor, **Dr. Praveen B. K.** MD,PDCC Assistant Professor, for their co-operation during the study and preparation of this dissertation.

I am thankful to **Mr. M. D. Mallapur** M.Sc., statistician for his help in statistical analysis.

I sincerely thank all my **Post Graduate Colleagues** for their help in the study.

I convey my heart felt gratitude to my Husband **Dr. Chetan Hoskatti** and Parents **Dr. Indira Patil** and **Dr. Suresh Patil** without whose support and cooperation this study would not have been complete.

Finally, I thank **Almighty** for all the blessings.

Date:

Place: **Dr. RASHMI PATIL**
(BA0109004)

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
PVR	-	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

ABSTRACT

Background and Objectives

Haemodynamic instability has been reported in association with laparoscopic surgery in humans. Pneumoperitoneum and Laryngoscopy causes stress response with wide variations in haemodynamics. The present study was conducted to evaluate the effects of IV clonidine on reduction of perioperative stress response, maintaining hemodynamic stability, reduction of intraoperative anaesthetic requirement and on modulation of postoperative pain.

Methods

In the present prospective randomised controlled trial of forty patients aged between 18 to 60 years of ASA I and II undergoing laparoscopic cholesystectomy at KLES Dr. Prabhakar Kore Hospitals and Medical Research Centre, Belgaum were studied. Patients were divided into two groups of twenty each that is, Group I (Normal saline) and Group II (Clonidine 6 mcg/kg in normal saline). The study drugs were prepared by anaesthesiologist not involved in the study.

Results

Sex, age and weight and were comparable in both the groups. Study results clearly showed intraoperative MAP and HR changes were significantly at the lower level in clonidine group ($p<0.05$) at all intervals of procedure and also at laryngoscopy with consumption of isoflurane 0.2 -0.4% compared to control group at all intervals with consumption of isoflurane [1 - 1.5%]. VAS scores were

significantly lower in clonidine group 24 hour postoperatively and requirement of first postoperative analgesic was prolonged up to 8 hour postoperatively.

Conclusion and interpretation

Clonidine given as 6 mcg/kg IV in two stages that is, at pre-induction and just before PNO maintains HR during PNO but one should be watch full for bradycardia. The mean arterial blood pressure was maintained with clonidine as it gives more haemodynamic stability, reduces intraoperative anaesthetic requirement and VAS scores and prolongs the requirement of first postoperative analgesic.

Keywords: Clonidine; Hemodynamic stability; Laparoscopic surgeries; Perioperative stress response;

CONTENTS

LIST OF TABLES

LIST OF GRAPHS

LIST OF FIGURES

LIST OF PHOTOGRAPHS

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 tredelenburg 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 (IAP) 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 normocapnia.[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). Catecholamines mediate increase in systemic vascular resistance (SVR) during PNO. It stimulates a series of hormonal and metabolic changes that constitute stress response.[2]

In response to trauma, massive catecholamines, cortisol and glucagons are released while serum insulin can decrease relatively and decrease of insulin levels in correlation with severity of sepsis and trauma.[2]

Clonidine is centrally acting selective partial α2 adrenergic agonist (α2: α1-220:1). Clonidine acts acutely by stimulating α2 adrenoceptors thereby decreasing non adrenergic release from sympathetic nerve terminals and consequently decreasing sympathetic rate. The drug acts by reducing responsiveness of peripheral vessels to vasoactive substances and to sympathetic stimulation. The analgesic effects are mediated by activation of α2

adrenoreceptors in dorsal horn of spinal cord. The IV dose is 0.15 to 0.3 mg. The drug acts in 10 minutes and lasts for three to seven hours.[3]

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

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]

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

OBJECTIVES

The objectives of the present study were;

1. To study the efficacy of IV clonidine six µg/kg in normal saline (NS) in comparison with 10 ml normal saline in patients undergoing laparoscopic cholecystectomy in maintaining perioperative BP and HR.

2. To determine usefulness of six µg/kg of IV clonidine during perioperative period as regards laryngoscopy and decrease in intra-operative anaesthetic requirement and post operative analgesic requirement.

REVIEW OF LITERATURE

Historical perspective of laparoscopy[4]

In 1988 Dr. Dubois performed first laparoscopic Cholecystectomy. 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 by gynaecologists, 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 [0.0008] and there fore 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]

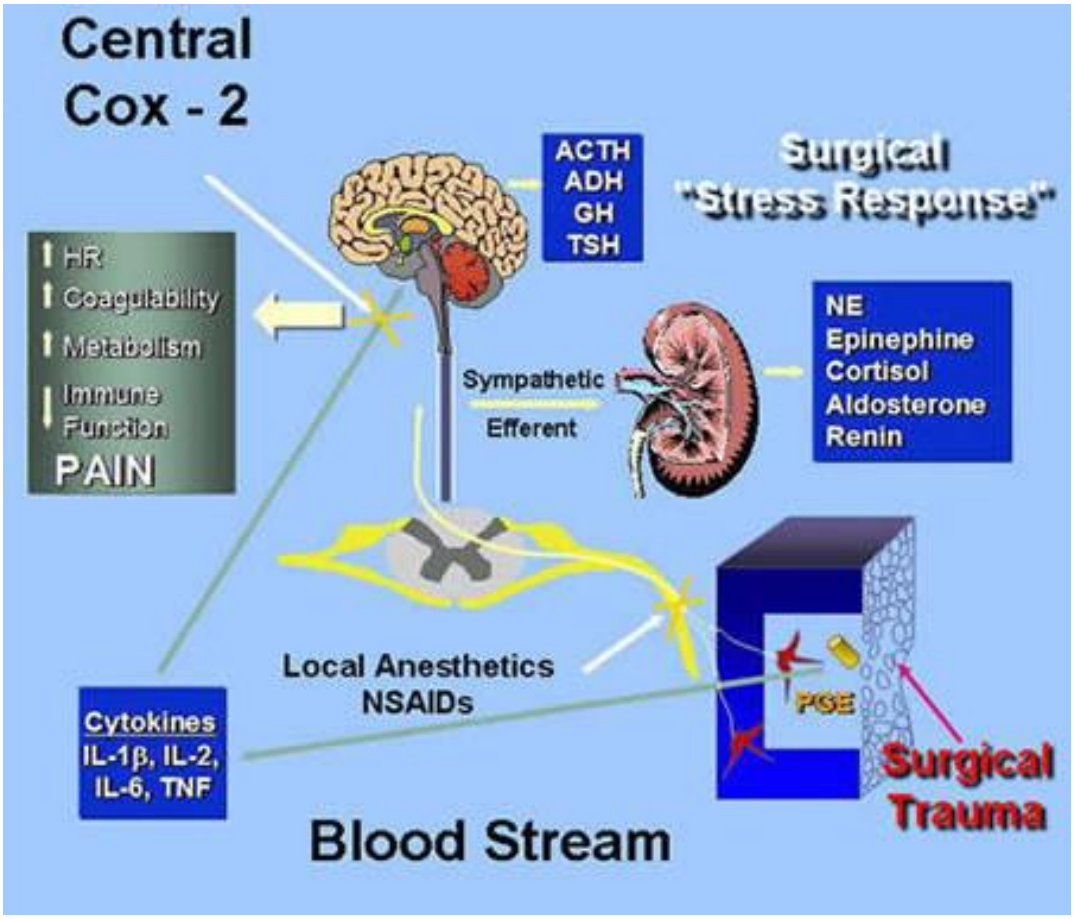


Figure 1. Effects of surgical stress response and pneumoperitoneum

In a study authors assessed the haemodynamic effects of intra-abdominal insufflation with either CO_2 or N_2O in undergoing laparoscopic surgery. The cardiac index (CI) decreased more in the N_2O group than CO_2 group. In the CO_2 group; MAP, systemic vascular resistance index and CVP increased without change in heart rate. During N_2O insufflations MAP decreased without change in vascular resistance. After desufflation MAP increased in the N_2O group to pre-insufflation levels and CI increased in both groups ($p<0.001$), but reached pre-insufflation levels only in the CO_2 group. They concluded that laparoscopic insufflation with either CO_2 or N_2O results in cardiovascular depression.

Insufflation with N_2O may decrease BP, whereas MAP is better preserved with CO_2 insufflation.[6]

Therapeutic Role of Clonidine in Anaesthesia during Laparoscopic Surgeries

Haemodynamic Stability

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 anaesthesia 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]

In another study, authors assessed the effects of clonidine on twenty patients without cardiac pathology or medications scheduled to for elective LC on hemodynamic changes. Clonidine group received clonidine 4 mcg/kg IV over 10 minutes and same dose infused one hour before PNO and placebo group received same volume of saline. MAP, HR were recorded before PNO (T1), 5 min (T2), 15 min (T3), 30 min (T4) after PNO and 5 min (T5), 30 min (T6) after exsufflation. Clonidine blunts hemodynamic changes induced by PNO.[8]

Another study showed clonidine has antihypertensive properties. Fifty patients were divided to receive oral clonidine 150 mcg (n=25) and placebo (n=25) in patients under going LC and compared the haemodynamic parameters, isoflurane use, pain, sedation postoperative request of analgesia. Clonidine group of patient showed improved hemodynamic stability, reduced intraoperative anaesthetic requirement and post operative analgesia.[9]

A study of 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.[10]

In a prospective, randomized, single-blind, comparative study to investigate the clinical efficacy of oral clonidine premedication in anesthesia and

analgesia among 110 patients undergoing LC were randomly allotted to the clonidine group (n=45) and premedicated with oral clonidine 150 μg prior to anesthesia. Oral clonidine premedication helped to provide perioperative hemodynamic stability, spared the use of isoflurane and reduced the requirement of postoperative analgesia so as to smoothen recovery.[11]

In a study authors assessed the potential for myocardial ischaemia 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.[12]

Another study reported 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.[13]

In 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 ($p<0.001$) after both ways of administration, as well as of diastolic pressure ($p<0.01$ for IV and $p<0.05$ for IM premedication). They recommended premedication with IV clonidine as a routine procedure before laparoscopic cholecystectomies.[14]

Another study 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 ($p<0.01$). However, the plasma concentrations of the other hormones did not differ between groups.[15]

A study was conducted to assess the efficacy of clonidine in achieving perioperative hemodynamic stability in 24 patients undergoing 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.[16]

In another study, authors 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. They concluded that both clonidine 4 mcg/kg and dexmedetomidine 2.5 mcg/kg decreased perioperative oxygen consumption effectively with a similar haemodynamic profile. The reduction in heart rate, systolic and diastolic arterial pressures were similar in the clonidine and dexmedetomidine groups compared with placebo.[17]

In a study to compare the effect of oral clonidine 3mcg /kg versus hydroxyzine 1 mg /kg on the haemodynamic 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.[18]

In a study of 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. MAP 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

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.[19]

Clonidine during layngoscopy

In a study to assess 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 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 (101.6±10.4) in placebo group and lowest HR was noted in clonidine group (69.12±9.89) in 10 min 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.[20]

In another study, authors assessed efficacy of 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 90-120 min before surgery. HR, SBP were recorded before, immediately and after every 5 min after intubation until 20 minutes. The clonidine group showed superiority over placebo group. A significant difference was observed in both heart rate and SBP were significantly observed in control group at three subsequent measurements following intubation.[21]

In another study authors assessed the effects of oral clonidine premedication on laryngoscopy and endotracheal intubation in 100 ASA grade I and II patients of 18 to 45 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 anaesthesia). Clonidine produced marked anxiolysis and better sedation compared to placebo but less sedation and same level of anxiolysis compared to diazepam. Clonidine provided extra advantage over diazepam and placebo by blunting haemodynamic responses during laryngoscopy and endotracheal intubation and also by its antisialoggogue effect.[22]

Influence of Clonidine on Anaesthetic Requirements

In a study, authors assessed the effect of clonidine premedication in thirty patients. Clonidine 5 mcg/kg PO provided stable hemodynamics and reduced isoflurane requirement up to 40% less compared to placebo group who received diazepam 0.15 mg/kg.[23]

In another study of 41 patients, randomly assigned to atropine + hydroxyzine group (AH group) and clonidine group (C group) the total amount of propofol in C group was significantly less than AH group. There were no significant differences in the mean pressure between two groups. The heart rate of AH group was significantly higher than C group. Within AH group, the MAP and heart rate changed significantly at several points compared with before admission. Study concluded that, oral clonidine premedication has anesthetic sparing activity with hemodynamic-stabilizing effects during LC.[24]

A study of 41 patients who had received clonidine 3 mcg/kg IV or placebo at induction of isoflurane and nitrous oxide in oxygen anaesthesia 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 anaesthetist, able to respond to any adverse effects.[25]

A study was conducted 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 mg/kg); or clonidine (5 mg/kg). 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 mg/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

In 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]

Another study was conducted to assess the effects of small doses of oral clonidine in perioperative out comes among 61 patients under going 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 through out 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]

Another study pain was assessed postoperatively by VAS score in 40 ASA I, II patients. 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%) 0f initial VAS score and 14.7 (25.2%) in ES group. The post operative analgesic effect was prolonged in EC group for 210 ± 87 min and 47 ± 27 min in ES group.[29]

A study reported that 75 mcg of epidural clonidine increased the duration of epidural bupivacaine analgesia in labour with no adverse effects to mother or neonate.[30]

Another study on effects of the addition of epidural clonidine 150 mcg to epidural fentanyl 100 mcg analgesia reported that, the onset of action remained the same, but the duration of analgesia was doubled, without any effect on fentanyl pharmacokinetics.[31]

In a study sixty ASA grade I/II patients scheduled for elective short laparoscopic procedures under spinal anaesthesia 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 post-operative period and at the same time abolishes shoulder tip pain during laparoscopic procedures. In addition, no significant changes in haemodynamics occur with the low dose of clonidine used.[32]

In another study authors reported that, epidural clonidine was effective in treating cancer pain in patients tolerant to opioids. Topical clonidine has been used to control sympathetically maintained pain.[33]

BASIC SCIENCES

Minimally 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 insufflation combined with variations in patient positioning can have a major impact on cardiorespiratory function, particularly in elderly patients with co-morbidities.[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 anaesthetic technique used (ventilatory technique and anaesthetic 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. Insufflation of CO_2 increasing IAP higher than 10 mm hg induces significant alterations of hemodynamics which are characterized by

decrease in cardiac out put, 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.[35]

Caval compression, pooling of blood, and increase in venous resistance is observed by increased IAP. Decline in venous return parallels decrease in cardiac out put 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.[35]

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%. Reduction in FRC and development of atelectasis due to elevation of diaphragm and changes in ventilation and perfusion results from increased airway pressure.[35]

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 renin-angiotensin-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.[36]

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.[37]

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 laproscopic 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.[37]

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.[38]

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 20^0) and must be slow and progressive to avoid sudden haemodynamic 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.[39]

Venous congestion of head and neck may compromise cerebral perfusion and produce intracerebral and intraocular hypertension. Anaesthetic 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.[39]

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.[39]

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 anaesthesia, 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;[39]

- Decreased risk of regurgitation from increased intraabdominal 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 haemodynamic 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.[39]

Isoflurane is the volatile anaesthetic agent of choice because it is less arrhythmogenic and causes less myocardial depression.Nitrous oxide (N_2O) is widely used in anaesthesia 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.[39]

MONITORING DURING LAPAROSCOPY

Routine intraoperative monitors include ECG, pulse oximetry, blood pressure, pulse rate, and EtCO2 (End Tidal carbon di oxide) are essential. Anaesthetic 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 haemodynamically 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.[39]

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[39]

Complications from surgical instrumentation

- Misplacement of veress needle
- Uncontrolled haemmorrhage

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 anaesthetics 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.[39]

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 anaesthetic) 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.[39]

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 sub-diaphragmatic 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.[39]

Organization of pain pathways[40]

The cell bodies of the primary pain afferents (that is, the first order neurons) are located in the dorsal root ganglia. Central extensions of the primary neurons project, via the dorsal root, to the dorsal horn of the spinal cord and in the case of cranial pain afferents, to the nucleus of the trigeminal nerve. These A-delta and C fibers occupy the lateral part of the root entry zone and within the spinal cord form a discrete bundle, the 'tract of lissauer' (Neospinothalamic tract). After traversing the lissauer's tract, they terminate in the dorsal horn of the spinal cord. In the dorsal horn, cell bodies are arranged in series of laminae some of which have classical names, but which are most simply given roman numerical by Rexed i.e. laminae I-IX.

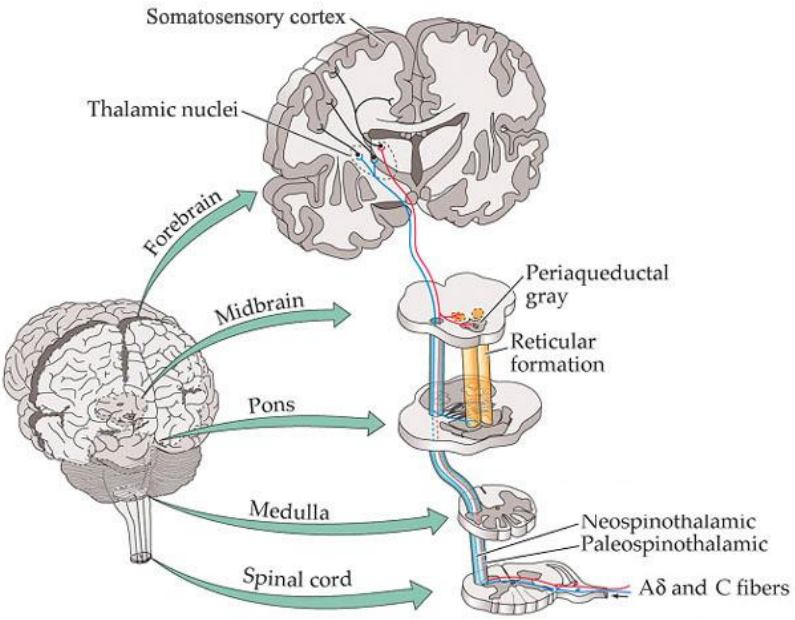


Figure 2. Pain Pathway

The A-delta fibers terminate in lamina I, also known as the marginal cell layer of Waldeyer, whereas "C" fibers terminate in the lamina II also known as 'substantia gelationosa'. Many of the afferents ending in these marginal layers contain neuropeptides, including substance – p, cholecystokinin and somatostatin. There is increasing evidence that these peptides play an important role in the normal transmission of pain. Chemical destruction of fibers containing substance – P in animals produces analgesia. Most of the fibers terminate in the segment of their entry into the cord, but some extend rostrally and caudal tone or two adjacent segments ipsilaterally and some via the anterior commissure to the contralateral dorsal horn. Some pain fibers penetrate the dorsal gray matter and terminate in lamina V.

The secondary neurons connect with ventral and lateral horn cells in the same and adjacent spinal segments and subserve somatic and autonomic reflexes. In addition to this the secondary neurons decussate in the anterior spinal commissure to the opposite side and ascend in the anterolateral fasciculus (of which the lateral spinothalamic tract forms a major part) to the brain stem and thalamic structure.

The axon form each dermatome enters the spinal cord one to the three segments higher than the level of root entry. Crossing fibers are added to the inner side of the spinothalamic tract, so that the longest fibers from successively rostral segments occupy a progressively deeper position. Thus at the cervical level the fibers in the spinothalamic tract form without inwards are sacral lumbar, thoracic and cervical.

In addition to the lateral spinothalamic tract which is a fast conduction pathway that projects directly to the thalamus, the anterolateral fasiculus of the spinal cord contains a slowly conducting, medially placed system of fibers, which reaches the thalamus via one or more relays in the reticular core of the brain stem. This latter group of fibers if referred to as spinoreticulothalamic tract or paleospinothalamic tract. The conduction of diffuse, poorly localized pain arising from the deep structures (gut/periosteum) has been ascribed to this tract.

Visual Analog Scale (VAS) is currently, the most commonly used method; first described by AITKEN is 1966. The subject makes a mark on a 10cms 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 Aδ and C fibres.[41]

Use of analgesics before pain stimulus (preventive analgesia) obstructs development of neuroplastic changes in central nervous system and reduces pain.[42]

CLONIDINE

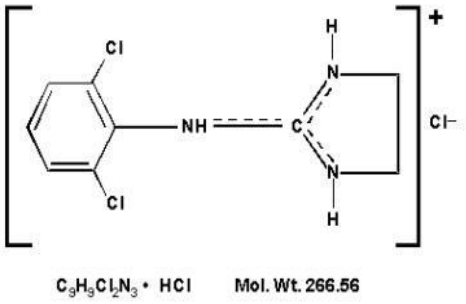


Figure 3. Chemical structure of clonidine

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.[43] 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.[44]Clonidine is an imidazoline and is the alpha-2 adrenoceptor agonist currently available for use in anaesthetic practice.

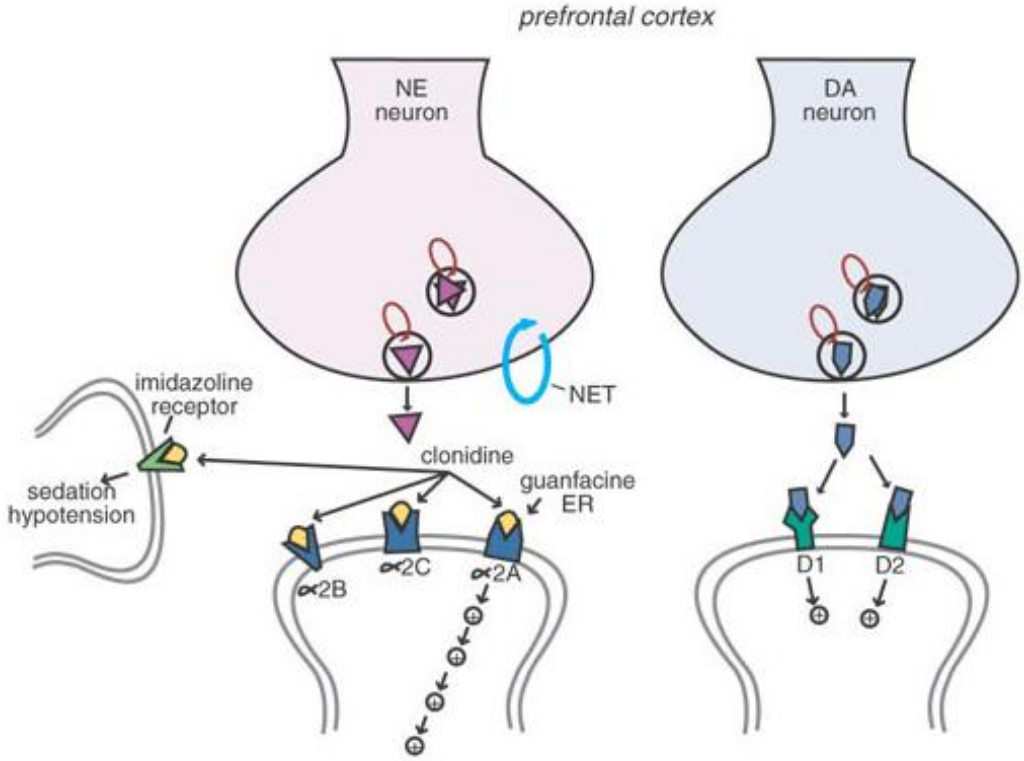


Figure 4. Clonidine - Mechanism of action

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 5 mcg/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.[45]

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 mg/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.[46]

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 faeces. 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.[47]

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.[47]

Central alpha-2 adrenoceptor agonists attenuate sympathoadrenal 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	Dexmedetomidine
Adrenaline	Mivazerol
	Clonidine
	A-Methyl dopa

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 anaesthesia has been described. The use of clonidine as an antihypertensive has been limited by its sedative effects, but offers advantages in anaesthetic 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.[47]

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.[47]

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 β cells of the islets of Langerhans can temporarily

cause direct inhibition of insulin release; clinical hyperglycaemia 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.[47]

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.[47]

In a study authors compared the effects of clonidine 4.5 mg/kg or saline on hemodynamics, neuroendocrine response, and renal parameters in 30 healthy patients undergoing laparoscopic cholecystectomy. 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.[48]

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.[49]

Cardiovascular System Effects

There are both alpha-1 and alpha-2 postjunctional receptors in the arterial and venous vasculature where they both mediate vasoconstriction.[50] The alpha-1 and alpha-2 adrenoceptors differ in their location and their utilisation 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.[51] 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.[52]

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.[53]

A study evaluated the dose-response effects of different doses of clonidine (0, 2, 4, or 6 mcg/kg as an intravenous (IV) infusion) on the stress response to laryngoscopy and endotracheal intubation in 48 coronary artery

bypass grafting (CABG) patients. Clonidine four and six mcg/kg significantly attenuated hemodynamic and adrenergic reactions to stress, reduced pharmacologic interventions, and increased sedation. However, clonidine 6 mcg/kg was not more effective than 4 mcg/kg, and clonidine 2 mcg/kg was equally effective as placebo. The study concluded that, a minimum dose of 4 mcg/kg intravenous clonidine is the appropriate dose to significantly attenuate the stress response to laryngoscopy.[54]

Another study detected a significant reduction in peri-operative ischaemia was by monitoring critical ST depression in cardiac revascularisation patients who received clonidine 5 mcg/kg.[55]

In a study authors assessed the effect of clonidine on the pressor and heart rate response to tracheal intubation in 30 patients who were pretreated with either intravenous clonidine 1.25 mcg/kg, or clonidine 0.625 mcg/kg or an equivalent volume of normal saline. The attenuation of the pressor response to intubation of both clonidine groups was statistically significant compared to the saline group. Neither dose of clonidine completely abolished the increase in either heart rate or blood pressure. There was no difference in attenuation between the clonidine treatments; this indicated that the lower dose may be the more appropriate.[56]

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 21. 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.[57]

A study evaluated the haemodynamic and respiratory changes during laparoscopic cholecystectomy in elderly ASA III patients. This clinical descriptive study included 16 patients aged more than 75 years. Anaesthesia was induced with fentanyl and etomidate and maintained with N_2O in O_2 (50%), fentanyl and isoflurane as needed. Inspired minute volume was kept constant during anaesthesia. Cardiovascular monitoring included a radial artery catheter and a pulmonary artery catheter for measurement of CO, RVEF and SvO_2, and calculation of right ventricular end diastolic volume indexed (RVEDVI). Peritoneal insufflation resulted in improvement of cardiovascular function with increases in cardiac index (+19%), heart rate (+21%), MAP (+19%) and SvO_2 (+8%), ($p<0.05$) which may be the result of a sympathetic stimulation. No change in preload (RVEDVI) and SVR was recorded. Cardiac index was unchanged during pneumoperitoneum. Laparoscopy was associated with an increase in $PaCO_2$ 15 min after CO_2 insufflation (from 33.9 to 38.3 mm Hg, $p<0.05$) and a further elevation after 60 min (44.4 mm Hg) without any sign of extra peritoneal diffusion. There was no change in the intra-pulmonary shunt and the Pa-$ETCO_2$ gradient remained stable (mean 7.2 mm Hg).[58]

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.[59]

METHODOLOGY

The present study was conducted in the Department of Anaesthesiology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of January 2010 to December 2010.

Study design

One year randomized controlled trial.

Source of Data

Patients undergoing laparoscopic cholesystectomy at KLES Dr. Prabhakar Kore Hospitals and Medical Research Centre, Belgaum attached to Jawaharlal Nehru Medical College, Belgaum.

Study Period

One year from January 2010 to December 2010.

Sample Size

A total of 40 patients divided into two groups using computer randomization.

Sampling procedure

Using results of previous studies[3,8,] and pilot study and using the formula 20 patients are selected in each group based on the following calculation.

$$\text{Sample Size (n)} = \frac{2 \times (Z\alpha + Z\beta)^2 (S1^2 + S2^2)}{(X_1 - X_2)^2}$$

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

$$\text{Sample Size (n)} = \frac{2 \times (1.96+1.282)^2 \ (7^2 + 5^2)}{(14)^2}$$

$= 1555.48/196$

$= 8$

However it was decided that to do 20 cases in each group.

= 20 patients were selected in each group.

Selection criteria

Inclusion

- Patients undergoing laparoscopic cholecystectomy.
- Age 15 to 60 years
- Weight between 40 to 60 Kg
- ASA grade I and II

Exclusion

- Patient refusal
- Patients with cardiovascular pathology

  - Diabetes
  - Hypertension
  - Ischaemic heart disease
  - Valvular heart disease
  - Left ventricular hypertrophy
  - Arrhythmia
- On treatment with beta blocker, methyldopa angiotensin converting enzyme inhibitors.
- Renal or hepatic dysfunction

Randomization

Patients were randomly allocated into one of the two groups by computer generated randomization that is

- Group I -n=20; receiving 10 ml normal saline (0.1 ml/kg IV) over 10 min.
- Group II- n=20 receiving clonidine IV 6 mcg /kg that is, 3 mcg/kg (300 mcg diluted in 10ml normal saline given as 0.1 ml /kg over 10 min) administered at two stages
  - Preinduction period (30 min before surgery)
  - Just before creation of PNO
- Preparation of drugs was made by anaesthesiologist 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 KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum were screened for eligibility and a written informed consent (Annexure I) 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 (Annexure II).

Investigations like, complete blood count, urine routine and microscopy, blood urea nitrogen, serum creatinine, fasting and post prandial blood sugar, X-ray Chest PA view, electrocardiography (ECG) and bleeding and clotting time were done.

Alprazolam 0.25 mg was given to all patients previous night. Further, Nil by mouth (NBM) status was confirmed. Patient was taken in pre anaesthetic room. Monitors like, ECG, NIBP, Pulse oximetry were applied. Intravenous line (IV) was secured with appropriate IV cannula and 500 ml crystalloids were started. Heart rate, NIBP and O_2 saturation were monitored before and during the surgery. Drugs were given intravenously as slow infusion to patients 30 minutes before surgery in pre operative room. Group I received saline 10 ml (0.1 ml/kg IV) and Group II received clonidine 300 µg/Kg diluted to 10 ml (0.1 ml/kg IV) infused over 10 minutes.

After premedication with glycopyrrolate 0.005 mg/Kg and fentanyl 0.15 mcg/Kg. Patients were then induced with thiopentone 5 mg/Kg and vecuronium 0.1 mg/Kg. Further they were intubated with appropriate sized cuffed endotracheal tube and maintained on nitrous oxide and oxygen (66:33), isoflurane 0.5%, -1.5%. Just before creation of pneumoperitoneum group I received NS 10 ml (0.1 ml/kg IV) and Group II received clonidine 300 µg/Kg diluted to 10 ml (0.1 ml/kg IV) infused over 10 minutes. After pneumoperitoneum if there was increase in BP more than 20% of basal BP, isoflurane concentration was increased accordingly as a rescue agent.

Systolic BP, DBP, MAP, HR were noted at T1 (Baseline), T2 (laryngoscopy), T3 (After pneumoperitoneum), T4 (15 minutes), T5 (30 minutes), T6 (Exsufflation), T7 (Post operatively 5 minutes), T8 (30 minutes) and End tidal carbon di-oxide [$ETCO_2$], SPO_2 were noted at all intervals.

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

Statistical analysis

Demographic data were analyzed by Analysis of Variance Test [ANOVA]. Parametric variables like systolic BP, diastolic BP 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 and analyzed by Mann Whitney 'U' test. VAS score up to 3/10 was standardized as satisfactory analgesia. Diclofenac injection was standardized as rescue analgesic.

RESULTS

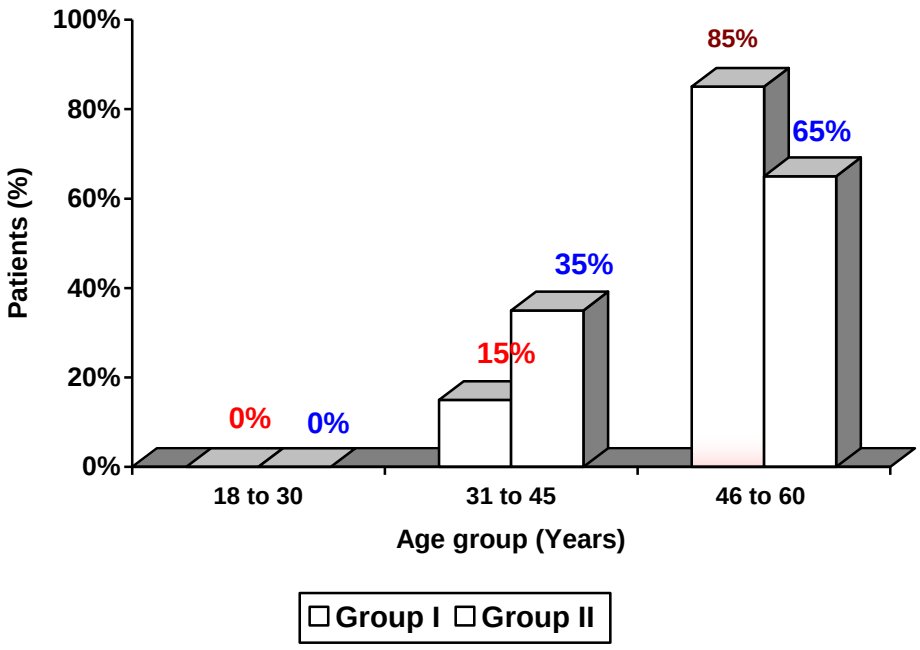
In the present prospective randomized controlled trial of forty patients aged between 18 to 60 years of ASA I and II undergoing LC were studied to evaluate the intraoperative hemodynamic effects and anaesthetic requirement and post operative analgesic requirements. Patients were divided into two groups of twenty each namely Group I (Normal saline) and Group II (Clonidine 6 mcg/kg in normal saline).

The data recorded on predesigned and pretested proforma was tabulated and master chart was prepared. The analysis was done as below.

Table 1. Age distribution

Age group (Years)	**Group I (n=20)**		**Group II (n=20)**	
	Number	**Percentage**	**Number**	**Percentage**
18 to 30	00	00%	00	00%
31 to 45	03	15%	07	35%
46 to 60	17	85%	13	65%
Total	**20**	**100%**	**20**	**100%**

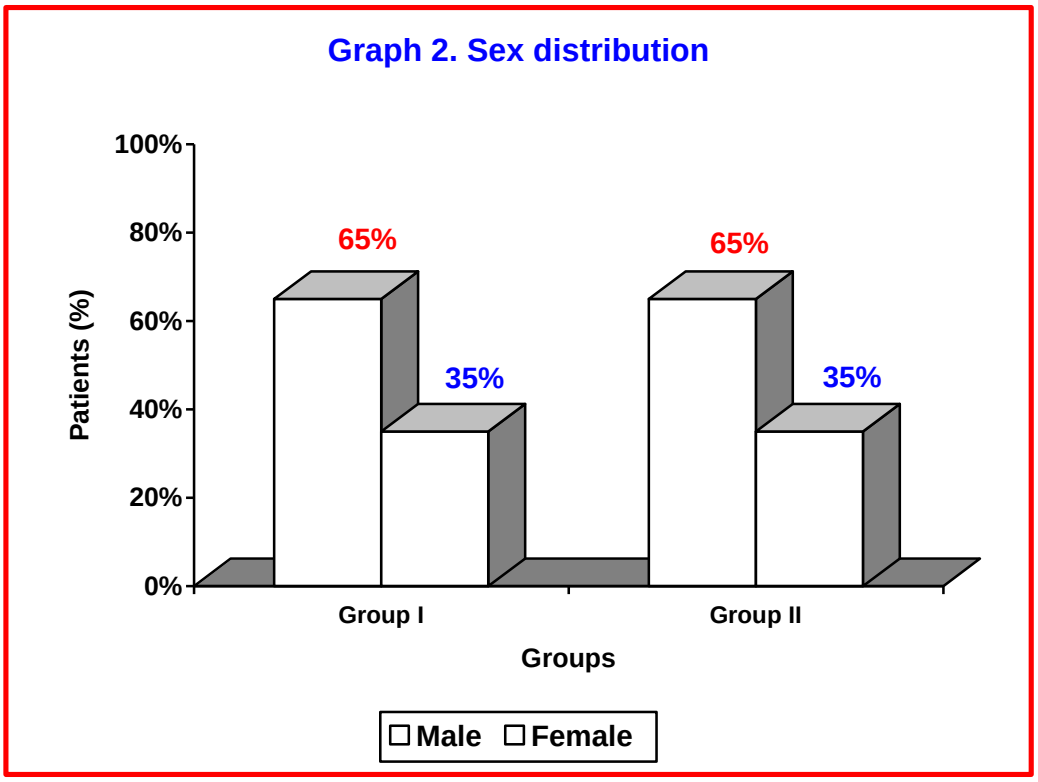
Graph 1. Age distribution



In this study most of the patients (Group I 65% and group II 85%) in both the groups were aged between 46 to 60 years. The mean age in group I was 46.80 ± 3.55 years and in group II it was 49.75 ± 4.19 years suggesting both the groups had comparable demographic characteristics.

Table 2. Sex distribution

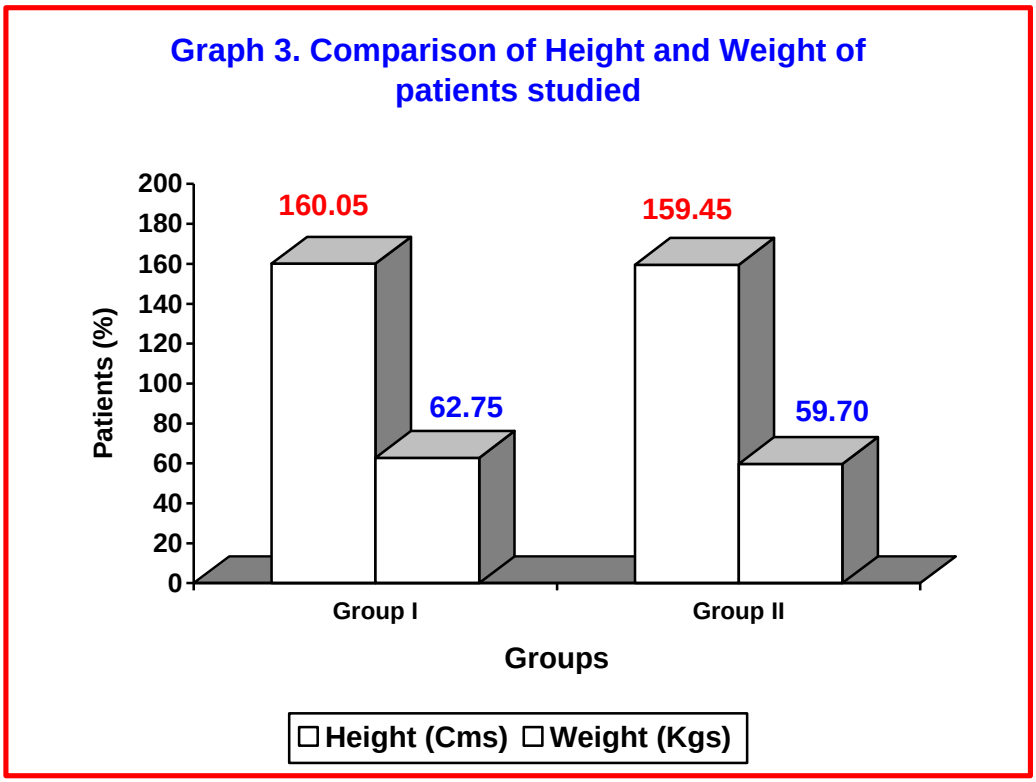
Gender	Group I (n=20)		Group II (n=20)	
	Number	**Percentage**	**Number**	**Percentage**
Male	13	65%	13	65%
Female	07	35%	07	35%
Total	**20**	**100%**	**20**	**100%**



In this study 65% were males and 35% were females in group I and II with male to female ratio of 1.85:1.

Table 3: Comparison of Height and Weight of patients studied

Variables	Group I (n=20)	Group II (n=20)
Height (Cms)	159.45 ± 2.35	160.05 ± 3.17
Weight (Kgs)	59.70 ± 3.10	62.75 ± 3.97



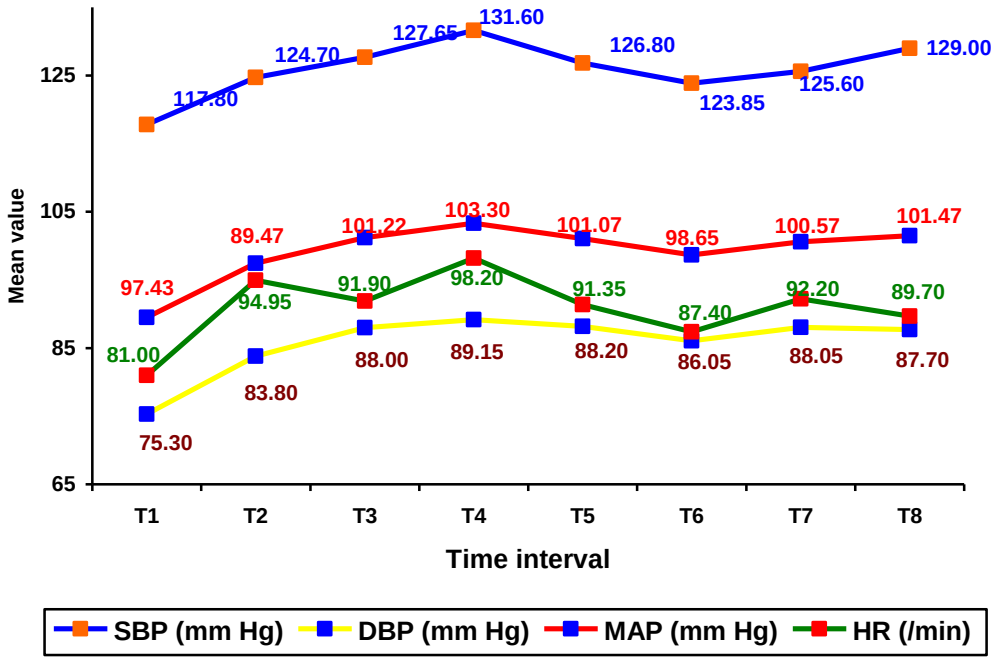
The mean height in group I was 159.45 ± 2.35 Cms and in group II it was 160.05 ± 3.17 Cms. The mean weight in group I was 59.70 ± 3.10 Kgs and in group II it was 62.75 ± 3.97 Kgs suggesting mean weight and height in both groups were comparable.

In both the groups 70% of patients had ASA status I and 30% had II.

Table 4. Haemodynamic parameters

	SBP (mm Hg)	DBP (mm Hg)	MAP (mm Hg)	HR (/min)
Group I				
T1	117.80 ± 1.28	75.30 ± 1.59	89.47 ± 1.34	81.00 ± 1.89
T2	124.70 ± 1.87	83.80 ± 2.67	97.43 ± 1.90	94.95 ± 2.24
T3	127.65 ± 4.03	88.00 ± 2.83	101.22 ± 2.22	91.90 ± 2.00
T4	131.60 ± 5.02	89.15 ± 1.18	103.30 ± 1.91	98.20 ± 3.05
T5	126.80 ± 3.61	88.20 ± 1.28	101.07 ± 1.53	91.35 ± 2.08
T6	123.85 ± 1.66	86.05 ± 2.21	98.65 ± 1.47	87.40 ± 2.16
T7	125.60 ± 3.27	88.05 ± 1.47	100.57 ± 1.64	92.20 ± 2.91
T8	129.00 ± 11.76	87.70 ± 2.18	101.47 ± 4.70	89.70 ± 2.08
Group II				
T1	114.30 ± 3.05	72.65 ± 1.87	86.53 ± 2.11	81.80 ± 2.14
T2	119.00 ± 1.52	77.10 ± 1.52	89.43 ± 1.19	84.90 ± 1.89
T3	110.50 ± 3.09	71.30 ± 1.49	84.37 ± 1.77	79.20 ± 2.09
T4	107.50 ± 3.35	71.20 ± 1.20	83.30 ± 1.13	75.80 ± 1.58
T5	104.30 ± 3.33	61.85 ± 2.23	76.00 ± 1.60	72.90 ± 2.38
T6	103.90 ± 3.86	62.40 ± 3.73	76.23 ± 2.92	74.60 ± 3.38
T7	105.15 ± 2.03	66.00 ± 3.84	79.05 ± 1.98	79.20 ± 1.64
T8	103.95 ± 1.96	68.80 ± 3.27	80.52 ± 1.68	79.50 ± 2.14

Graph 4. Haemodynamic paramters in group I



Graph 5. Haemodynamic paramters in group II

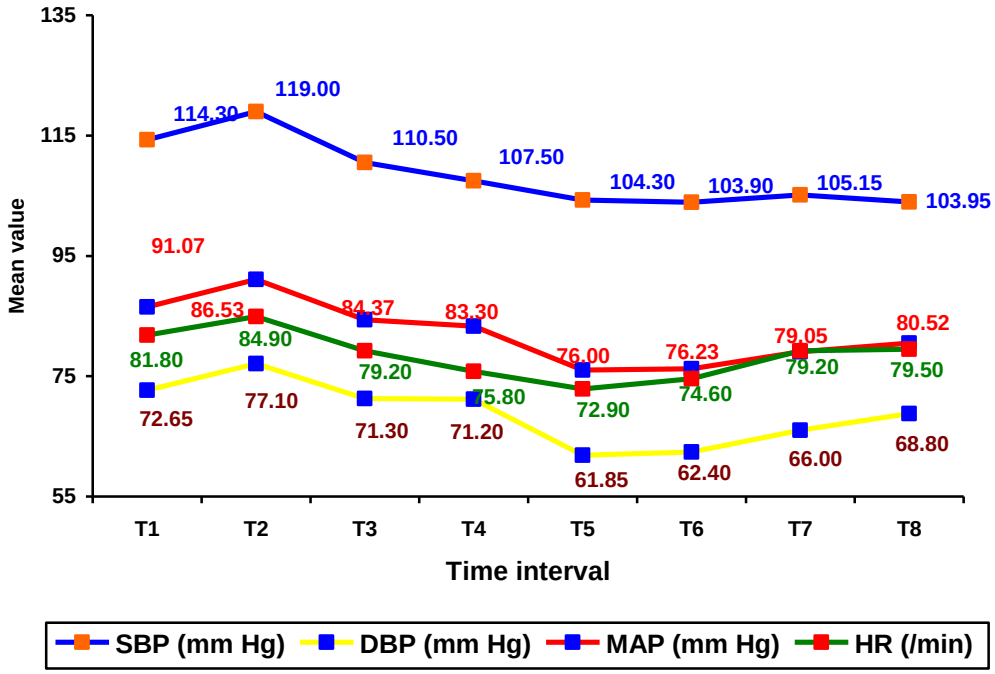
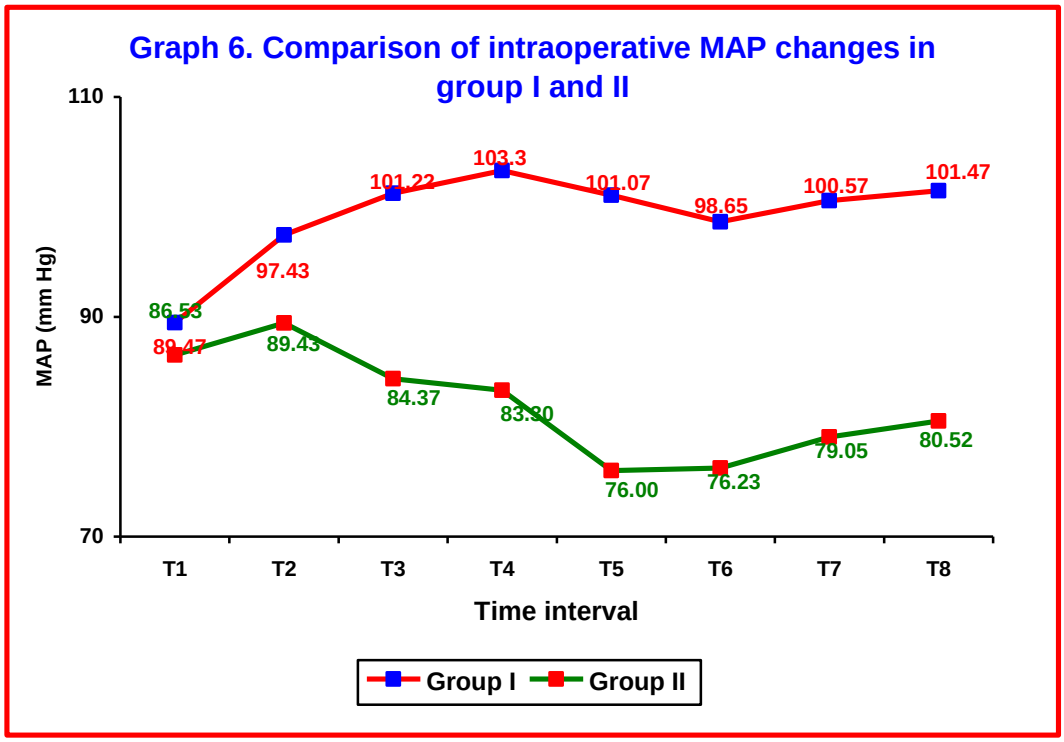


Table 5. Comparison of intraoperative MAP changes in group I and II

Time interval	Group I (n=20)	Group II (n=20)	'p' value
T1	89.47 ± 1.34	88.53 ± 2.11	0.221 NS
T2	97.43 ± 1.90	89.43 ± 1.19	<0.001 HS
T3	101.22 ± 2.22	84.37 ± 1.77	<0.001 HS
T4	103.30 ± 1.91	83.30 ± 1.13	<0.001 HS
T5	101.07 ± 1.53	76.00 ± 1.60	<0.001 HS
T6	98.65 ± 1.47	76.23 ± 2.92	<0.001 HS
T7	100.57 ± 1.64	79.05 ± 1.98	<0.001 HS
T8	101.47 ± 4.70	80.52 ± 1.68	<0.001 HS

NS – Not Significant, HS – Highly Significant

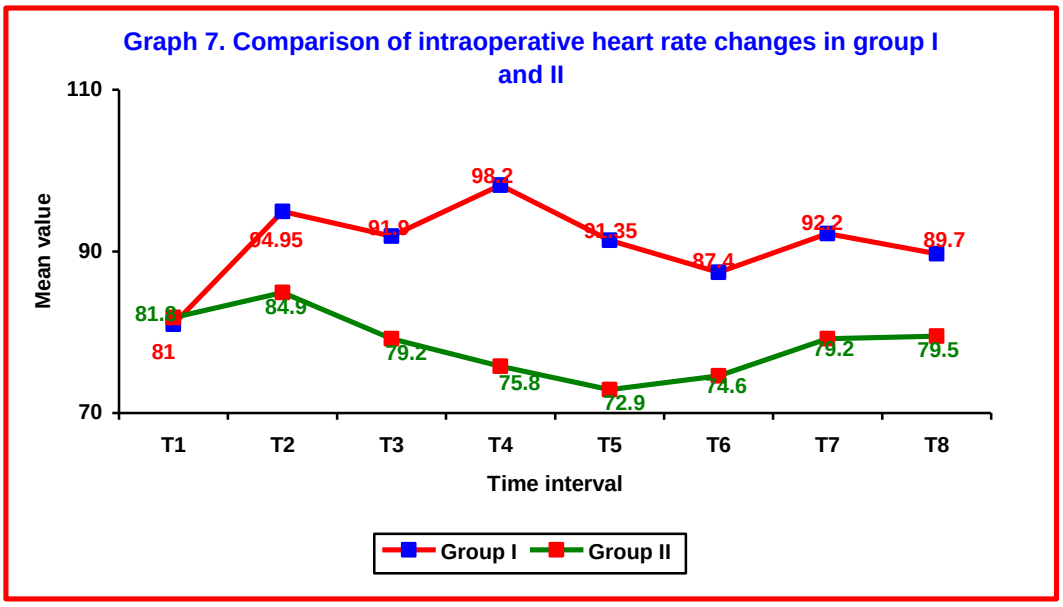


The figure shows intraoperative MAP changes of clonidine groups of patients with isoflurane (0.2 to 0.4%) are at lower level compared to placebo groups with isoflurane 1.0 to 1.5% at various periods of procedure

Table 6. Comparison of intraoperative heart rate changes in group I and II

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

NS – Not Significant, HS –Highly Significant

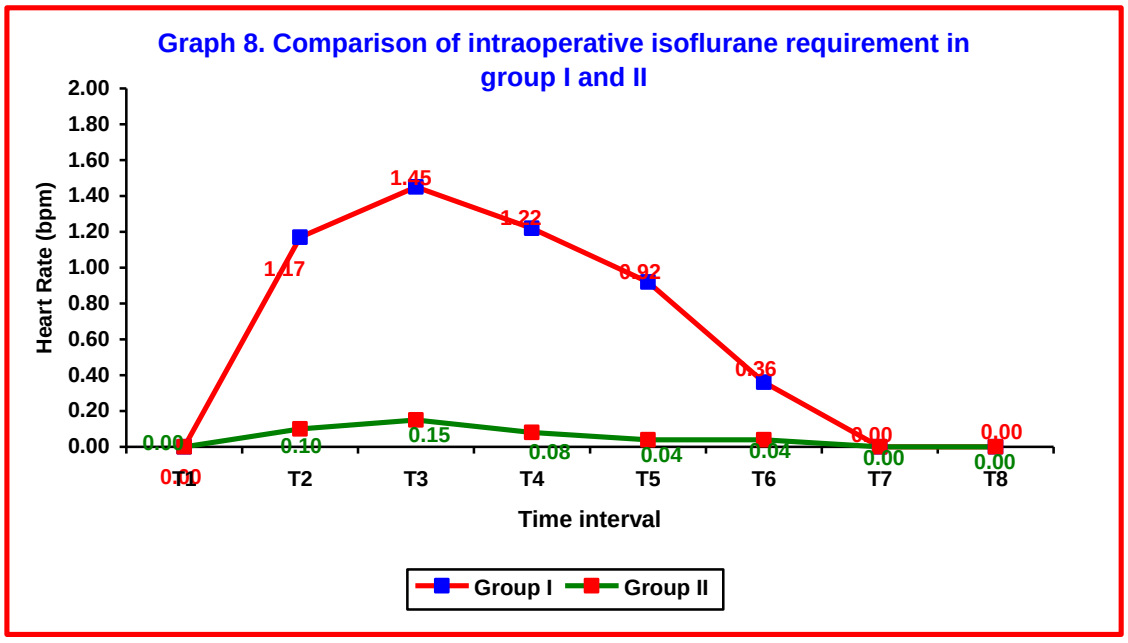


The figure shows intraoperative intraoperative heart rate changes of clonidine groups of patients with isoflurane (0.2 to 0.4%) are at lower level compared to placebo groups with isoflurane 1.0 to 1.5% at various periods of procedure.

Table 7. Comparison of intraoperative isoflurane requirement in group I and II

Time interval	Group I (n=20)	Group II (n=20)	'p' value
T1	0.00 ± 0.00	0.00 ± 0.00	1.000 NS
T2	1.17 ± 0.18	0.10 ± 0.10	<0.001 HS
T3	1.45 ± 0.07	0.30 ± 0.13	<0.001 HS
T4	1.22 ± 0.20	0.12 ± 0.15	<0.001 HS
T5	0.92 ± 0.18	0.04 ± 0.08	<0.001 HS
T6	0.36 ± 0.13	0.04 ± 0.08	<0.001 HS
T7	0.00 ± 0.00	0.00 ± 0.00	<0.001 HS
T8	0.00 ± 0.00	0.00 ± 0.00	<0.001 HS

NS –Not Significant , HS –Highly Significant



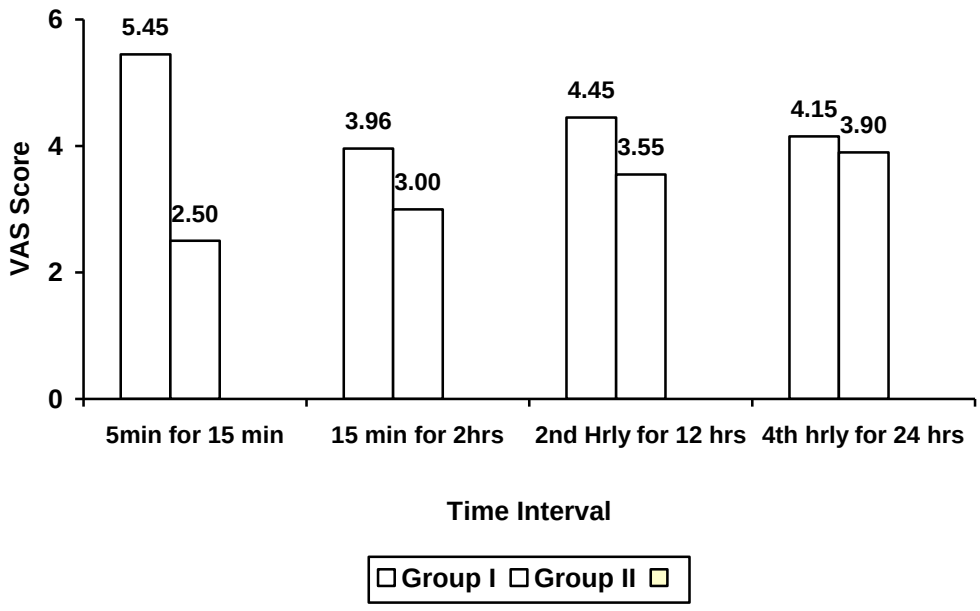
The figure shows that isoflurane concentration in clonidine group (0.2 to 0.4%) is significantly lower than in placebo group with isoflurane concentration (1.0 to 1.5%) to maintain hemodynamic stability.

Table 8. Comparison of post operative VAS scores in group I and II

Time interval	Group I (n=20)	Group II (n=20)	'p' value
5 min to 15 min	5.45 ± 0.69	2.50 ± 0.51	< 0.001 HS
15 min to 2 hrs	3.96 ± 0.64	3.00 ± 0.44	< 0.001 HS
2nd hrly for 12 hrs	4.45 ± 1.10	3.55 ± 0.51	0.002 HS
4th hrly for 24 hrs	4.15 ± 0.81	3.90 ± 0.99	0.387 NS

{HS –Highly Significant ,S –Significant}

Graph 9. Comparison of post operative VAS scores in group I and II

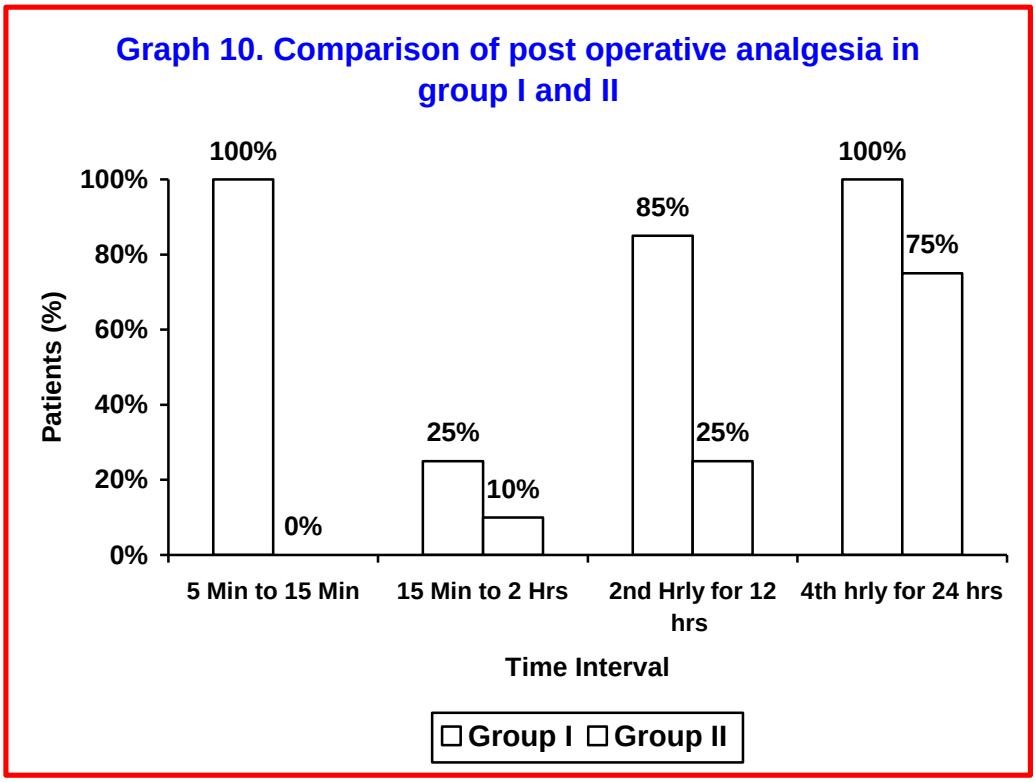


The table shows that VAS scores are significantly lower in Clonidine group ($p<0.0001$) with out the use of analgesic for the first 7 to 8 hours whereas in control group with the use of analgesic VAS scores are higher.

Table 9. Comparison of post operative analgesia in group I and II

Time interval	Group I (n=20)		Group II (n=20)	
	Number	Percentage	Number	Percentage
5 min for 15 min	20	100%	00	00%
15 min for 2 hrs	05	25%	01	10%
2 hrly for 12 hrs	17	85%	05	25%
4th hrly for 24 hrs	20	100%	15	75%

x^2 (with Yates Correction)=26.189 DF=1 p<0.001



Requirement of first dose of analgesic was prolonged in clonidine group for upto first 8 hrs postoperatively (p<0.0001). Diclofenac sodium was used as rescue analgesic in both the groups.

DISCUSSION

No other operation has been so profoundly affected by the advent of laparoscopy as cholecystectomy. In fact, the converse may be more accurate; laparoscopic cholecystectomy (LC) has been instrumental in ushering in the laparoscopic era. 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.[60]

The initial driving force behind the rapid development of LC was patient demand. 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).[61,62]

Laparoscopic 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.[9]

Pneumoperitoneum results in caval compression and increase in venous resistance.[35]

Peritoneal carbondioxide 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 α–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.[43]

These characteristics suggest that clonidine may be useful in the anaesthetic 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 anaesthetic requirement and on modulation of postoperative pain in 40 patients undergoing LC at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum, divided into two groups (Group I normal saline and group II clonidine IV 6 mcg/Kg in NS).

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

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

Present study results clearly showed intraoperative MAP changes were significantly lower in clonidine group that is { T2(91±1.19) mmHg, T3 (84.26 ±1.77)mm Hg , T4 (83.3±1.12)mm Hg and T5(76.2±1.52) mm Hg with (isoflurane 0.2 to 0.4%) and at T6 (76.23±2.92)mm Hg,T7 (79 ±1.98)mm Hg,T8 (80.52±1.68) mm Hg} p = <0.001** compared to control group at all intervals where in consumption of isoflurane was [1 -1.5%]. Thus MAP remained under satisfactory control (** Highly significant * Significant).

Also intraoperative heart rate changes were found to be significantly lower in clonidine group that is {T2 (84.9±1.88) bpm, T3 (79.2±2.09) bpm, T4 (75.8±1.57) bpm and T5 (72.9±2.38) bpm with (isoflurane 0.2 to 0.35 %) and at T6 (74.6±3.38) bpm, T7 (79.20±1.64) bpm, T8 (79.50±2.14) bpm} p<0.001** compared to placebo group at all intervals with consumption of isoflurane {1 to 1.5 %}.Thus heart rate remained under satisfactory control.

Similar effects of clonidine were reported in other studies.[11,9,50,51]

A study[11] reported significant rise in MAP in Group P (placebo) as compared to Group C (clonidine 150 mcg) after intubation (113.56 ± 16.33 mm Hg vs 93.70 ± 7.33; p<0.001), after PNO at 15 minutes as (114.13 ± 16.57 mm 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 rise in MAP was noted in group I

as compared group II at intubation (97.43 ± 1.90 mm Hg vs 91.07 ± 1.19; p<0.001), after PNO at 15 minutes (103.30 ± 1.91 mm Hg vs 83.30 ± 1.13; p<0.001) and at 30 minutes (101.07 ± 1.53 mm Hg vs 76.00 ± 1.60; p<0.001).

The study[11] 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 bpm vs 75.76 ± 10.07 bpm; p=0.008), at 30 minutes (94.76 ± 19.79 bpm vs 75.70 ± 10.20 bpm; p=0.004) which were comparable to the present study that is, at intubation (94.95 ± 2.24 bpm vs 84.90 ± 1.89 bpm; p<0.001), after PNO at 15 minutes (98.20 ± 3.05 bpm vs 75.80 ± 1.58 bpm; p<0.001) and at 30 minutes (91.35 ± 2.08 bpm vs 72.00 ± 2.35 bpm; p<0.001).

In another study[9] rise in MAP in placebo group compared to clonidine group (clonidine 150 mcg) 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 ± 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=0.021). These results were comparable with the present study that is, at T2 (laryngoscopy; 97.43 ± 1.90 mm Hg vs 91.07 ± 1.19; p<0.001), at T3 (after PNO; 101.22 ± 2.22 mm Hg vs 84.37 ± 1.77; p<0.001), T4 (at 15 minute after PNO; 103.30 ± 1.91 mm Hg vs 83.90 ± 1.13; p<0.001), T5 (at 30 minute after PNO; 101.07 ± 1.53 mm Hg vs 76.00 ± 1.00; p<0.001).

The same study[9] also reported that, rise in HR in placebo group compared to clonidine group at T2 (laryngoscopy; 114.80 ± 14.08 bpm vs 101.92 ± 10.45

bpm; p=0.001), at T3 (after PNO; 109.70 ± 11.27 bpm vs 102.41 ± 10.35 bpm; p=0.001), T4 (at 15 minute after PNO; 107.65 ± 8.37 bpm vs 100.75 ± 6.59 bpm; p=0.002), T5 (at 30 minute after PNO; 97.17 ± 6.19 bpm vs 106.16 ± 7.70 bpm; p=0.007) and these results were comparable with the present study that is, at T2 (laryngoscopy; 94.95 ± 2.24 bpm vs 84.90 ± 1.89 bpm; p<0.001), at T3 (after PNO; 91.90 ± 2.00 bpm vs 79.20 ± 2.00 bpm; p<0.001), T4 (at 15 minute after PNO; 98.20 ± 3.05 bpm vs 75.80 ± 1.58 bpm; p<0.001), T5 (at 30 minute after PNO; 91.35 ± 2.08 bpm vs 72.90 ± 2.38 bpm; p<0.001).

In another study[48] significant rise in average MAP was observed in control group compared clonidine (4mcg/kg I. V at two stages)group (before PNO; 79mm Hg vs 70 mm Hg): at (15 minutes after PNO; 100mm Hg vs 79mm Hg) and at(30 minutes; 88mm Hg vs 79 mm Hg)(p<0.001). In our study also mean MAP significantly raised in group I that is,(before PNO; 97.43 ± 1.90mm Hg vs 91.07 ± 1.19 mm Hg): at(15 minutes after PNO; 101.22 ± 2.22mm Hg vs 84.37 ± 1.77 mm Hg) and at (30 minutes; 103.30 ± 1.91mm Hg vs 83.30 ± 1.13 mm Hg:(p<0.001).

In the same study[48] significant rise in average HR was observed in control group compared clonidine group (before PNO; 70bpm vs 62 bpm: 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 I that is,(before PNO; 94.95 ± 2.24 bpm vs 84.90 ± 1.89 bpm): at (15 minutes after PNO; 98.20 ± 3.05 bpm vs 75.80 ± 1.58 bpm and at (30 minutes; 91.35 ± 2.08 bpm vs 72.90 ± 2.38 bpm): p<0.001).

In another study[8] significant rise in average MAP was observed in control group compared clonidine group (8mcg /kg) (preinduction 98mm HgVs 75mm Hg) ,at (15 minutes after PNO; 90 vs 72 mm Hg) and at (30 minutes; 89 mm Hgvs 70 mm Hg): ($p<0.001$). In our study also mean MAP was significantly raised in group I that is, (base line 89.47+1.34 mm Hg Vs 88.53+2.11mm Hg) at 15 minutes after PNO; 101.22 ± 2.22mm Hg vs 84.37 ± 1.77 mm Hg) and at(30 minutes; 103.30 ± 1.91mm Hg vs 83.30 ± 1.13 mm Hg): ($p<0.001$).

In the same study[8] significant rise in average HR was observed in control group compared clonidine group (at preinduction 74 mm HgVs 66mm Hg)(,at 15 minutes after PNO; 76bpm vs 63 bpm) and at(30 minutes; 89bpm vs 70 bpm): ($p<0.001$). In our study also mean HR was significantly raised in group I (that is, base line 81 +1.89bpm Vs 81.8 +2.14 bpm),at (15 minutes after PNO; 98.20 ± 3.05bpm vs 75.80 ± 1.58 bpm and at (30 minutes; 91.35 ± 2.08 bpm vs 72.90 ± 2.38 bpm)($p<0.001$).

In the present study, clonidine 3 mcg/kg was used in two stages, one at preinduction and same dose repeated just before pneumoperitoneum as it is pharmacokinetics of IV clonidine explained by a study[45] showing plasma levels 1.5 to 2 ng/ml after loading dose of 5 mcg /kg of clonidine which results into sedation and hypotension effects. In order to avoid such effects of IV clonidine 3 mcg/kg at preinduction was used as given slowly over 10 minutes in this study and same dose repeated just before pneumoperitoneum. In total 6 mcg/kg of IV clonidine was given slowly over 10 minutes which did not result in any adverse hemodynamic changes like hypotension and bradycardia.

In this study, at laryngoscopy MAP and HR (97.43 ± 1.9 mm Hg and 101±2.0 /min) were significantly high compared to group II (91.06±1.19 mm Hg and 84.9±1.88 /Min) p=<0.001**. The results clearly showed that Group II patients showed greater hemodynamic stability than Group I patients.

In a study patients were premedicated with 0.2 mg clonidine, 900 mg gabapentin 120 min before operation.Patients showed highest rates of HR, SBP, DBP, MAP in placebo group and 1 min after intubation. The lowest rate was in gabapentin group at 1, 3, 5, 10 min after larynoscopy except 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 SBP as well as HR over the intubation.[20]

In a study HR, SBP were recorded before, immediately and every 5 min after intubation until 20 min. The clonidine (100 mcg) group showed superiority over placebo group. A significant difference was observed in both HR and SBP in control group at three subsequent measurements following intubation.[21]

Another study in which patients were premedicated with clonidine 4mcg/kg,diazepam 0.2 mg /kg and antacid placebo group.patients premedicated with clonidine produced marked anxiolysis and better sedation compared to placebo but less sedation and same level of anxiolysis compared to diazepam. Clonidine provided extra advantage over diazepam and placebo by blunting haemodynamic responses during laryngoscopy and endotracheal intubation and also by its antisialoggogue effect.[22]

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

A study[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 was reduced up to 75% with p<0.001

A study[23] done to assess the effect of clonidine premedication in thirty patients, clonidine 5 mcg/kg po provided stable hemodynamics and reduced isoflurane requirement up to 40% (0.61 ± 0.20 vs 1.03 ± 0.16% p<0.01) compared to placebo group who received diazepam 0.15 mg/kg. In our study requirement of isoflurane was reduced to 75% in group II compared to group I (0.27 ± 0.13 vs 1.45 ± 0.07; p<0.001 **).

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 Aδ and C fibres. Antinociception produced by alpha-2 adrenoceptor agonists may be due in part to acetylcholine 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.[41]

In the present study VAS scores were significantly lower in clonidine group in the first 24 hours, 5 minutes for 15 minutes 2.50 ± 0.51 (p<0.001 **), 15

min for 2 hour 3.00±0.44 (p<0.001**), 2 hourly for 12 hour 3.55 ± 0.51 (p=0.002**), 4 hourly for 24 hour 3.90 ± 0.99 (p=0.387*) (* Significant ** Highly Significant).

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

These findings suggest that, clonidine group of patients did not require analgesic for first seven to eight hour postoperatively.

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 min) in clonidine group p<0.005 where as in our study VAS scores were significantly lower in group II with statistical significance (p<0.001) up to 12 hr,p=0.002 up to 24 hr and the time for first postoperative analgesic was prolonged upto 480 min postoperatively(p<0.001**).

A study[29] to assess the effects of clonidine 100mcg on postoperative pain and morphine consumption after abdominal hysterectomy showed that, total morphine consumption and VAS scores were lower in clonidine group up to 48 hr compared to control group and morphine consumption was less in clonidine group 20 ± 1.28 Vs 26.9 ± 2.8 (p<0.05) comparable to our study VAS scores were significantly lower in group II with (p<0.001) up to 12 hr and (p=0.002) up

to 24 hr and the time for first postoperative analgesic was prolonged upto 480 min postoperatively ($p<0.001$).

In another study[31] extradural clonidine 2mcg /kg in isotonic saline 15 mcg /ml and extradural saline group received equivalent saline .pain was evaluated at 15 minute for 2 hour and 30 minute for 4 hour mean (SD) maximum pain relief was 68.2 (24.1%) 0f initial VAS scores in clonidine group compared to 14.7(25.2%) in saline group and duration of analgesia was 210 ± 87 minutes in clonidine group compared to 45 ± 27 minutes in saline group.In our study VAS scores significantly lower up to 12 hr with statistical significance ($p<0.001$).

Overall the present study showed that, the administration of IV clonidine 6 μg/Kg given at two stages in patients undergoing LC resulted in improved perioperative haemodynamic stability, reduction in intraoperative anaesthetic requirement, reduction in post operative pain and requirement of analgesic. 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 6 mcg/kg IV in two stages that is, at pre-induction and just before creation of pneumoperitoneum.

1. Maintains heart rate during PNO but one should be watch full for bradycardia.

2. Mean arterial blood pressure is maintained with clonidine as it gives more haemodynamic stability.

3. Reduces intraoperative anaesthetic requirement

4. Reduces VAS scores and 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 haemodynamics. Alpha-2 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 20 each that is group I- placebo 10 ml NS (0.1 ml/kg IV) over 10 minutes, group II - IV clonidine 6 µg/kg i.e 300 mcg diluted in 10 ml NS given as (0.1 ml/Kg IV) over 10 min in two stages. All the patients were given tablet Alprazolam 0.25 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 through out the procedure

The study drugs were prepared by anaesthesiologist not involved in the study. Group I - placebo 10 ml NS (0.1 ml/kg IV) over 10 minutes, group II - IV clonidine 300 mcg diluted in 10 ml NS given as (0.1 ml/Kg IV) over 10 min in 2 stages. They were induced and intubated with appropriate endotracheal tube and

maintained on oxygen, nitrous oxide and isoflurane. Just before creation of pneumoperitoneum the same dose of clonidine was infused to group II and 10 ml saline to group I. 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. Systolic BP, Diastolic BP, MAP, HR were recorded

Study results clearly showed intraoperative MAP and HR changes were significantly at the lower level in clonidine group $p<0.05$ at all intervals of procedure and also at laryngoscopy with consumption of isoflurane 0.2 -0.4 % compared to control group at all intervals with consumption of isoflurane [1 - 1.5%]. VAS scores were significantly lower in clonidine group 24 hour postoperatively and requirement of first postoperative analgesic was prolonged up to 8 hour postoperatively.

Hence clonidine given as 6 mcg/kg IV in two stages i.e at pre-induction and just before creation of PNO maintains HR during PNO but one should be watch full for bradycardia. The mean arterial blood pressure was maintained with clonidine as it gives more haemodynamic stability, reduces intraoperative anaesthetic requirement and VAS scores and prolongs the requirement of first postoperative analgesic.

BIBLIOGRAPHY

1. Moynihan GA. The Gall Bladder and Bile Ducts In: Bailey and Love's – Short Practice of Surgery. 24th ed., Hachette UK: Hodder Arnold Publications; 2004.

2. Antony C, Noreen D. Intraabdominal laparoscopic Surgery; Anaesthetic Implications in Wylie and Churchill Davidsons - A practice of Anaesthesia. 7th ed., London: Hodder Arnold Publications; 2003.

3. Sung CS, Lin SH, Chan KH, Chang WK, Chow LH, Lee TY. Effect of oral clonidine premedication on perioperative hemodynamic response and postoperative analgesic requirement for patients undergoing laparoscopic cholecystectomy. Acta Anaesthesiol Sin. 2000; 38(1): 23-9.

4. Sood J, Jayaraman L, Kumra VP. Historical Forum Endoscopic Surgery Anaesthetic Challenges – A Historical Review. Indian J Anaesth 2006; 50 (3): 178-82.

5. Ott DE. Chapter 1. Pneumoperitoneum: Production, Management, Effects and Consequences. Prevention and management of the laproendoscopic surgical procedures. 1st ed., Miami: Society of Laparoscopic surgeons; 2006.

6. Rademaker BM, Odoom JA, de Wit LT, Kalkman CJ, ten Brink SA, Ringers J. Haemodynamic effects of pneumoperitoneum for laparoscopic

surgery: A comparison of CO_2 with N_2O insufflation. Eur Anaesthesiol 1994; 11(4): 301-6.

7. Joris JL, Noirot DP, Legrand MJ, Jacquet NJ, Lamy ML. Hemodynamic Changes During Laparoscopic Cholecystectomy Anesthesia and Analgesia 1993; 76: 1067-71.

8. Joris J, Chiche JD, Lamy M. Clonidine reduced haemodynamic changes induced by pneumoperitoneum during laparoscopic cholecystectomy. Br J Anaesth 1995; 74 (suppl): A124.

9. Singh S, Arora K. Effect of oral clonidine premedication on perioperative hemodynamic response and postoperative analgesic requirement in patients under going laparoscopic Cholecystectomy. Indian J Anaesth 2011; 55: 26-30.

10. Passi Y, Raval B, Rupakar VB, Chadha IA. Effect of oral clonidine premedication on haemodynamic response during laparoscopic cholecystectomy. J Anaesth Clin Pharmacol 2009; 25(3): 329-32.

11. Das M, Ray M, Mukherjee G. Haemodynamic Changes During Laparoscopic Cholecystectomy: Effect Of Clonidine Premedication. Indian J Anaesth 2007; 51(3): 205-10.

12. O'Leary E, Hubbard K, Tormey W, Cunningham AJ. Laparoscopic Cholecystectomy: Hemodynamic and neuroendocrine responses after pneumoperitoneum and changes in position. Br J Anaesth 1996; 76: 640–4.

13. De Kock M, Laterre PF, Van Obbergh L, Carlier M, Lerut J. The effects of intraoperative intravenous clonidine on fluid requirements, hemodynamic variables, and support during liver transplantation: a prospective, randomized study. Anesthesia and Analgesia. 1998; 86: 468-76.

14. Málek J, Knor J, Kurzová A, Lopourová M. Adverse hemodynamic changes during laparoscopic cholecystectomy and their possible suppression with clonidine premedication. Comparison with intravenous and intramuscular premedication. Rozhl Chir 1999; 78 (6): 286-91.

15. Yotsui T. Clonidine premedication prevents sympathetic hyperactivity but does not prevent hypothalamo-pituitary-adrenocortical responses in patients undergoing laparoscopic cholecystectomy. J Anesthesiology 2001; 15: 78-82.

16. Abi-Jaoude F, Brusset A, Ceddaha A, Schlumberger S, Raffin L, Dubois C, et al. Clonidine premedication for coronary artery bypass grafting under high-dose alfentanil anesthesia: Intraoperative and postoperative hemodynamic study. J Cardiothoracic Vasc Anesth. 1993; 7: 35-40.

17. Taittonen MT, Kirvelä OA, Aantaa R, Kanto JH. Effect of clonidine and dexmedetomidine premedication on perioperative oxygen consumption and haemodynamic state. Br J Anaesth 2009; 78: 400-6.

18. Boussofara M, Bracco D, Ravussin P. Comparison of the effects of clonidine and hydroxyzine on haemodynamic and catecholamine reactions to microlaryngoscopy. Eur J Anaesthesiol 2001; 18: 75-8.

19. Javaherfroosh F, Raza M, Pipelzadeh, Namazi M. Clonidine reduces post operative nausea and vomiting in laparoscopic gynecological surgery. Pak J Med Sci 2009 (Part-I); 25: 782-5.

20. Marashi MS, Ghafari MH, Saliminia A. Attenuation of haemodynamic responses following laryngoscopy and tracheal intubation. Middle Eur J Anaesth 2009; 20: 232-6.

21. Talebi H, Nourozi A, Fateh S, Mohammadzadeh A, Eghtesadi-Araghi P, Jabbari S, et al. Effects of oral clonidine premedication on haemodynamic response to laryngoscopy and tracheal intubation Pak J Biol Sci 2010; 13: 1146-50.

22. Raval DL, Mehta M. Oral clonidine premedication for attenuation of haemodynamic response to laryngoscopy and intubation. Indian J Anaesth 2002; 46: 124-9.

23. Ghigone M, Calvillo O, Quintin L. Anesthesia and Hypertension: The effect of Clonidine on Perioperative Hemodynamics and Isoflurane Requirements .Anesthesiology 1987; 67; 3-10.

24. Seo N, Sunagawa H, Otsuka Y, Sanui M, Murayama T, Oral Clonidine Premedication for Laparoscopic Cholecystectomy. Shimotsuke, Tochigi, Japan: Jichi Medical Uneversity; 2009; A53 ASA ABSTRACT.

25. Lee J, Lovell AT, Parry MG, Glaiser HR, Bromley LM. I.V. clonidine does it work as a hypotensive agent with inhalation anaesthesia. British J Anaesth 1999; 82(4): 639-40.

26. Leslie K, Mooney PH, Silbert BS. Effect of Intravenous Clonidine on the Dose of Thiopental Required to Induce Anesthesia. Anesth Analg 1992; 75: 530-5.

27. Ghafari MH, Akrami M, Nouralishahi B, Sadegh A. Preoperative Clonidine and Gabapentin decreases postoperative pain and morphine consumption after abdominal Jysterectomy. J Biol Sci 2009; 4: 458-63.

28. Hidalgo MP, Auzani JA, Rumpel LC, Moreira NL, Cursino AW, Caumo W. The clinical Effect of small Oral Clonidine Doses on Perioperative Outcomes in Patients Under going Abdominal Hysterectomy. Anaesth Analg 2005; 100: 795-802.

29. Bonnet F, Boico O, Rostaing S, Saada M, Loriferne JF, Touboul C, et al Postoperative analgesia with extradural clonidine. Br J Anaesth 1989; 63: 465-9.

30. Cigarini I, Kaba A, Bonnet F, Brohon E, Dutz F, Damas F, et al Epidural clonidine combined with bupivacaine for analgesia in labor. Reg Anesth 1995; 20: 113-20.

31. Rostaing S, Bonnet F, Levron J, Vodinh J, Pluskwa F, Saada M. Effect of epidural clonidine on analgesia and pharmacokinetics of epidural fentanyl in postoperative patients. Anesthesiology 1991; 75: 420-5.

32. Ghodki PS, Sardesai SP, Thombre SK. Evaluation of the effect of intrathecal clonidine to decrease shoulder tip pain in laparoscopy under spinal anaesthesia. Indian J Anaesth 2010; 54(3): 231-4.

33. Eisenach JC, Rauck RL, Buzzanell C, Lysak SZ. Epidural clonidine analgesia for intractable cancer pain: phase, 1. Anesthesiology 1989; 71: 647-52.

34. Leonard IE, Cunningham AJ. Anaesthetic considerations for laparoscopic cholecystectomy. Best Pract Res Clin Anaesthesiol 2002; 16(1): 1-20.

35. Joris J. Anaesthesia for Laparoscopic Surgery in Millers Anaesthesia. 7th ed., San Francisco, California: Churchill Livingstone Elsevier publications; 2010.

36. Hirvonen EA, Poikolainen EO, Pääkkönen ME, Nuutinen LS. The adverse hemodynamic effects of anesthesia, head-up tilt, and carbon dioxide pneumoperitoneum during laparoscopic cholecystectomy. Surg Endosc 2000; 14(3): 272-7.

37. Wahba RW, Béïque F, Kleiman SJ. Cardiopulmonary function and laparoscopic cholecystectomy. Can J Anaesth 1995; 42(1):51-63.

38. Kamolpornwijit W, lamtrirat P, Phupong V. Cardiac and Hemodynamic Changes during Carbon dioxide Pneumoperitoneum for Laparoscopic Gynecologic Surgery. J Med Assoc Thai 2008; 91[5]: 603-7.

39. Batra RK, Garg R. Anaesthesia for Laparoscopic and other Endoscopic Surgery. J Postgraduate Med Edu Training Res 2008; III(3):

40. Bonica JJ. History of pain concepts and therapies. The management of pain. 2nd ed., Philadelphia: Lea and Febiger; 1990.

41. Howe JR, Wan J-Y, Yaksh TL. Selective antagonism of the antinociceptive effect of intrathecally applied alpha adrenergic agonists by intrathecal prazosin and intrathecal yohimbine. Journal of Pharmacology and Experimental Therapeutics 1983; 224: 552-8.

42. Persec J, Persec Z, Husedzinovic I. Postoperative pain and systemic inflammatory stress response after preoperative analgesia with clonidine or levobupivacaine. Eur J Med 2009; 121: 558-63.

43. Schneemilch CE, Bachmann H, Ulrich A, Elwert R, Halloul Z, Hachenberg T. Clonidine Decreases Stress Response in Patients Undergoing Carotid Endarterectomy Under Regional Anesthesia: A Prospective, Randomized, Double-Blinded, Placebo-Controlled Study. Anesth Analg 2006; 103: 297-302.

44. De Noyer M, Laveleye F, Vauquelin G, Gobert J, Wülfert E. Mivazerol, a novel compound with high binding specificity for alpha α2 adrenergic receptors: binding studies on different human and rat membrane preparations. Neurochemistry International 1994; 24: 221-9.

45. Bernard JM, Hommeril J, Passuti N, Pinaud M. Postoperative Analgesia by IV Clonidine, Anaesthesiology 1991; 75: 577-582.

46. Maze M, Tranquilli W. Alpha 2 Adrenoceptor Agonists: Defining role in Clinical Anaesthesia. Anaesthesiology 1991; 74: 581-605.

47. Khan ZP, Ferguson CN, Jones RM. Alpha-2 and imidazoline receptor agonists-Their pharmacology and therapeutic role. Anaesthesia. 1999; 54: 146-65.

48. Laisalmi M, Koivusalo AM, Valta P, Tikkanen I, Lindgren L. Clonidine provides opioid-sparing effect, stable hemodynamics, and renal integrity during laparoscopic cholecystectomy. Surg Endosc (2001) 15: 1331-6.

49. Joris JL, Chiche JD, Canivet JL, Jacquet NJ, Legros JJY, Lamy ML. Haemodynamic changes Induced by laparoscopy and endocrine correlates: Effects of clonidine Journal of American College of Cardiology 1998; 32: 1389-96.

50. Ruffolo RR. Distribution and function of peripheral α-adrenoceptors on the cardiovascular system. Pharmacology, Biochemistry and Behavior 1985; 22: 827-33.

51. Nichols AJ. Alpha-adrenoceptor signal transduction mechanisms, alpha-adrenoceptors. In: Ruffolo RR Jr, ed. Molecular Biology, Biochemistry and Pharmacology. New York: Karger; 1991: 44-74.

52. Tibirica E, Feldman J, Mermet C, Gonon F, Bousquet P. An imidazoline specific mechanism for the hypotensive effect of clonidine. A study with yohimbine and idazoxan. J Pharmacol Exp Therapeutics 1991; 256: 606–13.

53. Zochowski RJ, Lada W. Intravenous clonidine in acute myocardial infarction in men. International J Cardiol 1984; 6: 189-201.

54. Kulka PJ, Tryba M, Zenz M. Dose–response effects of intravenous clonidine on stress response during induction of anesthesia in coronary artery bypass graft patients. Anesth Analg 1995; 80: 263-8.

55. Dorman BH, Zucker J, Verrier ED, Gartman DM, Slachman FN. Clonidine improves perioperative myocardial ischemia, reduces anesthetic requirements, and alters hemodynamic parameters in patients undergoing coronary artery bypass surgery. J Cardiothoracic Vasc Anesth 1993; 7: 386-95.

56. Carabine UA, Wright PMC, Howe JP, Moore J. Cardiovascular effects of intravenous clonidine: Partial attenuation of the pressor response to intubation by clonidine. Anaesthesia 1991; 46: 634-7.

57. Bailey PL, Sperry RJ, Johnson GK et al Respiratory effects of clonidine alone and combined with morphine, in humans. Anesthesiology 1991; 74: 43-8.

58. Dhoste K, Lacoste L, Karayan J, Lehuede MS, Thomas D, Fusciardi J. et al T Hemodynamic and Ventilatory Changes during Laparoscopic Cholecystectomy in elderly ASA III patients. Can J Anaesth 1996; 43: 783-8.

59. Watkins J, Gerald FG, Zamboulis C, Brown MJ, Dollery CT. Absence of opiate and histamine H2 receptor-mediated effects of clonidine. Clin Pharmacol Therapeutics 1980; 28: 605–10.

60. Litwin DE, Cahan MA. Laparoscopic cholecystectomy. Surg Clin North Am 2008; 88(6): 1295-313.

61. Calland JF, Tanaka K, Foley E, Bovbjerg VE, Markey DW, Blome S, et al. Outpatient laparoscopic cholecystectomy: patient outcomes after implementation of a clinical pathway. Ann Surg 2001; 233(5): 704-15.

62. Shea JA, Berlin JA, Bachwich DR, Staroscik RN, Malet PF, McGuckin M. Indications for and outcomes of cholecystectomy: a comparison of the pre and postlaparoscopic eras. Ann Surg 1998; 227(3):343-50.

ANNEXURE I – CONSENT FORM

CONSENT FOR PARTICIPATION IN RESEARCH STUDY

A study, **"INTRAVENOUS CLONIDINE FOR PERIOPERATIVE HAEMODYNAMIC STABILITY DURING LAPARO-SCOPIC CHOLECYSTECTOMY – A ONE YEAR RANDOMISED CONTROLLED STUDY"** is being conducted by Dr. Rashmi Patil, Post Graduate in Anaesthesiology at J. N. Medical College Belgaum, Karnataka under guidance of Dr. Lata Kulkarni, Professor, Dept. of Anaesthesiology, J. N. Medical College, Belgaum, under K.L.E.S. academy of Higher Education, Belgaum.

Respected Sir/Madam _____ we request you to participate in our study as you are eligible to be included. During the study you will be asked questions regarding your present and past medical history and you are suppose to answer to the best of your knowledge.

Your participation in this study is voluntary. Your decision whether or, not, to participate in the study will not affect your relationship with Jawaharlal Nehru Medical College, Belgaum. If you decide to participate you are free to withdraw at any point of time. The purpose of the study is to show that clonidine maintains haemodynamic stability during pneumoperitoneum by decreasing blood pressure, heart rate and maintains cardiac output.

Procedure involved

If you agree to enroll yourself in this study, you will be interviewed

regarding your present, past and family history then you will be clinically examined in detail and investigated accordingly. You will be randomly allocated either into study Group I or Group II, if you are in Group I, you will receive 10 ml of saline and if you belong to group II you will receive clonidine six µg/kg in NS.

Benefits and Risks

The benefits of taking part in this research are that, clonidine maintains haemodynamic stability by decreasing blood pressure, heart rate and maintains cardiac output. The risks associated are hypotension and bradycardia.

Privacy and Confidentiality

The only people to know that you are a research subject are members of the research team. No information about you or information provided by you during the research will be disclosed to other without your written permission except:

1. In emergency to protect your rights and welfare.
2. If required by law.

Authorization to publish results

When the results of research are published or discussed, in conference, no information will be displaced that would disclose your identity. Any information that is obtained in connection with this study and that can be identified with you will remain confidential and will be disclosed with your permission.

Voluntary participation / Withdrawal

Taking part in the study is voluntary. You may choose not to enroll yourself in this study. Your decision will not change present or future health care services offered to you at K.L.E.S. Hospital.

Alternatives

Even if you decline the participation in the study, you will get the routine line of management.

Financial Incentives for participation

No financial incentives are being offered to enrolled patients. It is purely being done with the idea of research and all the cost of the study will be borne by the investigator.

Compensation

In the event of injury, related to the study, treatment will be made available at KLES Hospital & MRC, Belgaum. No reimbursement, compensation or free medical care will be given, by law. If you are injured, you may contact Dr. Rashmi Patil at Department of Anaesthesiology, KLE's Hospital & MRC or by Ph. No. 9164558391.

Queries/ Contact details

If you have any queries, in future or in case of study related injury or illness, you may contact. Dr. Rashmi Patil at Department of Anaesthesiology, KLES Hospital and MRC, Ph No. 0831-2473777 or on phone 9164558391. Dr.

Lata Kulkarni, Professor Department of Anaesthesiology ,KLES Hospital and MRC, Ph No 9845734615

If you have any queries about your rights as a study subject, you may call Dr. V. D. Patil, Principal and Chairman, J. N. Medical College Institutional Ethical Committee for Human Subjects Research, Ph. 0831-2473777 at J. N. Medical College, Belgaum.

CONSENT TO PARTICIPATE IN A RESEARCH STUDY:

I, Mr./Mrs. _____

voluntarily agree for the participation as a subject of study. By signing this consent form I am not giving up any of my legal rights, I may withdraw from the study anytime. I am signing the consent form after having read or been read for me in vernacular languages, including the risks and the benefits and having all my questions answered.

Subject Name : _____

Signature or left impression of the participant: _____

Witness name: _____ Signature: _____

Signature of the participant: _____ Signature: _____

Date: _____

Place: _____

ANNEXURE II – PROFOMA

STUDY: "INTRAVENOUS CLONIDINE FOR PERIOPERATIVE HAEMODYNAMIC STABILITY DURING LAPARO-SCOPIC CHOLECYSTECTOMY – A ONE YEAR RANDOMISED CONTROLLED STUDY"

Patient Name	:	I.P. No	:
Age	:	Weight	:
Height	:	Gender	:
Date of Operation	:	Occupation	:
Address	:	Anaesthesiologist	:

Preanaesthetic evaluation

Chief Complaints

Past History

a. HTN / DM / IHD/ Arrhythmia / Left ventricular hypertrophy
b. H/o renal / hepatic dysfunction or use of angiotensin converting enzyme affecting drugs or angiotensin.
c. H/o drug intake – β-blockers / methyldopa / monoamine oxidase inhibitors / concomitantly on clonidine.

Family history

General Physical Examination

Weight (Kg)	:	Temperature (^{0}F)	:	Pallor	:
Cyanosis	:	Pedal oedema	:	Clubbing:	
PR	:	BP	:	RR	:

Systemic examination

R.S.	:	CNS	:
CVS	:	GIT	:

Airway & Spine assessment :

Investigations

Hb% : Haematocrit :

Urine routine : Blood urea :

Serum Creatinine: Fasting blood sugar:

CXR :

Diagnosis :

Proposed Surgery :

Preoperative physical status: ASA Grade I II III IV V

Observations

Time	**T1**	**T2**	**T3**	**T4**	**T5**	**T6**	**T7**	**T8**
MAP (mm Hg)								
HR (bpm)								

Intraoperative requirement of isoflurane (in Percentage)

	Group I	**Group II**
Anaesthesia (Isoflurane)		

<u>Details of Post-op Analgesia</u>

VAS recording

VAS Score	**Group I**	**GroupII**
Every 5mins for 15mins		
Every 15mins for 2hrs		
Every 2nd hrly for 12hrs		
Every 4th hrly for 24hrs		

Post operative requirement of analgesia according to VAS score

Analgesia	Group I	Group II
Required at		

Inclusion criteria

- Patients undergoing laparoscopic cholecystectomy.
- Age between 20 to 60 years.
- Weight between 40 to 60 Kg.
- ASA Grade I and II.

Exclusion criteria

- Patient refusal.
- Patients with cardiovascular pathology
  - Diabetes
  - Hypertension.
  - Ischaemic heart disease.
  - Volvular heart disease.
  - Left ventricular hypertrophy.
  - Arrhythmia.
- Patients on treatment with β blockers, methyldopa, monoamine oxidase inhibitors, concomittantly on clonidine.
- Patients with renal or hepatic dysfunction or use of angiotensin converting enzyme affecting drugs or angiotensin.

Date of surgery _____

From _____ To

_____

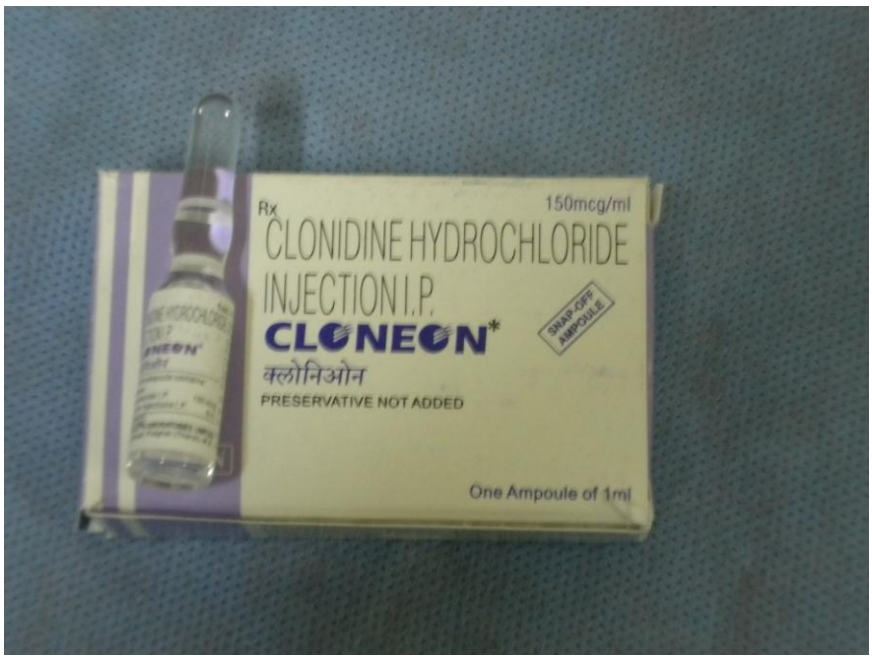
After having met all inclusion and exclusion criteria and obtaining written informed consent, patients will be randomised into two group of 20 each using computer generated randomisation.

Intravenous line will be secured with appropriate IV cannula and 500 ml of crystalloids will be started. Heart rate, non invasive BP and oxygen saturation will be monitored before and during surgery.

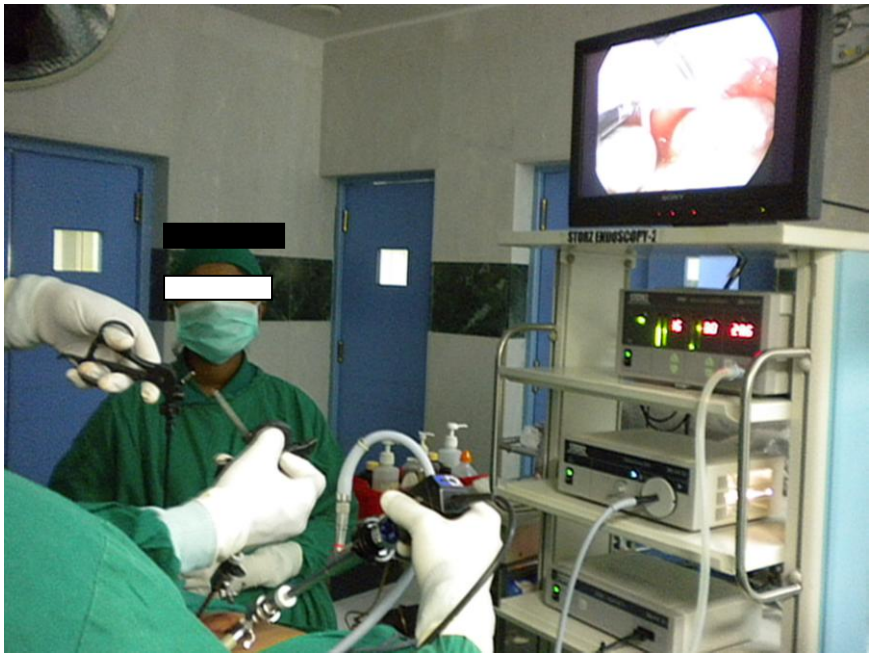
Study drug will be prepared and dispensed in syringe by an anaesthesiologist not involved in study. After premedication with glycopyrrolate 0.005 mg/kg midazolam 0.05 mg/kg and fentanyl 1.5 µg/kg. The placebo group (Group I) will receive saline 10 ml and clonidine (Group II) will receive 300 µg diluted to 10 ml (0.1 ml/kg) will be infused over 10 minutes. Patients will then be induced with thiopentone 5 mg/kg and vecuronium 0.1 mg/kg. Further they will be intubated with appropriate endotracheal tube and maintained with oxygen, nitrous oxide and isoflurane 0.5% to 1.5%. Just before creation of pneumoperitoneum the same dose of clonidine will be infused to group II and 10 ml of saline to group I. After pneumoperitoneum if there is increase in BP more than 20% of basal BP, isoflurane concentration will be increased accordingly as rescue agent. More than 20% fall in BP was treated with ephedrine (3 – 6 mg)

Systolic BP, DBP, MAP, HR will be noted at T1 (Basal), T2 (Laryngoscopy and after clonidine), T3 (after pneumoperitoneum, 5 min), T4 (15 min), T5 (30 Min), T6 (Exsufflation), T7 (Post operatively 5 Min), T8 (30 Min) and $ETCO_2$ noted at intervals. After surgery patients will be reversed with glycopyrolate 0.005 mg/Kg and neostigmine 0.05 mg/kg and extubated.

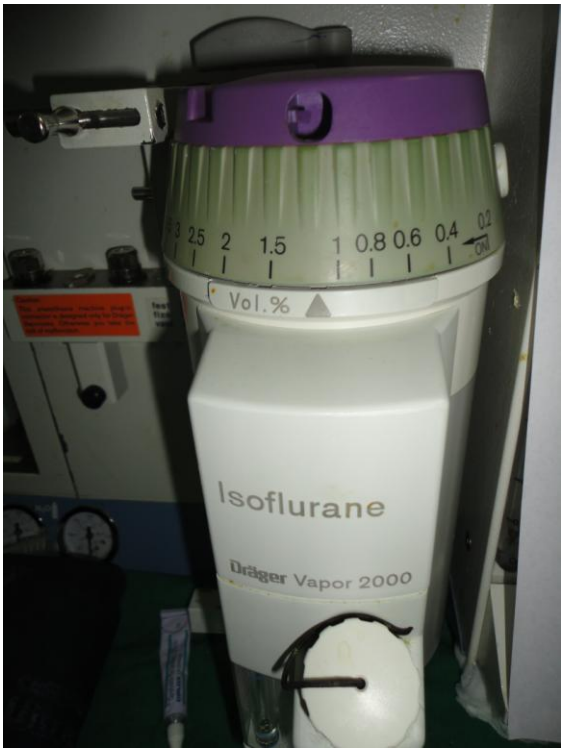
ANNEXURE III – PHOTOGRAPHS



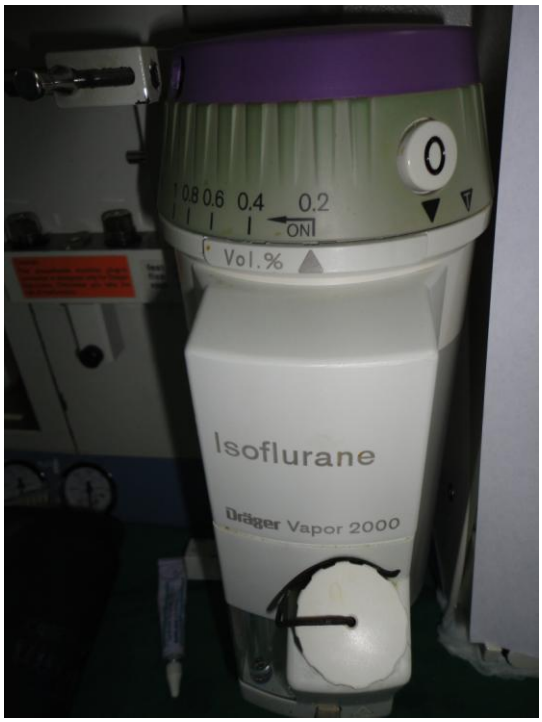
Photograph 1. Clonidine hydrochloride



Photograph 2. Laparoscopic cholecystectomy showing pneumoperitoneum



Photograph 3. Percentage of inhalational anaesthetic in group I (Placebo)



Photograph 4. Percentage of inhalational anaesthetic in group II (Clonidine)

ANNEXURE IV MASTER CHART - CLONIDINE GROUP

Serial Number	In Patient Number	Gender	Age (Years)	Weight (Kg)	Height (Cms)	ASA Grade	Observations at regular intervals (Time in minutes)																																Requirement of isoflurane (%) at regular intervals (Minutes)								VAS Score					Post-op analgesia			
							T1				T2				T3				T4				T5				T6				T7				T8																				
							SBP (mm Hg)	DBP (mm Hg)	MAP (mm Hg)	HR (/Min)	SBP (mm Hg)	DBP (mm Hg)	MAP (mm Hg)	HR (/Min)	SBP (mm Hg)	DBP (mm Hg)	MAP (mm Hg)	HR (/Min)	SBP (mm Hg)	DBP (mm Hg)	MAP (mm Hg)	HR (/Min)	SBP (mm Hg)	DBP (mm Hg)	MAP (mm Hg)	HR (/Min)	SBP (mm Hg)	DBP (mm Hg)	MAP (mm Hg)	HR (/Min)	SBP (mm Hg)	DBP (mm Hg)	MAP (mm Hg)	HR (/Min)	SBP (mm Hg)	DBP (mm Hg)	MAP (mm Hg)	HR (/Min)	T1	T2	T3	T4	T5	T6	T7	T8	5 to 15 min	15 min to 2 hrs	2 to 4 hrs	4 to 12 hrs	12 to 24 hrs	2 hrs	2 to 4 hrs	4 to 8 hrs	8 to 12 hrs
1	4E+05	M	44	69	160	I	116	74	88.00	82	118	78	91.33	86	112	70	84.00	82	106	70	82.00	76	100	63	75.33	74	108	60	76.00	80	104	70	81.33	78	106	66	79.33	82	0.0	0.2	0.0	0.0	0.0	0.2	0.0	0.0	3	3	3	4	5	0	0	0	1
2	4E+05	M	42	62	162	I	118	75	89.33	80	116	76	89.33	88	109	70	83.00	80	102	72	82.00	74	100	58	72.00	76	100	64	76.00	82	106	66	79.33	80	103	70	81.00	80	0.0	0.2	0.2	0.0	0.0	0.0	0.0	0.0	2	3	4	3	4	0	0	0	1
3	4E+05	M	45	64	166	I	117	72	87.00	78	118	78	91.33	84	106	72	83.33	78	108	72	84.00	76	108	60	76.00	72	100	63	75.33	76	106	66	79.33	82	102	70	80.67	78	0.0	0.2	0.0	0.0	0.0	0.0	0.0	0.0	3	3	3	4	4	0	0	1	1
4	4E+05	M	52	68	168	II	118	75	89.33	82	118	76	90.00	88	110	70	83.33	78	106	70	82.00	78	100	63	75.33	76	100	58	72.00	74	108	60	76.00	80	104	70	81.33	76	0.0	0.2	0.2	0.0	0.0	0.0	0.0	0.0	2	3	4	3	4	0	0	0	1
5	4E+05	F	39	55	158	I	114	72	86.00	84	118	74	88.67	88	114	72	86.00	76	109	72	84.33	74	100	64	76.00	78	108	60	76.00	76	103	70	81.00	78	104	72	82.67	78	0.0	0.2	0.2	0.0	0.0	0.2	0.0	0.0	2	3	4	3	5	0	0	0	0
6	4E+05	M	46	62	162	I	112	70	84.00	84	118	76	90.00	86	114	74	87.33	80	104	70	81.33	76	108	62	77.33	74	106	66	79.33	72	102	70	80.67	76	106	66	79.33	80	0.0	0.0	0.2	0.0	0.2	0.0	0.0	0.0	3	3	3	3	5	0	0	1	1
7	4E+05	M	48	64	160	I	114	72	86.00	82	116	72	86.67	84	112	70	84.00	82	108	72	84.00	78	108	60	76.00	72	104	66	78.67	78	106	66	79.33	78	102	70	80.67	82	0.0	0.0	0.0	0.0	0.2	0.0	0.0	0.0	2	3	3	3	3	0	0	0	0
8	4E+05	F	44	58	158	I	112	70	84.00	84	116	74	88.00	86	114	72	86.00	78	114	72	86.00	76	106	66	79.33	70	108	60	76.00	80	104	70	81.33	80	106	66	79.33	80	0.0	0.2	0.2	0.0	0.0	0.0	0.0	0.0	3	3	3	4	4	0	1	0	1
9	4E+05	M	52	56	159	II	114	72	86.00	82	118	78	91.33	84	112	74	86.67	76	110	72	84.67	74	108	62	77.33	72	100	64	76.00	72	102	70	80.67	78	104	70	81.33	82	0.0	0.0	0.3	0.0	0.2	0.0	0.0	0.0	3	3	3	3	5	0	0	1	1
10	4E+05	F	48	59	156	I	118	76	90.00	80	114	74	87.33	82	104	70	81.33	78	104	72	82.67	78	104	58	73.33	70	100	63	75.33	74	106	66	79.33	78	102	70	80.67	78	0.0	0.2	0.0	0.0	0.0	0.0	0.0	0.0	3	3	4	3	4	0	0	0	1
11	4E+05	F	49	60	156	I	112	74	86.67	84	118	76	90.00	84	112	72	85.33	80	112	70	84.00	76	108	60	76.00	74	100	64	76.00	72	106	64	78.00	82	108	60	76.00	82	0.0	0.0	0.2	0.0	0.0	0.0	0.0	0.0	3	3	4	4	5	0	0	0	1
12	4E+05	M	52	64	160	II	112	72	85.33	82	118	78	91.33	84	106	70	82.00	82	108	70	82.67	74	102	64	76.67	72	108	60	76.00	72	102	70	80.67	80	106	66	79.33	84	0.0	0.0	0.0	0.0	0.0	0.2	0.0	0.0	2	3	3	3	4	0	0	1	0
13	4E+05	M	43	66	158	I	117	72	87.00	82	118	80	92.67	84	108	70	82.67	78	112	70	84.00	78	108	60	76.00	70	108	60	76.00	74	106	66	79.33	78	102	70	80.67	80	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2	3	4	4	3	0	1	0	1
14	4E+05	F	50	62	157	II	116	74	88.00	80	118	78	91.33	82	112	72	85.33	76	106	72	83.33	76	108	64	78.67	76	106	58	74.00	76	102	72	82.00	80	106	64	78.00	78	0.0	0.0	0.3	0.0	0.0	0.0	0.2	0.0	3	3	4	4	5	0	0	0	0
15	4E+05	M	48	68	160	I	118	75	89.33	78	116	74	88.00	84	109	70	83.00	78	106	70	82.00	74	100	64	76.00	72	104	58	73.33	74	108	60	76.00	82	102	72	82.00	78	0.0	0.2	0.0	0.0	0.2	0.0	0.0	0.0	2	3	3	5	4	0	0	1	1
16	4E+05	F	46	64	158	I	112	72	85.33	84	118	76	90.00	86	114	72	86.00	80	112	70	84.00	74	102	63	76.00	70	100	63	75.33	76	106	66	79.33	78	106	70	82.00	80	0.0	0.0	0.4	0.0	0.0	0.0	0.0	0.0	2	3	4	5	4	0	0	0	1
17	4E+05	M	44	68	162	II	114	72	86.00	82	118	72	87.33	84	112	70	84.00	82	106	72	83.33	76	106	60	75.33	74	100	63	75.33	72	108	62	77.33	80	102	72	82.00	80	0.0	0.2	0.2	0.0	0.0	0.0	0.2	0.0	3	3	4	5	5	0	0	0	1
18	4E+05	F	50	62	158	II	114	74	87.33	84	114	72	86.00	86	106	70	82.00	78	102	74	83.33	78	104	62	76.00	70	108	72	84.00	72	106	62	76.67	78	102	70	80.67	78	0.0	0.2	0.0	0.0	0.0	0.2	0.0	0.0	2	3	3	5	3	0	0	0	0
19	4E+05	M	48	60	164	I	106	70	82.00	84	116	74	88.00	86	112	72	85.33	82	106	72	83.33	74	102	64	76.67	72	100	58	72.00	70	106	60	75.33	80	102	74	83.33	78	0.0	0.0	0.3	0.0	0.0	0.0	0.0	0.0	3	3	4	5	4	0	0	0	1
20	4E+05	M	46	64	159	I	112	70	84.00	78	118	76	90.00	82	112	74	86.67	80	109	70	83.00	76	104	60	74.67	74	110	68	82.00	70	106	64	78.00	78	104	68	80.00	76	0.0	0.0	0.2	0.0	0.0	0.0	0.0	0.0	2	3	4	5	5	0	0	0	1

ANNEXURE IV – KEY TO MASTER CHART

ASA	-	American Society of Anaesthesiologists
Cm	-	Centimeters
DBP	-	Diastolic blood pressure
F	-	Female
HR	-	Heart rate
hrs	-	Hours
Kg	-	Kilogram
M	-	Male
MAP	-	Mean arterial pressure
Min	-	Minute
mm Hg	-	Millimeter of mercury
Post op	-	Post operative
SBP	-	Systolic blood pressure
T	-	Time intervals
VAS	-	Visual analogue scale