"COMPARISON OF DEXMEDETOMIDINE AND CLONIDINE INFUSIONS ON HAEMODYNAMIC STABILITY IN PATIENTS UNDERGOING LAPAROSCOPIC CHOLECYSTECTOMY – A DOUBLE BLIND RANDOMIZED CONTROLLED TRIAL"

By

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Dissertation

Submitted to the
KLE University, Belgaum, Karnataka

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M. D.
in
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Under the Guidance of

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I hereby declare that this dissertation entitled **"COMPARISON OF DEXMEDETOMIDINE AND CLONIDINE INFUSIONS ON HAEMODYNAMIC STABILITY IN PATIENTS UNDERGOING LAPAROSCOPIC CHOLECYSTECTOMY – A DOUBLE BLIND RANDOMIZED CONTROLLED TRIAL"** is a bonafide and genuine research work carried out by me under the guidance of **Dr. LATA KULKARNI** $_{\text{MD, DA}}$ Professor, Department of Anaesthesiology, Jawaharlal Nehru Medical College, Nehru Nagar, Belgaum-590010.

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LIST OF ABBREVIATIONS USED

ACTH	-	Adreno corticotropic hormone
ADH	-	Anti diuretic hormone
ASA	-	American Society of Anaesthesiologists
AUC	-	Area under curve
BIS	-	Bi-spectral index
CCIP	-	Computer controlled infusion protocol
C_{CSF}	-	CSF concentration
CI	-	Cardiac index
Cl	-	Clearance
CO	-	Cardiac output
CO_2	-	Carbon dioxide
C_P	-	Plasma concentration
CPP	-	Cerebral perfusion pressure
CSF	-	Cerebrospinal fluid
CVP	-	Central venous pressure
DBP	-	Diastolic blood pressure
DSST	-	Digit symbol substitution test
$ETCO_2$	-	End tidal carbon dioxide
FiO_2	-	Inspired oxygen concentration
FRC	-	Functional residual capacity
GFR	-	Glomerular filtration rate
HES	-	Hydroxy ethyl starch
HR	-	Heart rate
IAP	-	Intra abdominal pressure

ICP	-	Intracranial pressure
IV	-	Intravenous
kg	-	Kilogram
KPa	-	Kilo pascals
L	-	Litres
MAC	-	Minimum alveolar concentration
MAP	-	Mean arterial pressure
mcg	-	Microgram
mg	-	Milligram
ml	-	Millilitre
N_2O	-	Nitrous oxide
O_2	-	Oxygen
$PaCO_2$	-	Partial pressure of carbon dioxide
PACU	-	Post anaesthesia care unit
Pa-$ETCO_2$	-	End tidal carbon dioxide gradient
PAOP	-	Pulmonary artery occlusion pressure
PAP	-	Pulmonary artery pressure
PCWP	-	Pulmonary capillary wedge pressure
PNP	-	Pneumoperitoneum
POD	-	Post operative day
PRA	-	Plasma rennin angiotensin
PUO_2	-	Urine oxygen tension
PVR	-	Pulmonary vascular resistance
RAP	-	Right atrial pressure
RVEDVI	-	Right ventricular end diastolic volume index

RVEF	-	Right ventricular ejection fraction
SBP	-	Systolic blood pressure
SD	-	Standard deviation
SI	-	Stroke index
SVO_2	-	Mixed venous oxygen saturation
SVR	-	Systemic vascular resistance
U-NAG	-	Urine N-acetyl β-D-glucosaminidase
V/Q	-	Ventilation/Perfusion
VAS	-	Visual analogue scale
VR	-	Venous return
V^{SS}	-	Steady state volume of distribution

ABSTRACT

Background and Objectives

Laparoscopic Cholecystectomy is a routinely performed surgery and it is desirable to have a stable intraoperative haemodynamic status by avoiding hypertension, hypotension or tachycardia. The present study has been conducted to compare the beneficial effect of the two alpha 2 agonists Clonidine and Dexmedetomidine in maintaining the perioperative haemodynamic parameters during laparoscopic cholecystectomy.

Methods

The present Double Blind Randomized Control Trial was conducted in the Department of Anaesthesiology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum attached to Jawaharlal Nehru Medical College, Belgaum during the period of Dec 2010 to June 2011. A total of 45 patients randomly allocated in three groups, Group I (Placebo Group), Group II (Clonidine Group) & Group III (Dexmedetomidine Group) of 15 patients each, undergoing elective laparoscopic cholecystectomy, under general anaesthesia were studied. The patients received preloaded and coded study drug as infusion (normal saline, Clonidine 4 mcg/kg/hr and Dexmedetomidine 0.4 mcg/kg/hr respectively) at the rate of 0.08 ml/kg/hr.

Results

Sex, age, weight and duration of surgery were comparable in all the three groups. Both the drugs, Clonidine and Dexmedetomidine, maintained cardiovascular stability during laparoscopic cholecystectomy. But Clonidine

appears more effective in maintaining perioperative cardiovascular system stability during laparoscopic cholecystectomy. In addition the isoflurane requirement in Clonidine Group and Dexmedetomidine Group was found to be considerably lower when compared to Placebo Group. Also, the mean recovery time as indicated by the ability to vocalize following extubation was found to be significantly less in Clonidine Group and Dexmedetomidine Group.

Conclusion and interpretation

Clonidine being more cost effective than Dexmedetomidine can be recommended for maintaining cardiovascular system stability during laparoscopic cholecystectomy.

Keywords: Clonidine; Dexmedetomedine; Haemodynamic parameters; Laparoscopy cholecystectomy;

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INTRODUCTION

Haemodynamic stability during perioperative period is of paramount importance as there are many patients who have a compromised cardiovascular status and are on medication. Critical events during perioperative period like induction, intubation and surgical stimulus initiate metabolic response to trauma that need to be considered and attended. In recent years the laparoscopic surgeries which once upon a time were considered to cause least trauma are reported to have haemodynamic instability.

The anaesthesiologist's traditional approach to anaesthesia for laparoscopic cholecystectomy has been the emphasis on the maintaining haemodynamic stability by avoiding hypertension, hypotension or tachycardia. The problem has been more complex than has been originally thought and most of the haemodynamic instability is persistent during the duration of Pneumoperitoneum (PNP) namely Carbon Dioxide (CO_2) insufflations. Numerous agents and combination of agents has been used in an effort to minimize the haemodynamic instability during this period. Volatile agents like isoflurane and sevoflurane[1] have been used with limited success in maintaining haemodynamic stability as volatile agents decrease surgical stimulus induced catecholamine secretion. Opiods have traditionally been used for blunting the perioperative stress response during general anaesthesia. Although general anaesthesia prevents haemodynamic instability by rendering patients insensate to pain of surgery and discomfort, it is unable to completely eliminate the perioperative stress response.

General anaesthesia has been supplemented on occasions with intraoperative infusions of Propofol due to its intrinsic ability to inhibit catecholamine secretion, infusions of Nitro glycerine or Beta blockers, to control preioperative stress. Again combined general anaesthesia with epidural anaesthesia[2] is yet another strategy employed by anaesthesiologists to control perioperative haemodynamic instability, with limited success. But the search for the ideal agent to control this instability in haemodynamics is still on.

Laparoscopic surgeries require creation of pneumoperitoneum (PNP) which is produced by insufflations of Carbon Dioxide (CO_2) in the abdominal cavity by using automated flow controlled Carbon Dioxide Insufflator which supply gas till the required intrabdominal pressure is reached. Inflation pressure can be varied from 0 – 30 mm Hg where as the total gas flow volume can be set from 0 – 9.9 L/min.

Problems encountered during laparoscopic surgeries result from the combined effects of PNP with insufflations of carbon dioxide and patient positioning.[3]

After creation of PNP, Intra abdominal pressure increases along with the increase in circulating blood volume which is due to shifting of blood from the splanchnic capacitance blood vessel. Also, there is moderate increase in Intra Abdominal pressure which raises cardiac output and mean arterial pressure.[4] As Intra abdominal pressures rises circulating blood volume falls as venous return decreases and there is a fall in cardiac output.

This fall in cardiac output is troublesome in hypovolemic patients and patients receiving anaesthetic agents with cardiac depressant effects.

Laparoscopy induces significant haemodynamic changes and leads to increased Systemic Vascular Resistance (SVR) and Pulmonary Vascular Resistance (PVR), increases in Mean Arterial Pressure (MAP), reduction in Stroke Volume, Cardiac Output, and the mechanism is mechanically and humoral mediated.[5]

Alpha 2 Agonists produce diverse responses, including analgesia, anxiolysis, sedation, and sympatholysis, each of which has been reported in the treatment of surgical and chronic pain patients and in panic disorders as well. Recently, the Food and Drug Administration registered two novel alpha 2-adrenergic agonists Clonidine and Dexmedetomidine.[6]

Clonidine with a elimination half life of 6 to 10 hours is a centrally acting selective partial alpha 2 agonist (220:1 alpha 2 to alpha 1). It is known to induce sedation, decrease anaesthetic drug requirement and improve perioperative haemodynamics by attenuating blood pressure and heart rate responses to surgical stimulation, and protection against perioperative myocardial ischaemia. It provides sympathoadrenal stability and suppresses renin angiotensin activity. There are studies indicating benefits of using Clonidine for maintenance of haemodynamic stability in laparoscopic cholecystectomy.

Dexmedetomidine with a elimination half life of two to three hours is a highly selective and potent and specific alpha 2 agonist (1620 : 1 alpha 2 to alpha 1), and is seven to ten times more selective for alpha 2 receptors compared to

Clonidine, and has a shorter duration of action. Dexmedtomidine is considered full agonist at alpha 2 receptors as compared to Clonidine which is considered as a partial agonist. Similar to Clonidine, Dexmedetomidine, also attenuates the haemodynamic response to tracheal intubation, decreases plasma catecholamine concentration during anaesthesia and decreases perioperative requirements of inhaled anaesthetics.[7]

As Laparoscopic Cholecystectomy is a routinely performed surgery, it is desirable to have a stable intraoperative haemodynamic status. Hence in this study, it has been attempted to compare the beneficial effect of the two alpha 2 agonists Clonidine and Dexmedetomidine in maintaining the perioperative parameters like MAP, Heart Rate (HR).

OBJECTIVES

To compare the efficacy of Dexmedetomidine versus Clonidine on Cardiovascular System stability in patients undergoing Laparoscopic Cholecytectomy.

REVIEW OF LITERATURE

Over recent years, Laparoscopic Cholecystectomy has become the treatment of choice for calculous cholecystitis, as this procedure is associated with less postoperative pain, more rapid mobilization and a shorter hospital stay. However, in some cases, these advantages may be associated with increased perioperative risks. The increase of intra-abdominal pressure induced by the pneumoperitoneum and positioning during the procedure may lead to intraoperative haemodynamic instability and respiratory compromise.[8]

Laparoscopic cholecystectomy involves the insufflation of carbon dioxide into the peritoneal cavity producing a PNP, causing an increase in intra abdominal pressure (IAP). Carbon dioxide is insufflated into the peritoneal cavity at a rate of four to six L/min to a pressure of 10 to 14 mm Hg. The PNP is maintained by a constant gas flow of 200 to 400 mL/min. The raised IAP of PNP, alteration in patient's position and effects of CO_2 absorption cause changes in physiology especially in cardiovascular and respiratory system, and may have significant effect in elderly and patients with associated morbidity.

Large increases in lung and chest wall elastance as well as lung resistance occur with abdominal insufflation of carbon dioxide during laparoscopic surgery. To examine whether these effects were reversible with abdominal deflation, lung and chest wall elastances and resistances were calculate from measurement of airway flow and pressure and oesophageal pressure in 17 anesthetized/paralyzed patients undergoing laparoscopic surgery. Measurements were made immediately prior to abdominal insufflation and after deflation. Lung and chest wall elastance

and resistance were not changed from baseline ($p>0.05$), although total respiratory elastance remained slightly increased compared to baseline ($p<0.05$). The change in total respiratory elastance did not correlate with abdominal insufflation time, surgical site, smoking history, or physical characteristics of the patients. There were no differences in frequency and tidal volume dependences of the elastance and resistance before and after abdominal insufflation ($p>0.5$). It was concluded that residual changes in respiratory mechanics caused by carbon dioxide insufflation during laparoscopic surgery are minor, and that the reported compromise of respiratory function indicated by pulmonary function tests after laparoscopy does not appear to be due to changes in passive mechanical properties of the lungs or chest wall.[9]

A study was conducted to determine whether laparoscopy impairs cardiac performance when preventive measures to improve venous return are taken, and to analyze the effects of positioning, anaesthesia, and increased intra-abdominal pressure. Using invasive monitoring, hemodynamic changes were investigated in 15 ASA class I or II patients under Isoflurane-Fentanyl anesthesia during laparoscopic cholecystectomy. Before laparoscopy, the patients received an intravenous (IV) infusion of colloid solution if cardiac filling pressures were low, and their legs were wrapped from toes to groin with elastic bandages. Measurements were taken while the patients were awake in the supine (baseline) and head-up tilt (15 to 20 degrees) positions, and after the induction of anesthesia in the same positions. Measurements were repeated at regular intervals during laparoscopy (intra-abdominal pressure at 13 to 16 mm Hg), after deflation of the gas, and in the recovery room. It was found that 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 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 pre laparoscopic 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. It was concluded that by correcting relative dehydration and preventing the pooling of blood, CI 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.[10]

In another study, cardiovascular changes associated with insufflation of carbon dioxide and reverse Trendelenburg position during laparoscopic cholecystectomy were measured using Transesophageal echocardiography in 13 ASA I and II patients. End tidal carbon dioxide was increased in after insufflation of carbon dioxide with values significantly ($p<0.005$) increased after lateral positioning. Creation of pneumoperitoneum was associated with increases ($p<0.01$) in peak airway pressure and systemic arterial pressure. Left ventricular end diastolic area decreased ($p<0.05$) after reverse Trendelenburg positioning. Left ventricular ejection fraction was maintained throughout the study.[11]

A clinical descriptive study was conducted on 16 ASA III patients aged > 75 years undergoing laparoscopic cholecystectomy under general anaesthesia, being induced with Fentanyl and Etomidate and maintained on nitrous oxide (N_2O) in oxygen (O_2) (50%), Fentanyl and sevoflurane as needed, and inspired minute ventilation being kept constant during anaesthesia. Cardiovascular monitoring included a radial artery catheter and a pulmonary artery catheter for measurement of cardiac output (CO), right ventricular ejection fraction (RVEF) and mixed venous oxygen saturation (SVO_2) and calculation of Right ventricular end diastolic volume index (RVEDVI). Haemodynamic variables MAP, right atrial pressure (RAP), pulmonary artery pressure (PAP), pulmonary artery occlusion pressure (PAOP), arterial and venous blood gas samples were recorded before and 10 minutes after anaesthetic induction, 15, 30 and 60 minutes after insufflation (IAP=12 mm Hg) followed by a 10 degree head up tilt, and after exsufflation. The mean age was found to be 81±4 years. The main cardiovascular depression was recorded after anaesthetic induction. Peritoneal insufflation resulted in improvement of cardiovascular function with increase in CI (+19%), HR (+21%), MAP (+19%) and SVO_2 (+8%), ($p<0.05$), which can be the result of a sympathetic stimulation. No changes in preload RVEDVI and Systemic vascular resistance (SVR) were recorded. Cardiac index was unchanged during pneumoperitoneum. Laparoscopy was associated with an increase of partial pressure of carbon dioxide ($PaCO_2$), 15 minute after insufflation (from 33.9 to 38.3 mm of Hg, $p<0.05$) and a further increase after 60 min (44.4 mm Hg) without any sign of extra peritoneal diffusion. There was no change in the intrapulmonary shunt and the end tidal carbon dioxide gradient ($Pa\text{-}ETCO_2$)

gradient remained stable (mean 7.2 mm Hg). It was concluded that gradual intra abdominal insufflation to 12 mm Hg followed by a limited 10 degree head up tilt is associated with cardiovascular stability in elderly ASA grade III patients.[12]

Hemodynamics (invasive arterial pressure, PAP, RAP, PCWP, HR, CO, SVR and pulmonary vascular resistance (PVR) were measured during laparoscopic cholecystectomy under general anesthesia (isoflurane in N_2O/O_2 (50%)) were investigated in 15 non-obese ASA Class I patients by using invasive haemodynamic monitoring including a flow-directed pulmonary artery catheter. During surgery, intra abdominal pressure was maintained automatically at 14 mm Hg by a CO_2 insufflator, and minute ventilation was controlled and adjusted to avoid hypercapnia. Hemodynamics were measured before anesthesia, after the induction of anesthesia, after tilting into 10° head-up position, 5, 15, and 30 minutes after peritoneal insufflation, and 30 minutes after exsufflation. Induction of anesthesia decreased significantly mean arterial pressure and CI. Tilting the patient to the head-up position reduced cardiac preload and caused further reduction of CI. Peritoneal insufflations resulted in a significant increase (35%) of mean arterial pressure, a significant reduction (20%) of CI, and a significant increase of systemic (65%) and pulmonary (90%) vascular resistances. The combined effect of anesthesia, head-up tilt, and peritoneal insufflations produced a 50% decrease in CI. Administration of increasing concentrations of isoflurane, via its vasodilatory activity, may have partially blunted these hemodynamic changes. These results demonstrated that laparoscopy for cholecystectomy in head-up position results in significant hemodynamic changes in healthy patients, particularly at the induction of pneumoperitoneum. These haemodynamic

changes are mediated both mechanically and humorally. These cardiovascular changes are not hazardous in healthy patients, special care and monitoring is mandatory for patients with impaired cardiac function.[5]

Perioperative role of alpha 2 agonists

Haemodynamic stability and peri-operative Ischaemia

One of the goals of anaesthesia, in patients who are at risk of cardiac ischaemia during surgery, is to maintain myocardial oxygen balance and can be achieved by attenuating sympathetically mediated hyperdynamic responses to stimulation, while maintaining peri-operative circulatory function. The ability of alpha-2 adrenoceptor agonists to modulate sympathetic tone leads to a desirable haemodynamic profile, which may help to maintain the myocardial oxygen supply/demand ratio.[13]

A study reported that a minimum dose of 4 mcg/kg intravenous clonidine is required to significantly attenuate the stress response to laryngoscopy in patients undergoing cardiac revascularisation surgery. In addition, a significant reduction in peri-operative ischaemia was detected by monitoring critical ST depression in cardiac revascularisation patients who received clonidine 5 mcg/kg.[14]

Lesser adverse haemodynamic events were reported in 350 patients who received intravenous clonidine 4 mcg/kg at induction followed by 2 mcg/kg/hr infusion undergoing major abdominal surgery compared with the 52 controls. Only two episodes of severe hypotension and bradycardia were recorded in the

Clonidine group. The same authors compared the haemodynamic stabilizing effects of epidural Clonidine 4 mcg/kg at induction followed by an infusion of 1 mcg/kg/hr with epidural sufentanil 0.5 mcg/kg followed by 0.2 mcg/kg/hr in patients undergoing major abdominal surgery with Propofol and nitrous oxide anaesthesia.[15]

Another study reported that a target plasma concentration of Dexmedetomidine of 0.45 ng/mL administered to patients with coronary artery disease undergoing vascular surgery resulted in less peri-operative ischaemia compared with placebo.[16]

Sedation and anxiolysis

Clonidine has been used as a premedication drug. Administered in doses of 100 to 300 mcg, Clonidine produced dose-related sedation. A Clonidine dose of 4 mcg/kg given as premedication to children resulted in sedation and anxiolysis.

Dexmedetomidine has similar effects to Clonidine when administered for premedication. Its disadvantage is that at present it can only be given as an intramuscular or intravenous injection. Dexmedetomidine administered at an intramuscular dose of 2.5 mcg/kg as a premedication produced sedation and anxiolysis comparable with a Midazolam dose of 80 mcg/kg.

Both Clonidine and Dexmedetomidine causes anxiolysis independent of sedation.

Anaesthetic requirements

Continuing Clonidine therapy peri-operatively in hypertensive patients on long-term clonidine medication resulted in a less variable haemodynamic profile and no hypertensive crisis. The dose of thiopentone required for induction of anaesthesia is reduced by clonidine premedication.[17]

The effects of Clonidine in patients undergoing coronary artery bypass surgery was studied, comparing placebo against clondine premedication of 200 or 300 mcg orally with a second dose given via a nasogastric tube during cardiopulmonary bypass. The clonidine-treated patients were more sedated and required 40% less sufentanil than placebo patients. They had a lower heart rate and blood pressure than placebo patients throughout the whole operative period.[18]

Administration of an infusion of Dexmedetomidine in patients undergoing abdominal hysterectomy was able to reduced isoflurane requirements by 90%.[19]

Dexmedetomidine has also been reported to be opioid- and barbiturate sparing.

Analgesia

Paalzow was the first to show the analgesic effect of Clonidine. Alpha-2 adrenoceptor agonists have analgesic properties when given parenterally, epidurally or intrathecally.

Descending noradrenergic antinociceptive systems originating in the brainstem contribute to pain control by suppressing the spinal centripetal

transmission of nociceptive impulses. These pathways are activated by stimulation of the locus coeruleus and dorsal raphe nucleus and analgesia may be mediated by noradrenaline release. Alpha-2 adrenoceptors, predominately the alpha-2a subtype, have been identified in the substantia gelatinosa of the dorsal horn of the spinal cord. Stimulation of these alpha-2 adrenoceptors by intrathecal noradrenaline or specific agonists inhibits the firing of nociceptive neurones stimulated by peripheral Aδ and C fibres. Also, intrathecal noradrenaline inhibits the release of substance P by primary afferents of the dorsal horn, and suppresses the activity of wide dynamic range neurones evoked by noxious stimulation.

It has been suggested that the spinal cord is the major site of analgesic action of alpha-2 adrenoceptor agonists, the epidural and intrathecal routes have been considered preferable to the intravenous route.

The analgesic effects of an intravenous infusion of clonidine after major spinal surgery was reported in a study where either clonidine 5 mcg/kg during the first hour followed by 0.3 mcg/kg/hr for 11 hour was injected or a placebo. A visual analogue scale assessed pain. Intramuscular morphine was used to supplement analgesia if the pain scores were above 50%. In the clonidine group, pain onset was delayed, total morphine requirements were decreased significantly and pain scores reduced compared with placebo.[20]

The analgesic effects of intravenous dexmedetomidine (0.2 and 0.4 mcg/kg) were demonstrated after laparoscopic tubal ligation. Dexmedetomidine 0.4 mcg/kg was reported to provide analgesia requiring significantly less supplementation with morphine compared with the analgesia provided by

diclofenac 250 mcg/kg. There was a high incidence of sedation and bradycardia in the Dexmedetomidine 0.4 mcg/kg group, but there was no increase in respiratory depression and the bradycardia responded to atropine.[21]

Perioperative role of alpha 2 agonists

Clonidine and Dexmedetomidine the two alpha 2 agonists were compared with effect to metabolic and haemodynamic effects in 30 ASA I patients undergoing plastic surgical procedures under general anaesthesia. Patients were premedicated with Clonidine 4 mcg/kg, Dexmedetomidine 2.5 mcg/kg or Saline intramuscularly. The doses of Clonidine and Dexmedetomidine were intended to be equipotent. The maximum decrease in preoperative oxygen consumption was 8% and decreases in systolic and diastolic arterial blood pressure were 11% from baseline after Clonidine and Dexmedetomidine. During operation the maximum reduction in heart rate was 18% in the Clonidine and Dexmedetomidine groups compared to the placebo group. After operation the maximum decrease in systolic arterial pressure was 11%, diastolic arterial pressure was 15% and oxygen consumption 17% in Clonidine and Dexmedetomidine group compared with placebo.[22]

Forty patients undergoing lumbar discectomy received Dexmedetomidine 1 mcg/kg over 10 minute followed by infusion of 0.2 mcg/kg or saline. Mean arterial Blood pressure, HR, CO and level of anaesthesia were recorded after both the groups were induced with Fentanyl, thiopentone, and rocuronium and were maintained with Desflurane in 50% Nitrous. It was found that the recovery time

were significantly shorter, and anaesthetic and analgesic requirement were significantly lesser in Dexmedetomidine group than the saline group.[23]

In one a prospectively randomized, double-blinded crossover study, volunteers received either placebo or low- or high dose Dexmedetomidine (target plasma concentrations 0.3 or 0.6 ng/mL, respectively) infusions. After 1 hour, baroreflex sensitivity was assessed, and then core body temperature was raised to the sweating threshold and then lowered to the shivering threshold. Plasma catecholamines and blood pressure were measured, and cardiac autonomic responses were assessed by analysis of heart rate variability. It was found that in comparison with placebo, plasma norepinephrine concentrations, blood pressure, heart rate, and some heart rate variability measures were lower after 1 hour infusion of Dexmedetomidine, but baroreflex responses did not differ significantly. Dexmedetomidine blunted the systemic and cardiac sympathetic effects of sweating observed during placebo infusion but had no effect on parasympathetic measures. Increases in blood pressure, and systemic catecholamines due to shivering were observed during placebo and Dexmedetomidine, but these responses were less with Dexmedetomidine. It was concluded that infusion of Dexmedetomidine resulted in compensated reductions in systemic sympathetic tone without changes in baroreflex sensitivity and Dexmedetomidine blunts heart rate and the systemic sympathetic activation due to sweating, but was less effective in blunting cardiac sympathetic responses to shivering.[24]

In another double blind study forty ASA Physical status I, non pregnant women scheduled for Dilatation and Curettage were investigated for vigilance,

thiopentone anaesthetic requirement and haemodynamic, catecholamine and hormonal response to surgery. Patients were divided in two groups and received either Dexmedetomidine (0.5 mcg/kg) or saline fifteen minutes before being induced with thiopentone and maintained on O_2:N_2O = 30:70 and thiopentone. It was found that the total amount of thiopentone needed to perform the surgery was reduced by approximately 30%, which was due to smaller induction doses in group receiving Dexmedetomidine. Also the plasma concentration of norepinephrine was decreased by 56% in Dexmedetomidine group implying decreased sympathetic activity. However, systolic and diastolic blood pressure were only moderately increased.[25]

Ten healthy men between 20 and 27 years were monitored with electrocardiography (ECG), MAP, CVP and PAP, CO, O_2 saturation, end-tidal carbon dioxide (ETCO2), respiration, blood gas, and catecholamines. Hemodynamic measurements, blood sampling, and psychometric, cold pressor, and baroreflex tests were performed at rest and during sequential 40 minute IV target infusions of Dexmedetomidine (0.5, 0.8, 1.2, 2.0, 3.2, 5.0, and 8.0 ng/mL and baroreflex testing only at 0.5 and 0.8 ng/mL). It was found that the initial dose of Dexmedetomidine decreased catecholamines 45 to 76% and eliminated the norepinephrine increase that was seen during the cold pressor test. Catecholamine suppression persisted in subsequent infusions. The first two doses of Dexmedetomidine increased sedation 38 and 65%, and lowered mean arterial pressure by 13%, but did not change central venous pressure or pulmonary artery pressure. At subsequent higher doses increased sedation, all pressures, and calculated vascular resistance occurred, and resulted in significant decreases in

heart rate, cardiac output, and stroke volume. Recall and recognition decreased at a dose of more than 0.7 ng/mL. The pain rating and mean arterial pressure increase to cold pressor test progressively diminished as the Dexmedetomidine dose increased. The baroreflex heart rate slowing as a result of phenylephrine challenge was potentiated at both doses of Dexmedetomidine. Respiratory variables were minimally changed during infusions, whereas acid–base was unchanged. It was observed that increasing concentrations of Dexmedetomidine resulted in progressive increases in sedation and analgesia, decreases in heart rate, cardiac output, and memory.[26]

Fifty patients scheduled for elective minor surgery were randomised into two groups (Dexmedetomidine group and placebo group, n=25 in each group). During and after drug administration, the Ramsay sedation scale was applied every five minutes. Fentanyl 1 μg/kg was administered to all patients and thiopental was given until eye lash reflex disappeared. Anaesthesia continuation was maintained with 50%**:**50%, O_2**:**nitrous oxide. Sevoflurane concentration was adjusted to maintain systolic blood pressure within 20% of preoperative values. After extubation, the Steward awakening score was applied at 5 and 10 minutes. Haemodynamic parameters and adverse effects were recorded every 10 minutes for one hour after surgery. It was found that during intubation the need for thiopental and sevoflurane concentration were decreased by 39% and 92%, respectively, in the Dexmedetomidine group compared with the placebo group. In all groups, blood pressure and heart rate increased after tracheal intubation; both were significantly lower in the Dexmedetomidine group than in the placebo group ($p < 0.05$). Fentanyl requirement during the operation was 74.20 ± 10.53μg

in the Dexmedetomidine group and 84.00 ± 27.04μg in the placebo group ($p<0.05$). At five minutes, the Steward scores were more than six in 56% of the Dexmedetomidine group and in four percent of the placebo group ($p<0.05$). At 10 minutes, sedation scores were more than or equal to foud in all patients in the Dexmedetomidine group ($p<0.05$). Arterial blood pressure and heart rate in the postoperative period were significantly lower in the Dexmedetomidine group compared with the placebo group ($p<0.05$).[27]

Dexmedetomidine has anaesthetic sparing effects. The pharmacokinetics and pharmacodynamic interaction between Dexmedetomidine and isoflurane has been determined in volunteers in a study. Nine male volunteers were allocated randomly to receive isoflurane anaesthesia preceded by Dexmedetomidine infusion on three separate occasions two weeks apart. Target plasma concentration of low Dexmedetomidine group was 0.3 ng/mL and high Dexmedetomidine group was 0.6 ng/mL. End tidal isoflurane concentration at which gross purposeful movement and response to verbal command occurred were recorded. Venous blood samples for measurement of plasma concentration of Dexmedetomidine and calculation of standard pharmacokinetic indices like area under the curve (AUC), systemic clearance (Cl), steady state volume of distribution (V^{ss}), etc were obtained before, during and after anaesthesia at predetermined intervals. The end tidal isoflurane concentration at which 50% of the subjects first responded to stimulus was 1.05%, 0.72% and 0.52% in placebo group, low Dexmedetomidine group and high Dexmedetomidine group respectively. During anaesthesia the mean values for heart rate, systolic arterial pressures and diastolic arterial pressures were significantly less ($p=0.003$, >0.001,

0.009 respectively) after both ; low dose and high dose Dexmedetomidine infusions compared to placebo. There were 12 hypotensive events in five subjects requiring observer intervention. Sedation and slight impairment of cognitive function persisted for several hours after anaesthesia and end of Dexmedetomidine infusion. Isoflurane did not appear to influence the pharmacokinetics of Dexmedetomidine.[28]

Dexmedetomidine was studied for its ability to attenuate stress responses during emergence from anesthesia after major vascular operations. Patients scheduled for vascular surgery received either Dexmedetomidine (n=22) or placebo (n=19) IV beginning 20 minutes before the induction of anesthesia and continuing until 48 hour after the end of surgery. All patients received standardized anesthesia. Heart rate and arterial blood pressure were kept within predetermined limits by varying anesthetic level and using vasoactive medications. Heart rate, arterial blood pressure, and inhaled anesthetic concentration were monitored continuously; additional measurements included plasma and urine catecholamines. During emergence from anesthesia, heart rate was slower with Dexmedetomidine (73±11 bpm) than placebo (83±20 bpm) ($p=0.006$), and the percentage of time the heart rate was within the predetermined hemodynamic limits was more frequent with Dexmedetomidine ($p<0.05$). Plasma norepinephrine levels increased only in the placebo group and were significantly lower for the Dexmedetomidine group during the immediate postoperative period ($p=0.0002$). It was concluded that Dexmedetomidine attenuates increases in heart rate and plasma norepinephrine concentrations during emergence from anaesthesia.[29]

In another study 72 patients, scheduled for elective craniotomy were randomly assigned to receive either sevoflurane–opioid or sevoflurane–opioid–Dexmedetomidine anaesthesia. Bispectral index was used to maintain a similar level of hypnosis in both groups (40 to 50). Opioids, sevoflurane, and vasoactive medications were titrated in a routine manner, at the discretion of the blinded anesthesiologist managing the case, to maintain systolic blood pressure (SBP) targeted within 90 to 130 mm Hg and HR between 50 and 90 bpm. Hemodynamic variables were continuously recorded and stored on a computer for analysis. Efficacy of the anesthetic technique in controlling SBP or HR is inversely proportional to the AUC outside the targeted range. Areas under the curves above and below targeted ranges for SBP - time (AUCsbp mm Hg * min/h) and HR-time (bpm * min/h) were compared. Coefficient of variation was used to assess hemodynamic stability. Computerized records of 56 patients only were analyzed because of technical problems with data collection in 14 cases. AUCsbp for above the targeted range was significantly lower for patients in the Dexmedetomidine group (p=0.044). The coefficient of variation for SBP or HR did not differ between groups. A significantly smaller proportion of patients in the Dexmedetomidine group required treatment with antihypertensive medications (12 of 28, 42% vs 24 of 28, 86%, *P*=0.0008). The Dexmedetomidine group required fewer opioids in the intraoperative period, but there were no differences in the use of sevoflurane. In the postanesthesia care unit, patients in the Dexmedetomidine group had fewer hypertensive episodes (1.25±1.55 vs 2.50±2.00, p=0.0114) and were discharged earlier (91±17 vs 130±27 min, p=0.0001). There were no differences in the requirement for postoperative

opioids or antiemetic. By using indices, which assess a global hemodynamic stability of the anaesthetic, it was determined that intraoperative Dexmedetomidine infusion was effective for blunting the increases in SBP perioperatively. The use of Dexmedetomidine did not increase the incidence of hypotension or bradycardia.[30]

A study evaluated: 1) pharmacokinetics of Dexmedetomidine in plasma and cerebrospinal fluid (CSF) in surgical patients; 2) precision of a computer-controlled infusion protocol (CCIP) for Dexmedetomidine during the immediate postoperative period; and 3) Dexmedetomidine sympatholytic effects during that period. Dexmedetomidine was infused postoperatively by CCIP for 60 min to eight women, targeting a plasma concentration (Cp) of 600 pg/mL. Before, during, and after infusion, blood was sampled to determine plasma concentrations of norepinephrine, epinephrine, and Dexmedetomidine, and CSF was sampled to determine Dexmedetomidine concentrations (Ccsf). Heart rate and arterial blood pressure were measured continuously from five minutes before until three hour after the end of infusion. During the infusion, Cp values generally exceeded the target value. Median percent error averaged 21% and ranged from -2% to 74%. Median absolute percent error averaged 23% and ranged from 4% to 74%. After infusion, Ccsf was 4% ±1% of Cp. During the infusion, norepinephrine decreased from 2.1±0.8 to 0.7±0.3 nmol/L, epinephrine decreased from 0.7±0.5 to 0.2±0.2 nmol/L, HR decreased from 76±15 to 64±11 bpm and SBP decreased from 158±23 to 140±23 mm Hg. It was concluded that infusion of Dexmedetomidine by CCIP using published pharmacokinetic parameters overshoots target Dexmedetomidine concentrations during the early postoperative period.

Hemodynamic and catecholamine results suggest that Dexmedetomidine attenuates sympathetic activity during immediate postoperative period.[31]

A study was devised to define the interaction between intravenous infusion of Dexmedetomidine and isoflurane in patients undergoing abdominal hysterectomy by using minimum alveolar concentration (MAC) of isoflurane as the measure of anaesthetic potency in forty nine women, randomly allocated to receive either a placebo infusion (n=16) or a two staged infusion of Dexmedetomidine with target plasma concentration of of 0.3 ng/mL (n=17) or 0.6 ng/mL (n=16). Study drug was started 15 minutes before induction with thiopentone and alfentanil, and was continued until skin incision. The end tidal concentration of isoflurane for each patient was predetermined according to the 'up down method' of Dixon and it was maintained for at least 15 minutes before the patient response to skin incision was assessed. It was found that the MAC of isoflurane was 0.85% end tidal in control group, 0.55% end tidal with the low dose Dexmedetomidine and 0.45% end tidal with high dose Dexmedetomidine. The MAC of isoflurane was lower in the control group, probably due to anaesthetic induction with thiopentone and alfentanil. However with high dose Dexmedetomidine the MAC value of isoflurane was 17% less than without Dexmedetomidine.[32]

Clonidine 5 mcg/kg causes a 45% reduction in Fentanyl requirement in patients given as premedication. The same dose also reduced the haemodynamic response to tracheal intubation.[33]

In a study 46 ASA I-II patients undergoing thyroid surgery, were designed to assess the interference of Clonidine with recovery from anaesthesia. Patients were allocated randomly to three groups to receive, 2 hour before surgery, flunitrazepam 1 mg, Clonidine 150 micrograms, or both drugs. Anaesthesia comprised thiopentone, alfentanil, isoflurane and 70% nitrous oxide in oxygen. Recovery from anaesthesia was assessed using a clinical score, electro-oculographic measurements and reaction times to auditory stimuli. Psychomotor tests were performed the day before surgery and 30, 60, 120 and 240 minute after arrival of the patient in the recovery room. Psychomotor performance was decreased significantly after operation in the three groups ($p<0.05$) and returned to baseline at 240 minutes. There was no significant difference between the three groups. This study indicates that Clonidine 150 μg orally before surgery does not delay recovery from anaesthesia.[34]

Eighty healthy subjects, aged 22 to 30 years, enrolled in a placebo controlled randomized study, evaluated on separate days, which evaluated the dose response relationships for one hour infusions of clonidine 1, 2 and 4 mcg/kg/hr. Response end points included sedation (Bi spectral index, visual analogue scale (VAS) and observer assessment of sedation), analgesia to a cold pressor test, memory (recall of word list) cognitive function, (digit symbol substitution test DSST), respiratory function (respiratory rate, end tidal carbon dioxide, oxygen saturation), and haemodynamic stability (heart rate and mean arterial pressure). Clonidine infusions resulted in significant and progressive sedation but all subjects were easily awoken to perform test and evaluation. It

was also found that clonidine infusions lowered heart rate and mean arterial pressure.[35]

Laparoscopic surgery and Clonidine

Both mechanical and neuroheumoral factors contribute to the hemodynamic changes induced by carbon dioxide PNO. Several mediators have been proposed. Two studies were conducted, to investigate the endocrine correlates of the hemodynamic changes induced by carbon dioxide pneumoperitoneum (PNP), and also studied whether Clonidine might modulate the hemodynamic changes induced by PNP by reducing release of catecholamines and vasopressin. Each study included 20 healthy patients scheduled for elective laparoscopic cholecystectomy. In the first study serial measurements of hemodynamics (thermodilution technique) were done during laparoscopy and after exsufflation. Plasma concentrations of cortisol, catecholamines, vasopressin, renin, endothelin and prostaglandins were measured at the same time points. In the second study patients were randomly allocated to receive 8 mg/kg clonidine infused over one hour or placebo before PNP. Hemodynamics and plasma levels of cortisol, catecholamines and vasopressin were measured during PNP and after exsufflation. Peritoneal insufflation resulted in a significant reduction of cardiac output (18±4%) and increases in mean arterial pressure (39±8%) and systemic (70±12%) and pulmonary (98±18%) 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 PNP (before PNP 6±4 pg/mL; during PNP 129±42 pg/mL;

p<0.05). The profile of vasopressin release paralleled the time course of changes in systemic vascular resistance. Prostaglandins and endothelin did not change significantly. Clonidine significantly attenuated the increase in MAP placebo + 28±7 mm Hg versus Clonidine +15±5 mm Hg, p=0.07), HR and the increase in systemic vascular resistance. Clonidine also significantly reduced catecholamine concentrations but did not alter vasopressin and cortisol plasma concentrations. Vasopressin and catecholamines probably mediate the increase in systemic vascular resistance observed during PNP. Clonidine before PNP reduces catecholamine release and attenuates hemodynamic changes during laparoscopy.[36]

Sixty adult patients of ASA physical status I and II, scheduled for elective laparoscopic cholecystectomy were recruited for a prospective randomized, double-blinded comparative study and were randomly allocated to one of the two groups to receive either oral clonidine 150 mcg (Group C) or ranitidine 150 mg (Group P), 90 minute before induction of anaesthesia. Significant rise in HR was observed following PNP in Group P as compared to Group C (99.23±14.02 Vs 81.26±8.40 bpm) was observed. Similarly, rise in systolic arterial pressure (143.63±19.60 Vs 119.6±10.06 mm Hg), diastolic arterial pressure (99.23±14.02 Vs 81.26±8.40 mm Hg) and MAP (114.13±16.57 Vs 93.83±8.107 mm Hg) was more in Group P following PNP. Nitroglycerine drip was started in 33.3% patients in Group P to control intraoperative hypertension. Incidence of postoperative nausea-vomiting and shivering was also less in Group C. It was concluded that clonidine premedication provides perioperative haemodynamic stability.[37]

Clonidine has anti-hypertensive properties and augments the effects of anaesthesia. The clinical efficacy of oral clonidine premedication was studied in fifty patients undergoing laparoscopic cholecystectomy under general anaesthesia. Patients were randomly allocated to receive premedication with either oral clonidine 150 μg (Group I, n=25) or placebo (Group II, n=25) 90 minutes prior to induction. The patients were managed with a standard general anaesthetic. The two groups were compared with respect to haemodynamic parameters, isoflurane concentration, pain and sedation scores, time to request of analgesic and cumulative analgesic requirements. Oral clonidine was found to be significantly better in terms of maintaining stable hemodynamics, having an isoflurane sparing effect and having a prolonged time interval to the first request of analgesia postoperatively compared to the control group. Perioperatively, the MAP was lower in group I compared to group II. MAP ranged from 88.77±7.99 to 102.41±10.35 mm Hg in group I, whereas it ranged from 96.99±6.37 to 114.8±14.08 mm Hg in group II. The difference in the MAP value between the two groups was significant at all time points except at 15 min after the release of pneumoperitoneum. Similarly perioperatively the mean HR was lower in group I as compared to group II. Mean HR ranged from 79.28±9.50 to 85.84±10.12 bpm in group I, whereas it ranged between 83.80±12.76 to 100.04±12.16 bpm in group II. Administration of oral clonidine 150 μg as a premedicant in patients undergoing laparoscopic cholecystectomy results in improved perioperative haemodynamic stability and a reduction in the intra-operative anaesthetic requirements.[38]

A prospective randomized double blinded study was conducted among 30 healthy patients undergoing elective laparoscopic Cholecystectomy, divided among two groups where fifteen patients received clonidine 4.5 mcg/kg (clonidine group) and rest fifteen received (control group) received the same volume of saline intramuscularly with oral premedication using diazepam (0.2 mg/kg). Before the induction of anaesthesia, acetated Ringer's solution 8 mL/kg was given intravenously. During operation, Ringer solution 10 mL/kg/hr was given along with Hydroxyethyl starch (HES) 500 ml. All patients received glycopyrollate 4 mcg/kg before induction of anaesthesia, and standardized anaesthesia with Midazolam 1 mg, Propofol 2 to 3 mg/kg, and alfentanil 20 mcg/kg IV. Endotracheal intubation was facilitated using cis atracurium 0.15 mg/kg. Anaesthesia was maintained with isoflurane 1 MAC in O_2 (FiO2 0.4). Before initiating laparoscopy, alfentanil 20 mcg/kg bolus followed by infusion was given. An increase in MAP or HR more than 20% of the basal was treated by increase in alfentanil infusion rate. Patients were mechanically ventilated keeping EtCo2 between 4.5 to 5 KPa. HR, MAP, CVP, IAP were recorded at 5 min interval during the surgery. Blood and urine samples for assessment of plasma rennin angiotensin (PRA), serum antidiuretic hormone (ADH), and urine N acetyl β – D- glucosaminidase (U-NAG) and Creatinine were taken before skin incision, then 15, 30 and 60 min after induction of pneumoperitoneum, after 60 and 180 minutes in postanesthesia care unit (PACU) and on the 1^{st} post operative day. Urine oxygen tension (PuO2) was determined at skin incision, every 10 minutes during laparoscopy, at arrival in PACU, and at 30, 60, 120 and 180 min of recovery period the total amount of intraoperative fluid, drug and CO_2 were

recorded. It was found that HR, arterial blood pressure, and plasma renin activity were lower during and after PNO in patients with Clonidine. There were no differences in urine output PuO_2 or ADH between the two groups. U–NAG, was minimally elevated after Clonidine. It was found that Clonidine enables stable hemodynamics, and prevented activation of Renin-Angiotensin-Aldosterone-System, and Clonidine may be beneficial during laparoscopy.[39]

Laparoscopic surgery and Dexmedetomidine

Eighty consenting ASA II–III morbidly obese patients were randomly assigned to 1 of 4 treatment groups: (1) control group received a saline infusion during surgery, (2) Dex 0.2 group received an infusion of 0.2 mcg/kg/hr Dexmedetomidine IV, (3) Dex 0.4 group received an infusion of 0.4 mcg/kg/hr Dexmedetomidine IV, and (4) Dex 0.8 group received an infusion of 0.8 mcg/kg/hr Dexmedetomidine IV. Mean arterial blood pressure values were maintained within ±25% of the preinduction baseline values by varying the inspired Desflurane concentration. Perioperative hemodynamic variables, postoperative pain scores, and the need for "rescue" analgesics and antiemetic were recorded at specific intervals. Follow-up evaluations were performed on postoperative days (PODs) one, two, and seven to assess severity of pain, analgesic requirements, patient satisfaction with pain management, quality of recovery, as well as resumption of dietary intake and recovery of bowel function. Dexmedetomidine infusion, 0.2, 0.4, and 0.8 mcg/kg/hr, reduced the average end tidal Desflurane concentration by 19, 20, and 22%, respectively. However, it failed to facilitate a significantly faster emergence from anaesthesia. Although the intraoperative hemodynamic values were similar in the four groups, arterial blood

pressure values were significantly reduced in the Dex 0.2, 0.4, and 0.8 groups compared with the control group on admission to the PACU ($p<0.05$). The length of the PACU stay was significantly reduced in the Dex groups (81±31 to 87±24 vs 104 ±33 min in the control group, $p<0.05$). The amount of rescue Fentanyl administered in the PACU was significantly less in the Dex 0.2, 0.4, and 0.8 groups versus control group (113 ±85, 108± 67, and 120 ±78 vs 187 ±99 mcg, respectively, $p<0.05$). The percentage of patients requiring antiemetic therapy was also reduced in the Dex groups (30, 30, and 10% vs 70% in the control group). However, the patient-controlled analgesia morphine requirements on PODs 1 and 2 were not different among the four groups. Pain scores in the PACU, and on PODs one, two, and seven, in the three Dex groups were not different from the control group. Finally, quality of recovery scores and times to recovery of bowel function and hospital discharge did not differ among the four groups. To conclude adjunctive use of an intraoperative Dexmedetomidine infusion (0.2 to 0.8 mcg/kg/hr) decreased Fentanyl use, antiemetic therapy, and the length of stay in the PACU. However, it failed to facilitate late recovery (bowel function) or improve the patients' overall quality of recovery. When used during bariatric surgery, a Dexmedetomidine infusion rate of 0.2 mcg/kg/hr is recommended to minimize the risk of adverse cardiovascular side effects.[40]

A randomized double blind prospective clinical study designed to evaluate the efficacy of Dexmedetomidine to provide perioperative haemodynamic stability in sixty patients, of either sex (18 to 65 years of age) undergoing elective laparoscopic cholecystectomy, randomly allocated in one of the two parallel groups containing 30 patients each. Group D received

Dexmedetomidine intravenous infusion at a rate of 0.2 μg/kg/hr. Group S received 0.9% saline in the same rate. Mean arterial pressure and HR in Group D were significantly less after intubation and throughout the period of pneumoperitoneum. No significant differences in the parameters of recovery were observed between the two groups. Dexmedetomidine improved intra and post-operative haemodynamic stability during laparoscopic surgery without prolongation of recovery.[41]

BASIC SCIENCES

I. Physiology of Laparoscopy

   a. Physiological effect of pneumoperitoneum

   b. Physiological effect of positioning

   c. Physiological effects of carbon dioxide absorption

   d. Effects of gas insufflation

II. Physiology of alpha 2 adrenoreceptors

III. Pharmacology of alpha-2 agonists

I. PHYSIOLOGY OF LAPARSCOPY

a. Physiological effects of Pneumoperitoneum

Cardiovascular System

Increased IAP affects venous return (VR), SVR and myocardial function. Initially owing to auto transfusion of pooled blood from splanchnic circulation, there is an increase in circulating blood volume, resulting in an increase in VR & cardiac output. Further increase in IAP results in compression of inferior vena cava, reduction in VR and subsequent decrease in cardiac output. Systemic Vascular Resistance increases because of direct effects of IAP, but also because of increase in release of circulating catecholamines, epinephrine and norepinephrine. Change in SVR is greater than the reduction in cardiac output, leading to an increase in cardiac output. Increase in SVR, systolic and diastolic pressures and tachycardia leads to an increase in myocardial workload, and myocardial ischaemia may result. Further, increase in IAP, leads to decreased cardiac output with a subsequent fall in blood pressure.

The effects of general anesthetics and intravascular volume on hemodynamic function during creation of PNO also have been investigated. A study[42] reported a 35% reduction in inferior vena caval blood flow and cardiac output of dogs when intraperitoneal insufflation of N_2, N_2O, and CO_2 produced an IAP of 40 mm Hg during basal pentobarbital anesthesia. The combination of 1.0 minimum alveolar anaesthetic concentration (MAC) of halothane and hypovolemia (resulting from 15% blood volume loss) decreased the pre induction

cardiac output more than either halothane anesthesia alone, or the induction of hypovolemia alone.

Another study[43] compared the hemodynamic effects of 2 kPa (15 mm Hg) IAP pressure to those due to a 30 degree Trendelenburg tilt in a prospective study of 16 mechanically ventilated patients, randomized to receive either halothane anesthesia or balanced anesthesia with meperidine and thiopental. It was found that irrespective of the anaesthetic technique used, an IAP of 15 mm Hg or a 30 degree head-down tilt produced similar reductions in cardiac index which were accompanied by significant elevations in systemic vascular resistance.

Respiratory System

The supine position and general anaesthesia decreases functional residual capacity (FRC). Pneumoperitoneum and Trendelelenburg position cause cephalad shift of the diaphragm, further decreasing FRC, to values less than the closing volume, causing airway collapse, atelectasis, ventilation perfusion (V/Q) mismatch , potential hypoxaemia and hypercarbia. There is an increase in airway resistance and decrease in compliance which potentiates the risk of barotrauma with positive pressure ventilation.

A reduction in FRC relative to closing volume may be associated with the development of intraoperative atelectasis and intrapulmonary shunting. These changes may occur during general anesthesia because of a variety of factors:

a. Cephalad shift of the diaphragm associated with supine position.[44]
b. Loss of inspiratory muscle tone.

c. Appearance of endexpiratory muscle tone in the abdominal expiratory muscles.
d. Changes in intrathoracic blood volume associated with induction of anesthesia.
e. Influence of muscle relaxants on diaphragmatic excursion.[45]

The reduction in FRC associated with general anesthesia may be compounded by the CO_2 induced pneumoperitoneum during laparoscopic cholecystectomy. A reduced cardiac output secondary to reduction in venous return or drug-induced myocardial depression may reduce mixed-venous O_2 tension.

Renal System

Marked increased IAP reduces renal function and urine output owing to increase in renal vascular resistance and reduction in glomerular filtration rate (GFR), which is compounded by the decrease in cardiac output.

Gastrointestinal System

Increased IAP cause regurgitation of gastric contents with associated risk of pulmonary aspiration and is particularly significant in obese patients.

Nervous System

Intracranial pressure (ICP) is increased by the rise in IAP which may result in decrease in cerebral perfusion pressure (CPP), and especially when there is decrease in cardiac output.

b. Physiological effect of positioning

Trendelenburg position

Respiratory effects include further decrease in FRC, more V/Q mismatch and greater risk of atelectasis. Endobronchial intubation, attributable to cephalad movement of lungs and carina in relation to fixed endotracheal tube, should be prevented. Initially there is an increase in venous return with subsequent increase in cardiac output but this causes compensatory vasodilatation. Increased venous return with Trendelenburg position may not be tolerated in patients with compromised myocardial compliance.[46]

Reverse Trendelenburg position

There are few respiratory effects in reverse Trendelenburg position but more marked effects on cardiovascular system. A decrease in venous return results in decreased cardiac output and blood pressure more marked in hypovolaemic and cardiovascular compromised patients.[47]

c. Physiological effects of carbon dioxide absorption

Carbon dioxide is the most commonly used gas for insufflation of abdomen as it is colourless, non toxic, non flammable, and has greatest margin of safety in event of venous embolism as it is highly soluble. It is absorbed readily from peritoneum causing an increase in $PaCO_2$. This has direct as well as indirect (by raising catecholamine level),[48] effects on cardiovascular system. Thus, tachycardia, decreased cardiac contractility, and reduction in diastolic filling can

result in decreased myocardial oxygen supply to demand ratio and greater risk of myocardial ischaemia.

d. Effects of gas insufflation

Arrhythmias

Nodal rhythm, sinus bradycardia and asystole attributable to vagal stimulation can be initiated by stretching of peritoneum. Such effects are more pronounced at the beginning of insufflation because of rapid stretching of peritoneum.[49]

Subcutaneous emphysema, pneumomediastinum, and pneumothorax

It may occur because of incorrect positioning of gas insufflation needles or trocars, anatomical anomalies or by gas dissecting across weak tissue planes attributable to increased abdominal pressures.[50]

Venous gas embolism

It is a rare, but a potentially fatal complication. It may occur if CO_2 is insufflated directly into a blood vessel or by gas being drawn into an open vessel by venture effect. Hypotension, desaturation and a mill wheel murmur may result. Treatment includes rapid deflation of abdomen and resuscitation of the patient.[51]

Trauma

Introduction of trocars may cause damage to underlying organs eg intestine, liver, spleen), which may not be diagnosed immediately at the time of

surgery. Damage to blood vessels may occur, resulting in massive haemorrhage, which may require an open procedure.

II. PHYSIOLOGY OF ALPHA 2 ADRENORECEPTORS

Structure of alpha-2 adrenoceptors

The alpha-2 adrenoceptor is a transmembrane receptor. This is an excitable protein which traverses the cell membrane and reacts selectively with extracellular ligands (endogenous hormones or exogenous molecules such as drugs) to initiate a cascade of events leading to a physiological effect. The long chain of amino acids making up the alpha-2 adrenoceptor protein contains hydrophobic and hydrophilic areas. It winds in and out of the cell membrane, crossing the cell membrane seven times at the hydrophobic areas. The seven hydrophobic segments are made up of 20 to 25 amino acids forming alpha helices that are embedded in the membrane. The three alpha-2 receptor subtypes are 72–75% identical to each other with respect to amino acid sequence in the membrane-spanning domains.

To bind a ligand, a receptor must have charged counterbalancing ions located within it, but the transmembrane region itself is nonpolar. The structure of the ligand determines whether it has agonistic or antagonistic effects on the receptor. Mutation of amino acids in these regions affects the binding of agonists and antagonists and their physiological effects. The cytoplasmic aspect of the receptor protein forms a contact point for the G-protein providing a means of signal transduction and therefore rapid stimulation of the effector system.[52]

Distribution of alpha-2 adrenoceptors

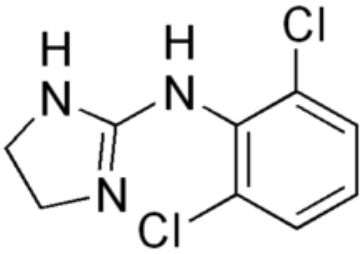
Presynaptic alpha-2 adrenoceptors are present in sympathetic nerve endings and noradrenergic neurones in the central nervous system where they inhibit the release of noradrenaline. Postsynaptic alpha-2 adrenoceptors exist in a number of tissues where they have a distinct physiological function. These include the liver, pancreas, platelets, kidney, adipose tissue and the eye. The medullary dorsal motor complex in the brain has a high density of alpha-2 adrenoceptors and activation of these may be responsible for the hypertensive and bradycardic effects of alpha-2 adrenoceptor agonists.[53]

The locus coeruleus is a small neuronal nucleus located bilaterally in the upper brainstem and is the largest noradrenergic cell group in the brain. The locus coeruleus is an important modulator of wakefulness and may be the major site for the hypnotic action of alpha-2 adrenoceptor agonists mediated by alpha-2a adrenoceptors located there.[54]

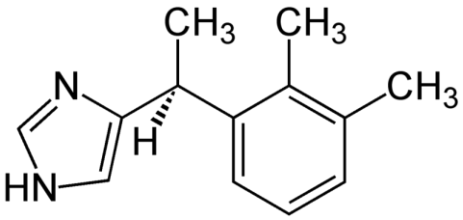
The locus coeruleus has a number of efferent connections. Cortical activity is influenced by the connection with the subthalamic relay nucleus and the thalamus via noradrenergic fibres. Nociceptive transmission at a spinal level is decreased via descending fibres in the dorsolateral funiculus tracts. There are also efferent fibres to the reticular formation with connections to the vasomotor centres. There are afferent connections from the rostral ventrolateral medullary nuclei. A high density of alpha-2 adrenoceptors has also been demonstrated in the vagus nerve, intermediolateral cell column and the substantia gelatinosa. The dorsal horn of the spinal cord contains alpha-2a subtype adrenoceptors, while the

primary sensory neurones contain both alpha-2a and alpha-2c subtypes of adrenoceptors.

III. PHARMACOLOGY OF ALPHA-2 RECEPTOR AGONISTS



Clonidine



Dexmedetomidine

Clonidine is an imidazoline and is the only alpha-2 adrenoceptor agonist currently available for use in anaesthetic practice . It is available as 100/250/300 mcg tablets for oral administration, as a transdermal patch releasing 100/200/300 mcg over 24 hour and in an injectable solution containing 150 mcg/mL for intravenous, intramuscular, local and regional use. 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. The adult oral dose is 100–600 mcg administered 8 hourly. The corresponding intravenous dose is 150 to 300 mcg, a dose of 150 mcg has been used epidurally.

Currently under investigation is Dexmedetomidine, a more specific and shorter-acting alpha-2 adrenoceptor agonist with an alpha-2a-to-alpha-1 ratio of 1300 and alpha-2a-to-imidazoline selectivity ratio of 32. Dexmedetomidine is a potent drug, at plasma concentrations less than 1.0 ng/mL it can produce profound physiological alterations. Dexmedetomidine is an isomer and the active component of medetomidine.[55] The intravenous dose is 1mcg/kg bolus over 10 min followed by infusion at the rate of 0.2 to 0.7 mcg/kg/hr.

Pharmacokinetics

Clonidine is lipid soluble and so has both rapid and complete absorption after oral administration, reaching peak plasma level in 60 to 90 min. Time release transdermal patches are available and 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 CSF. The elimination half-life after epidural injection of Clonidine 150 mcg is 30 min. 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% metabolised in the liver to inactive metabolites, the remaining drug being excreted unchanged in the kidney and about 20% is excreted in the faeces. The elimination half-life is around 6 to 23 h and is prolonged if renal impairment exists. The clearance is 1.9 to 4.3 mL/min/kg.

Dexmedetomidine has a volume of distribution of around 200 L and a systemic clearance of 0.5 L/min after administration of an intravenous infusion. Dexmedetomidine exhibits a concentration-dependent nonlinear pharmacokinetic profile. At high concentrations following an intravenous bolus, Dexmedetomidine decreases the initial volume of distribution and intercompartmental clearance due to its peripheral vasoconstrictive action. Dexmedetomidine behaves in a biphasic manner, as the concentration declines vasodilatation occurs due to its central effect. Therefore, Dexmedetomidine should not be administered rapidly as it can result in undesirable hypertension as well as altered pharmacokinetics. The decline in the plasma concentration of Dexmedetomidine following the cessation of an infusion is described by its

context-sensitive half-life, which is similar to that of Fentanyl. The intramuscular route probably offers the better predictability as well as reasonably rapid onset, the peak plasma concentration occurring within 15 min. [56]

Pharmacodynamics

Central nervous system effects

On administration of adrenaline intracerebroventricularly, to avoid blood brain barrier in a number of mammals including man, sedation ranging from sleep to surgical anaesthesia has been described. This effect may be mediated by postsynaptic alpha-2a subtype adrenoceptors located in the locus coeruleus, causing a decrease in noradrenergic activity. 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 adrenoceptor agonists and benzodiazepines produce comparable anxiolysis. Clonidine at high doses can be anxiogenic owing to alpha-1, but paradoxically it has been used to treat panic disorders.[57]

Dexmedetomidine decreases cerebral blood flow in dogs during anaesthesia with both halothane and isoflurane, without evidence of global ischaemia. It has little effect on intracranial pressure and in the animal models of brain ischaemia has been shown to be neuroprotective.[58]

Cardiovascular system effects

There are both alpha-1 and alpha-2 post junctional receptors in the arterial and venous vasculature where they both mediate vasoconstriction. 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 utilising intracellular calcium while the alpha-2-adrenoceptor-mediated vasoconstriction uses extracellular calcium. This makes the alpha-2 adrenoceptor agonist's pressor response more sensitive to calcium antagonists.

Intravenous alpha-2 adrenoceptor agonist administration leads to a decrease in heart rate and a transient increase in arterial blood pressure and systemic vascular resistance, but a decrease in cardiac output due to the activation of postjunctional vascular alpha-2 adrenoceptors. This is followed by a longer lasting decrease in heart rate and blood pressure due to a centrally mediated decrease in sympathetic tone and an increase in vagal activity. Neither the exact location nor the specific receptors responsible for the central hypotensive action of alpha-2 adrenoceptor agonists are yet known. It seems that postsynaptic alpha-2 adrenoceptors and imidazoline receptors in the brainstem are involved.

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.

The bradycardia commonly seen after administration of alpha-2 adrenceptor agonists may be due to the central sympatholytic action of these drugs leaving vagal tone unopposed. It may also be due to presynaptic-mediated reduction of noradrenaline release or a direct vagomimetic action.

Although bradycardia can be a problem with the administration of alpha-2 adrenoceptor agonists, Dexmedetomidine has been shown to protect against adrenaline-induced arrhythmia during halothane anaesthesia in dogs. This anti-arrhythmic action may be due to stimulation of imidazoline receptors.[59]

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. These all result in a decrease in the myocardial oxygen requirements. This is may be the reason behind the success of Clonidine in the treatment of angina pectoris.

Respiratory system effects

Alpha-2 adrenoceptors have a minimal effect on ventilation. Clonidine in doses up to 300 mcg, seems to cause a small reduction in resting minute ventilation and an increase in expired carbon dioxide.[60]

Dexmedetomidine has a biphasic effect on respiratory drive, with low doses decreasing and higher doses increasing resting ventilation. Dexmedetomidine in doses up to 2mcg/kg caused mild ventilatory depression, but this was not significantly different from that seen with placebo.[61]

The locus coeruleus, described earlier, is an important site for the action of alpha-2 adrenoceptor agonists. 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.

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.[62]

Neuroendocrine system effects

The alpha-2 adrenoceptor agonists have neuroendocrine effects, mainly related to their inhibition of sympathetic outflow and the decrease in plasma levels of circulating catecholamines. Stimulation of alpha-2 adrenoceptors located on the beta cells of the islets of Langerhans can temporarily cause direct inhibition of insulin release and clinical hyperglycaemia. 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.[63]

Gastrointestinal system effects

Alpha-2 adrenoceptors regulate vagally mediated increases in gastric and intestinal motility and secretions. It has been postulated that gastric cholinergic prejunctional alpha-2 adrenoceptors inhibit gastric secretions during stress. Activation of alpha-2 adrenoceptors inhibits water secretion and increases net absorption in the large bowel. This is the mechanism by which clonidine has been used to successfully treat diarrhoea. Stimulation of alpha-2 adrenoceptors is known to reduce salivary secretions and may lead to a dry mouth.[64]

Platelet effects

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.[65]

Drug and receptor interactions

Alpha-2 adrenoceptor agonists and opioids have some similar pharmacological effects. It is known that they have a similar distribution in the brain and that they function through the activation of the same transduction and

effector mechanisms, that is, G-proteins and coupling to potassium channels. Therefore, if alpha-2 adrenoceptor agonists and opioids are administered together they may exhibit a synergistic action. It may also be possible to reduce the opioid dose and therefore decrease the respiratory and addictive side-effects.

Alpha-2 adrenoceptor agonists also have a synergistic action with benzodiazepines.[66]

The duration of the hypnotic action of Dexmedetomidine was increased by the administration of verapamil, a calcium channel blocker, the reverse effect was seen with the administration of a calcium antagonist.

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 Dec 2010 to June 2011.

Study Design

Study design was Double Blind Randomized Control Trial.

Study period

The present study was conducted between December 2010 to June 2011.

Place

This study was carried out at Department of Anaesthesiology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum attached to Jawaharlal Nehru Medical College, Belgaum.

Source of Data

Patients undergoing elective laparoscopic cholecystectomy, under general anaesthesia during the study period.

Sample Size

A sample size of 15 patients each, randomly allocated in three groups using computerized randomization.

Sample size calculation

Based on previous studies[22,41] the sample size was calculated using the formula as below;

$$n = \frac{2(Z\alpha + Z\beta)^2 \times s^2}{(x1 - x2)^2}$$

Where, S = Variance

$S^2 = (S_1)^2 + (S_2)^2$

S_1, S_2 = Standard Deviations

X_1, X_2 = Means

A = Error is taken as 5%

Power = 80%

$$n_1 = \frac{2(Z\alpha + Z\beta)^2 \times s^2}{(x1 - x2)^2}$$

$X_1 = 60$

$S_1 = 7.8$

$X_2 = 94$

$S_2 = 12.4$

$$n_2 = \frac{2(1.96 + 0.84)^2 \times \{(94)^2 + (12.4)^2\}}{(60 - 7.8)^2}$$

The minimum value of n_1 is found to be 7

$$n_2 = \frac{2(Z\alpha + Z\beta)^2 \times s^2}{(x1 - x2)^2}$$

$$= \frac{2(1.96 + 0.84)^2 \times \{(5)^2 + (7)^2\}}{(15 - 28)^2}$$

X1 = 15

S1 = 5

X2 = 28

S2 = 7

The minimum value of n_2 is found to be 7.

The n_1 and n_2 were calculated and among the two the larger value that is, seven was taken as the minimum sample size for each of the three groups. However, it was decided to study 15 cases in each group.

Selection Criteria

Inclusion

1. ASA Grade I and II.
2. Age between 20 to 60 years

Exclusion

1. Patient refusal.
2. Patient with known allergy to drug.
3. Patients with IHD, valvular heart diseases.
4. Hypertensive patients on treatment with Beta Blockers, Methyl Dopa, MAO inhibitors.
5. Patients with Renal dysfunction.
6. Patients with elevated AST, ALT values.

7. Pregnant and lactating patient.

Randomization

Based on the computer generated randomization, patients were randomly allocated to three group as below.

- Group I (Placebo group; n=15) - Received normal saline
- Group II (Clonidine group; n=15) – Received 4 mcg/kg/hr of Inj Clonidine in 0.9% normal saline
- Group III (Dexmedetomidine group; n=15) – Received 0.4 mcg/kg/hr of Inj Dexmedetomidine in 0.9% normal saline.

Methodology

The ethical clearance for the study was obtained from the Institutional Ethics Committee, Jawaharlal Nehru Medical College, Belgaum. Patients undergoing elective laparoscopic cholecystectomy, under general anaesthesia were screened for the eligibility. Patients fulfilling selection criteria were selected for the study and briefed about the nature of study and explained about anaesthetic procedure. A written informed consent was obtained from the patient (Annexure I).

A thorough pre-anaesthetic evaluation was performed by taking history and clinical examination and recorded on predesigned and pretested proforma (Annexure II). In all patients age, weight, height, SBP, DBP and HR were recorded. Patients were randomized according to the computer generated randomization procedure.

The study drug was provided as prefilled and coded identical 50 ml syringes containing study drugs, as per the randomization protocol, in dilutions of:

1. Normal saline 0.9% - 20 ml
2. Clonidine – 20 ml (50 mcg/ml)
3. Dexmedetomidine 20 ml (5 mcg/ml)

The doses of Clonidine and Dexmedetomidine were intended to be equipotent. All prefilling, coding and decoding was done in the Department of Clinical Pharmacy. The investigators involved in the study did not knew about the content of the syringes. Patients were explained about the study, but did not know which drug was used. The study drug prefilled and coded Syringes were obtained from the Clinical Pharmacy on the day of the surgery.

Two IV line were secured, one 20 G IV canula in right hand for the infusion and another 18 G IV canula in left hand for Intravenous fluids and drug administration. 500 ml of crystalloids (Ringer Lactate) was started. HR, MAP and SpO_2 using pulse oximeter were monitored before, during and after the surgery. End Tidal Carbon Dioxide was monitored intraoperatively and kept between 25 to 30 mm of Hg.

The study drug in the prefilled coded 50 ml Syringe was started 30 minute before induction using infusion pump at the rate of 0.08 ml/kg body weight /hour and the code number of the study drug Syringe was noted down in the proforma.

After shifting to operating room monitors, ECG, NIBP and Pulse Oximeter were attached. Patients were premedicated with Inj Midazolam 0.05

mg/kg, Inj Fentanyl 1.5 mcg/kg followed by preoxygenation for three minutes. Induced with Propofol 2 mg/kg, muscle relaxation was facilitated with Inj Vecuron 0.1 mg/kg. Patients were intubated using an appropriate size endotracheal tube and maintained on O_2:N_2O (30:70) and Isoflurane 1% was started.

Throughout the procedure any 20% rise in MAP above the basal MAP, Isoflurane concentration was increased to maintain the basal MAP. For fall in MAP of more than 20% of basal MAP Isoflurane was stopped. Heart rate less than 50 bpm was treated with atropine 0.6 mg intravenous.

Mean arterial pressure and HR was measured at;

- Preoperative (M1)
- 10 min after starting Study Drug Infusion(M2)
- At Induction (M3)
- After intubation (M4)
- Before Pneumoperitoneum (M5)
- 10 min after pneumoperitoneum (M6)
- 20 min after pneumoperitoneum (M7)
- 30 min after pneumoperitoneum (M8)

Then every 30 min till end of surgery

- End of Pneumoperitoneum (N1)
- After Reversal (N2)
- Postoperative in Recovery room (N3)

Study drug infusion was discontinued at the end of pneumoperitoneum.

After surgery patients were reversed with Inj Glycopyrrolate 0.01 mg/kg and Inj Neostigmine 0.05mg/kg. Patients were extubated and time to recovery was measured, recovery being defined as the time to vocalize after extubation. At the end of the study, the data were decoded and analysis was done as per the analysis plan.

Statistical analysis

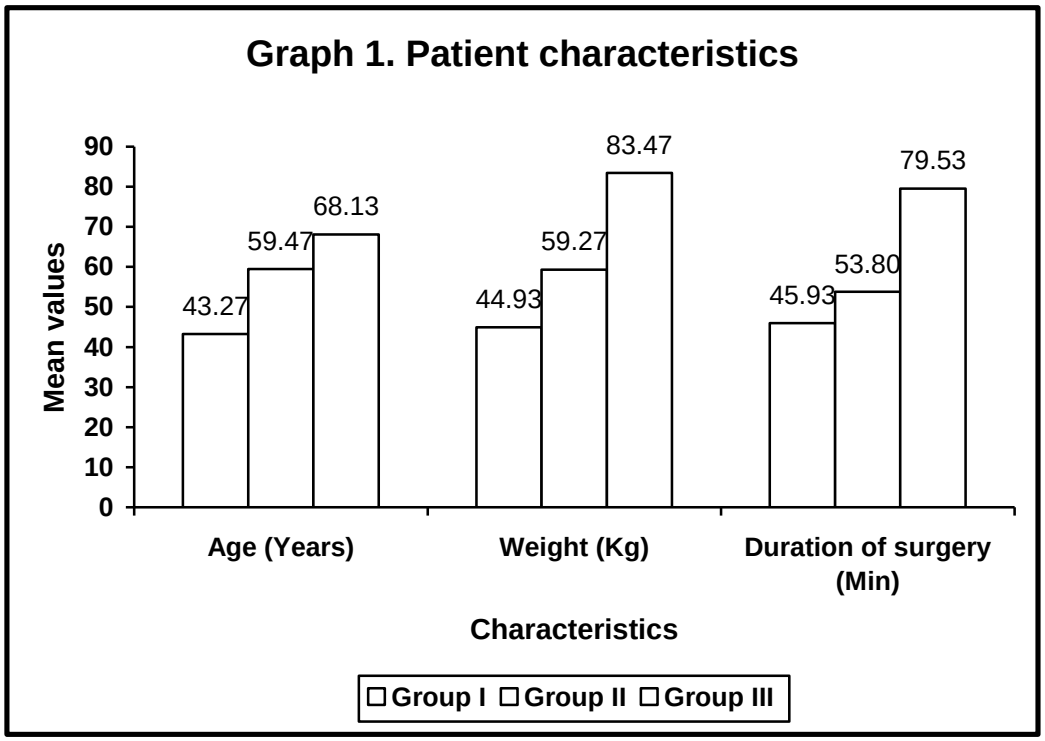
Data was expressed as mean and standard deviation (SD). The homogenecity in three groups of mean and SD was analysed using SSPS version 17.0, one way analysis of variance for each parameter. Scheffe's test is used to compare pair wise data. Tables of mean and standard deviation were prepared for meaningful comparison of the three groups. A p value of less than or equal to 0.05 was considered as significant.

RESULTS

A comparative study between dexmedetomidine and clonidine was done for assessing the cardiovascular system stability on 45 patients undergoing elective laparoscopic cholecystectomy at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of Dec 2010 to June 2011 under general anaesthesia. The results were noted.

Table 1. Patient characteristics

Characteristics	Group I	Group II	Group III	'p' value
Age (Years)	43.27 ± 13.14	44.93 ± 8.16	45.93 ± 11.20	0.800
Weight (KG)	59.47 ± 8.57	59.27 ± 4.96	53.80 ± 7.31	0.057
Duration of surgery (Min)	68.13 ± 12.38	83.47 ± 27.67	79.53 ± 19.89	0.127



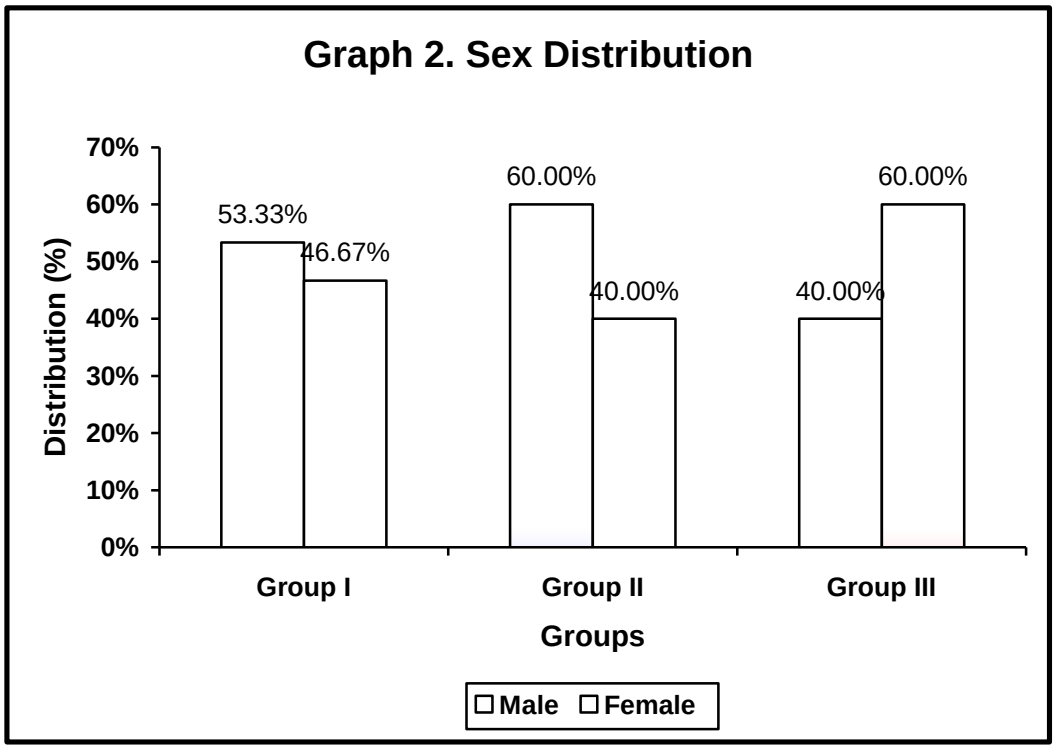
Mean age (year), weight (kg) and duration of surgery (min) have been depicted in table above.

Average age in Group I (Placebo Group) was 47.23 year, in Group II (Clonidine Group) was 44.93 year and in Group III (Dexmedetomidine Group) was 45.93 years. Average weight in Group I (Placebo Group) was 59.47 kg , in Group II (Clonidine Group) was 63.60 yr and in Group III (Dexmedetomidine Group) was 53.80kg.

Average duration of surgery in Group I (Placebo Group) was 68.13 min, in Group II (Clonidine Group) was 83.47 min and in Group III (Dexmedetomidine Group) was 79.53 min.

Table 2. Sex distribution

Sex	Group I	Group II	Group III
Female	7 (46.67%)	6 (40%)	9 (60%)
Male	8 (53.33%)	9 (60%)	6 (40%)

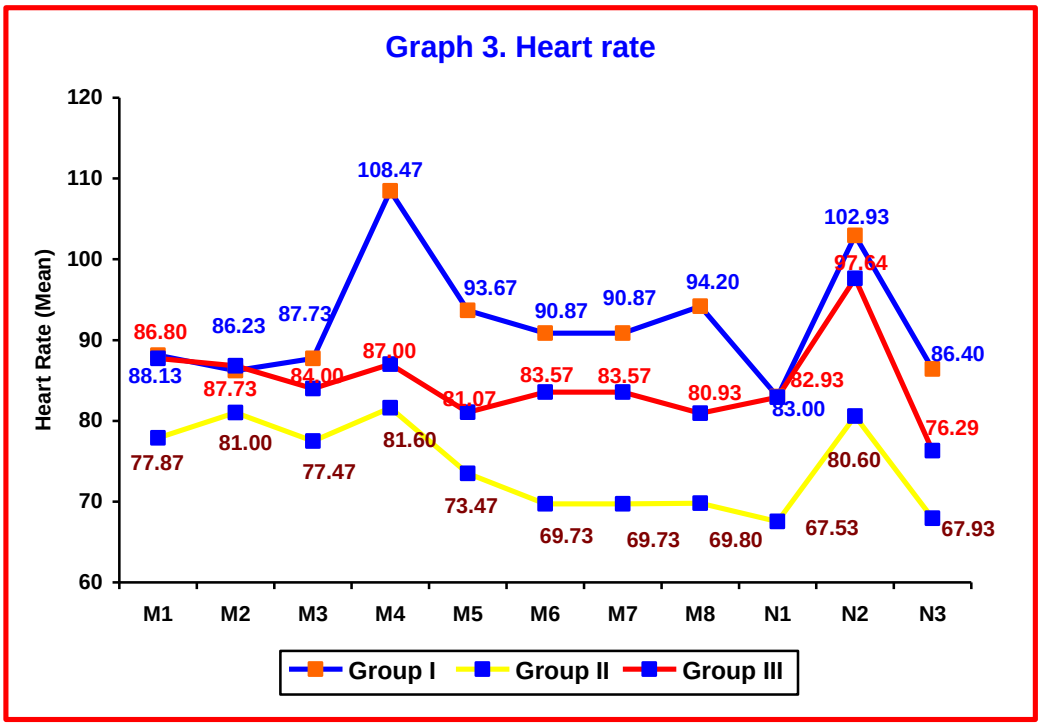


The sex distribution in the three groups have been depicted in the table above.

Table 3. Heart rate

Time interval	Group I	Group II	Group III	'p' value
M1	88.13 ± 13.88	77.87 ± 8.03	87.73 ± 16.35	0.936
M2	86.27 ± 12.49	81.00 ± 12.07	86.80 ± 14.99	0.423
M3	87.73 ± 16.05	77.47 ± 13.13	84.00 ± 15.73	0.179
M4	108.47 ± 17.35#	81.60 ± 10.40	87.00 ± 19.65	0.0001
M5	93.67 ± 15.50*	73.47 ± 12.56*	81.07 ± 19.18	0.005
M6	90.87 ± 12.55*	69.73 ± 11.55*	83.57 ± 22.38	0.004
M7	90.87 ± 12.55*	69.73 ± 11.55*	83.57 ± 22.38	0.003
M8	94.20 ± 14.25	69.80 ± 11.35	80.93 ± 20.62	0.001
N1	83.00 ± 11.10	67.53 ± 12.22#	82.93 ± 18.73	0.006
N2	102.93 ± 10.52	80.60 ± 8.83#	97.64 ± 19.02	0.0002
N3	86.40 ± 10.45*	67.93 ± 9.87*	76.29 ± 16.43	0.001

* - Differ significantly with each other
# - Differs significantly with other two



Group I (Placebo Group) and Group II (Clonidine Group)

Heart rate in Group I (placebo group) increased significantly when compared to Group II (Clonidine group), after intubation (M4), before pneumoperitoneum (M5), 10 min after pneumoperitoneum (M6), 20 min after pneumoperitoneum (M7), 30 min after pneumoperitoneum (M8), end of pneumoperitoneum (N1), after reversal (N2) and post operatively in recovery (N3) ($p=<0.05$)

Group I (Placebo Group) and Group III (Dexmedetomidine Group)

No statistically difference in heart rate was found between the two groups except after intubation (M4) ($p<0.05$), when heart rate increased significantly in Group I (Placebo Group) compared to Group III (Dexmedetomidine Group)

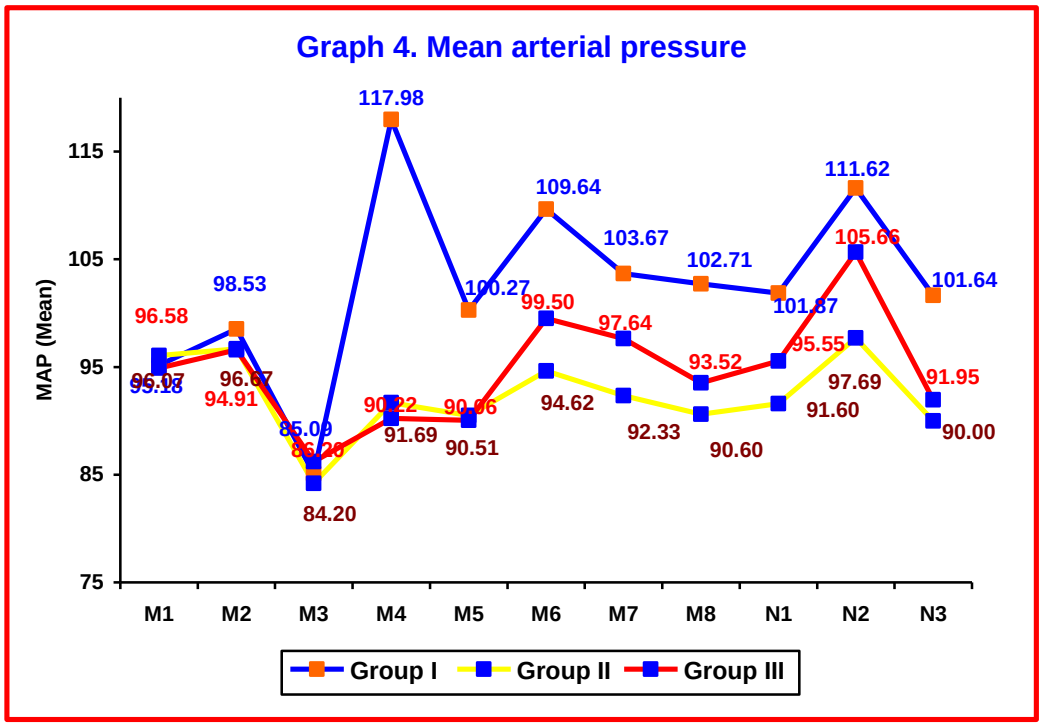
Group II (Clonidine Group) and Group III (Dexmedetomidine Group)

The decrease in heart rate appeared more in Group II (Clonidine Group) at all intervals when compared to Group III (Dexmedetomidine Group) but the decrease was found to be statistically significant only at end of pneumoperitoneum (N1) and after reversal (N2) ($p<0.05$) when heart rate was found to be more in Group III (Dexmedetomidine group).

Table 4. Mean arterial pressure

Time interval	Group I	Group II	Group III	'p' value
M1	95.18 ± 8.65	96.07 ± 9.47	94.91 ± 8.67	0.936
M2	98.53 ± 8.36	96.67 ± 7.52	96.58 ± 8.86	0.779
M3	85.09 ± 11.64	84.20 ± 9.44	86.20 ± 8.39	0.860
M4	117.98 ± 14.03#	91.69 ± 10.97	90.22 ± 8.94	0.0001
M5	100.27 ± 18.52	90.51 ± 12.70	90.06 ± 12.86	0.209
M6	109.64 ± 12.03*	94.62 ± 11.08*	99.50 ± 17.05	0.014
M7	103.67 ± 6.82*	92.33 ± 9.32*	97.64 ± 16.34	0.034
M8	102.71 ± 8.93*	90.60 ± 10.25*	93.52 ± 11.87	0.007
N1	101.87 ± 6.15*	91.60 ± 10.15*	95.55 ± 13.01	0.025
N2	111.62 ± 8.70*	97.69 ± 7.23*	105.66 ± 14.22	0.003
N3	101.64 ± 8.26#	90.00 ± 6.19	91.95 ± 11.08	0.001

* - Differ significantly with each other
# - Differs significantly with other two



Group I (Placebo Group) and Group II (Clonidine Group)

Mean arterial pressure (MAP) in Group I (Placebo Group) were significantly higher after intubation (M4), 10 min after pneumoperitoneum (M6), 20 min after pneumoperitoneum (M7), 30 min after pneumoperitoneum (M8), end of pneumoperitoneum (N1), after reversal (N2) and post operatively in recovery (N3) (p=<0.05) compared to Group II (Clonidine group).

Group I (Placebo Group) and Group III (Dexmedetomidine Group)

Mean arterial pressure (MAP) in Group I (Placebo Group) were significantly higher after intubation (M4) and post operatively in recovery (N3) (p=<0.05) compared to Group III (Dexmedetomidine group)

Group II (Clonidine Group) and Group III (Dexmedetomidine Group)

There was no statistically significant difference in MAP between two groups. MAP between the two groups were found to be comparable.

Table 5. Recovery time following extubation

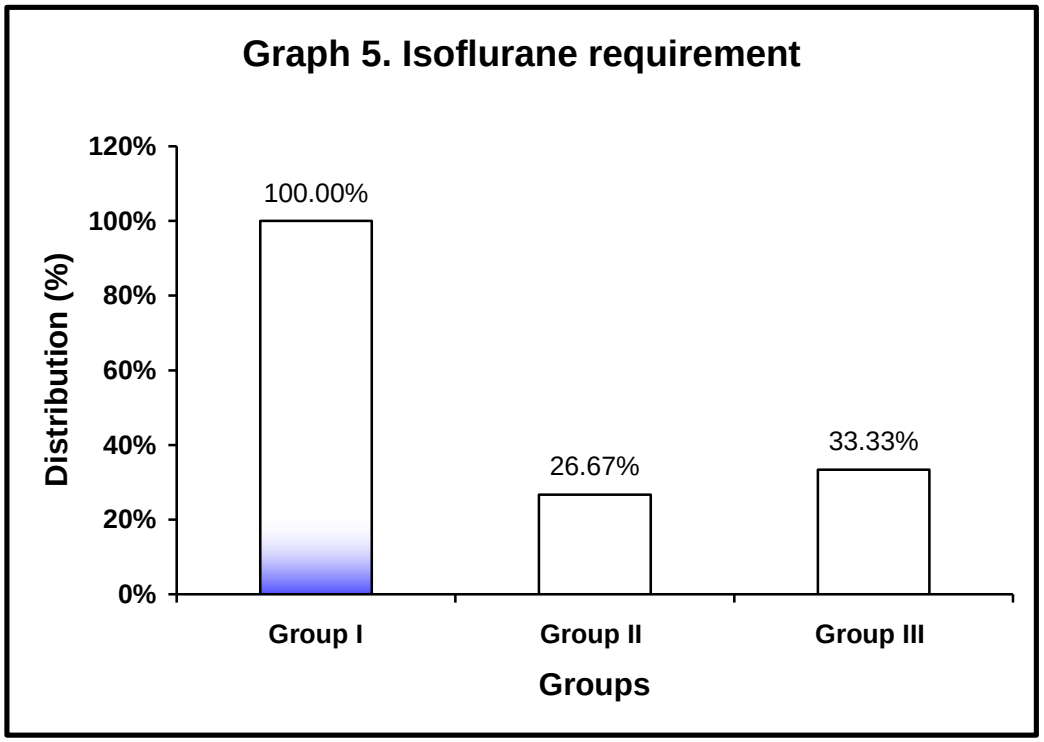
Time (Min)	Group I	Group II	Group III	'p' value
Ability to vocalize following extubation	6.8 ± 2.40#	2.67 ± 0.98	3.46 ± 2.03	<0.0001

Ability to vocalize following extubation was significantly prolonged in Group I (Placebo Group) when compared to Group II (Clonidine Group) and Group III (Dexmedetomidine group).

There was no significant difference in recovery profile between Group II (Clonidine Group) and Group III (Dexmedetomidine group).

Table 6. Isoflurane requirement (Number of patients requiring 1 to 1.5% Isoflurane)

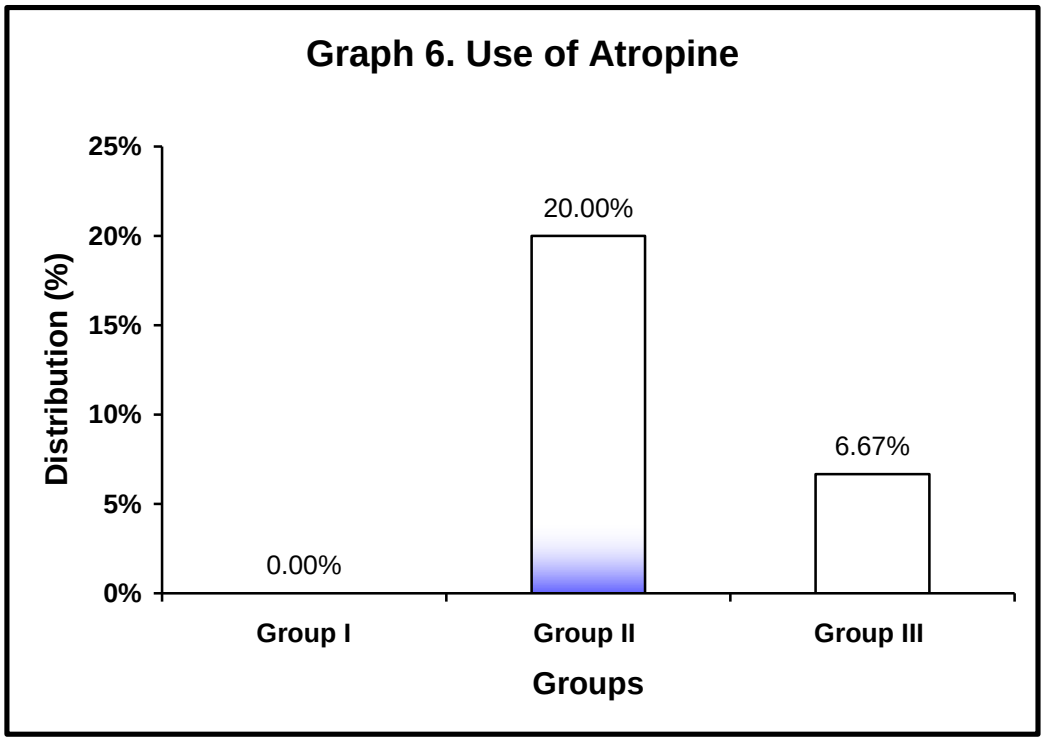
Drugs	Group I	Group II	Group III
Isoflurane	15 (100%)	4 (26.67%)	5(33.33%)



All the patients in group I required 1 to 1.5% isoflurane during the intraoperative period whereas 26.67% patients in group II and 33.33% patient in group III required isoflurane 1 to 1.5% isoflurane during the intraoperative period.

Table 7. Use of Atropine (0.6 mg IV)

Drugs	Group I	Group II	Group III
Atropine	0 (0%)	3 (20%)	1 (6.67%)



In this study atropine requirement was found in 20% of the patients (3/15) in group II whereas, 6.67% patients (1/15) required atropine in group III.

DISCUSSION

Intraoperative hypertension and tachycardia are common hemodynamic disturbances in patients undergoing laparoscopic cholecystectomy. In addition there is increase in systemic vascular resistance, and is associated with a decrease in cardiac index and metabolic changes. Various studies have been conducted with various pharmacological interventions that results in reduced incidence of tachycardia, hypertension during laparoscopic cholecystectomy and provide a stable haemodynamic state, without significant undesirable effects.

In our study we compared the efficacy of Dexmedetomidine and Clonidine infusions on haemodynamic stability in patients undergoing Laparoscopic Cholecystectomy.

We found a statistically significant change between Placebo (Group I) and Clonidine (Group III) groups as regards to heart rate after laryngoscopy and intubation (M4),before pneumoperitoneum (M5),10 min after pneumoperitoneum (M6) and throughout the period of pneumoperitoneum i.e. 20 min after pneumoperitoneum (M7), 30 min after pneumoperitoneum (M8). At end of pneumoperitoneum (N1), after reversal (N2), and post operative in recovery (N3) the change in heart rate were found to be significant.

As regards to mean arterial blood pressure statistically significant changes were found between Placebo (Group I) and Clonidine (Group III) groups similar to heart rate changes viz after laryngoscopy and intubation (M4),10 min after pneumoperitoneum (M6), 20 min after pneumoperitoneum (M7), 30 min

after pneumoperitoneum (M8). Again at end of pneumoperitoneum (N1), and after reversal (N2) the changes were found to be significant.

When Dexmedetomidine group (Group III) was compared to Placebo Group (Group I) the heart rate and mean arterial blood pressure were found to be statistically significant only after laryngoscopy and intubation (M4) and post operative in recovery (N3) and not at other intervals.

The decrease in heart rate appeared more in Clonidine group at all intervals when compared to Dexmedetomidine group but the fall was found to be statistically significant only after laryngoscopy and intubation (M4), at end of pneumoperitoneum (N1), and after reversal (N2). Similarly the fall in mean arterial pressure appeared more in Clonidine group at all intervals when compared to Dexmedetomidine group but the fall was found to be statistically significant only after laryngoscopy and intubation (M4), and during post operative period in recovery (N3).

In a study[22] Clonidine 4 mcg/kg and Dexmedetomidine 2.5 mcg/kg were given 40-50 min before the anticipated induction of anaesthesia and it was found that heart rate and mean arterial pressure were found to be lower in Clonidine and Dexmedetomidine group when compared to placebo group. In our study we found that heart rate and mean arterial pressure were significantly lower in the Clonidine group when compared to saline group than the Dexmedetomidine group. We used a lower dose of Dexmedetomidine.

A study[33] found the intraoperative fluctuation in both Heart rate and Blood pressure to less than 20 % of the pre induction values, and also blunted the

cardiovascular response to intubation effectively, in patients receiving Clonidine 5 mcg/kg orally 90 minute before induction. They found the heart rate and mean systolic and diastolic blood pressure consistently lower in Clonidine group when compared to control group during the intraoperative period. In our study too we have found similar results.

A study[35] compared the dose response relationship for one hour infusions of Clonidine 1, 2, and 4 mcg/kg/hr and placebo. Mean arterial pressure had increased by 10% over the baseline in the placebo group and mean arterial pressure decreased by 13% of the baseline in Clonidine 4mcg/kg/hr. In our study also in the placebo group the mean arterial pressure raised by 15 % above the baseline 60 mins after starting the infusion and decrease in mean arterial blood pressure was found to be 6.2%.

Another study[36] found that Pneumoperitoneum results in an increase in MAP, SVR and PVR and a decrease in cardiac output. The increase in SVR is associated with a marked release of vasopressin and catecholamines. Clonidine given before pneumoperitoneum reduces the release of catecholamines and provides intraoperative hemodynamic stability Clonidine before creation of pneumoperitoneum, reduces catecholamine release thus significantly attenuated the increase in mean arterial pressure and heart rate in comparison to placebo in a study where patients received 8 mcg/kg Clonidine infused over one hour before pneumoperitoneum. It was intended to study the propensity of Clonidine to modulate the haemodynamic changes during laparoscopic cholecystectomy. We had used a dose of 4 mcg/kg/hr of Clonidine and our findings are correlated by this study.

The effect of 150 mcg of oral Clonidine 90 min prior to induction in patients undergoing laparoscopic cholecystectomy was studied[38] and compared with placebo and found that the perioperative mean arterial blood pressure and heart rate were significantly lower in Clonidine group at all time points. Our results are also similar to the above said study.

In another study[39] in healthy individuals undergoing laparoscopic cholecystectomy who received intramuscular Clonidine 4.5 mcg/kg or saline preoperatively, the heart rate and arterial blood pressure were lower during and after pneumoperitoneum in patients who received Clonidine, consistent with the findings of our study.

Prevention of tachycardia, slowing of the heart rate and preventing hypertension is probably due to a complex mechanism. Centrally the activation of alpha 2 adrenoreceptors cause a reduction in peripheral sympathetic tone and an increase of vagally induced reflex bradycardia and peripherally it causes stimulation of Presynaptic alpha 2 adrenoreceptors and which leads to diminished release of norepinephrine from the nerve endings towards the vasculature and reducing the peripheral sympathetic tone towards the heart. Clonidine therefore serves as a effective and specific regimen to blunt the cardiovascular response.

In our study we found that in the Dexmedetomidine group (Group III), the heart rate and mean arterial pressure remained similar to the pre operative value during the pneumoperitoneum thus indicating the haemodynamic stability during pneumoperitoneum with Dexmedetomidine when compared to Placebo group.

However statistically significant difference was found only during laryngoscopy and intubation (M4).

A study[40] compared three infusion doses of Dexmedetomidine 0.2, 0.4 and 0.8 mcg/kg/hr with saline in morbidly obese patients undergoing Laparoscopic Bariatric surgery. Mean arterial blood pressure values were maintained within ±25% of the preinduction baseline values by varying the inspired Desflurane concentration. It was found that intraoperative hemodynamic values were similar in the four groups, arterial blood pressure values were significantly reduced in the Dex 0.2, 0.4, and 0.8 groups compared with the control group on admission to the postanesthesia care unit (PACU) ($p<0.05$). In our study also, the mean arterial pressure in Dexmedetomidine group was significantly less in PACU ($p<0.05$).

A study[41] showed the effects of Dexmedetomidine infusion (0.2 mcg/kg/hour) for haemodynamic stability in patients undergoing laparoscopic cholecystectomy and found that mean arterial pressure and heart rate in Dexmedetomidine group were significantly less after intubation and throughout the period of pneumoperitoneum. We found similar result only after intubation but there was no statistically significant difference during the period of pneumoperitoneum between the Dexmedetomidine and saline group. It appears that Dexmedetomidine group maintained mean arterial blood pressure and heart rate throughout the pneumoperitoneum without additional isoflurane requirement, whereas in saline group, higher MAC values of isoflurane were required to control 20% rise above pre operative values.

Mean recovery time as indicated by ability to vocalize following extubation was found to be significantly less in both Dexmedetomidine (Group III) and Clonidine (Group II) groups in our study as there was a reduction in isoflurane requirement in the two groups as compared to Placebo group. Isoflurane was used in 4 of 15 patients (23%) in Clonidine group, 5 of 15 patients (33%) in Dexmedetomidine group and in all the patients (100%) in the saline group. A reduction of isoflurane requirement was observed in our study. The patients required significantly lower concentrations of isoflurane in Clonidine and Dexmedetomidine group. Our findings were in accordance with other studies, in which there was decrease in MAC and inhalational agent requirement.[32,38]

Delayed recovery in Placebo group compared to Clonidine and Dexmedetomidine group appears to be due to higher consumption of Isoflurane.

Atropine was used in 3 out of 15 patients (20% patients) in Clonidine group, 1 out of 15 patients (6.67% patients) in Dexmedetomidine group, when the heart rate decreased to less than 50 per minute. Previous studies[67] have demonstrated severe bradycardia associated with Clonidine administration. Even Dexmedetomidine required atropine in some studies.[68]

In one patient receiving Dexmedetomidine infusion, the ECG rhythm became irregular and the infusion was stopped.

We did not perform intra group comparisons between time intervals, which can be the limitation of the study. Further studies need to be conducted with a larger sample size to corroborate the findings of this study, which may

enlighten further the usefulness of two alpha 2 agonists in the anaesthetic management of Laparoscopic Cholecystectomy.

CONCLUSION

Both the drugs, Clonidine and Dexmedetomidine, maintained cardiovascular stability during laparoscopic cholecystectomy. But Clonidine appears more effective in maintaining perioperative cardiovascular system stability during laparoscopic cholecystectomy. In addition Clonidine being more cost effective than Dexmedetomidine can be recommended for maintaining cardiovascular system stability during laparoscopic cholecystectomy.

SUMMARY

Laparoscopic Cholecystectomy is a routinely performed surgery and it is desirable to have a stable intraoperative haemodynamic status by avoiding hypertension, hypotension or tachycardia. Opioids, volatile agents like isoflurane, sevoflurane, nitroglycerine, beta blockers etc have been used to control perioperative stress during laparoscopy. Two novel alpha 2 adrenergic agonists Clonidine and Dexmedetomidine have been introduced recently, and have been used for maintaining haemodynamic stability during perioperative period in separate studies. Hence the present study has been conducted to compare the beneficial effect of the two alpha 2 agonists Clonidine and Dexmedetomidine in maintaining the perioperative haemodynamic parameters during laparoscopic cholecystectomy.

The present Double Blind Randomized Control Trial was conducted in the Department of Anaesthesiology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum attached to Jawaharlal Nehru Medical College, Belgaum during the period of Dec 2010 to June 2011. A total of 45 patients randomly allocated in three groups, Group I (Placebo Group), Group II (Clonidine Group) & Group III (Dexmedetomidine Group) of 15 patients each, undergoing elective laparoscopic cholecystectomy, under general anaesthesia were studied. The patients received preloaded and coded study drug as infusion (normal saline, Clonidine 4 mcg/kg/hr and Dexmedetomidine 0.4 mcg/kg/hr respectively) at the rate of 0.08 ml/kg/hr,

Sex, age, weight and duration of surgery were comparable in all the three groups. Both the drugs, Clonidine and Dexmedetomidine, maintained cardiovascular stability during laparoscopic cholecystectomy. But Clonidine appears more effective in maintaining perioperative cardiovascular system stability during laparoscopic cholecystectomy. In addition the isoflurane requirement in Clonidine Group and Dexmedetomidine Group was found to be considerably lower when compared to Placebo Group. Also, the mean recovery time as indicated by the ability to vocalize following extubation was found to be significantly less in Clonidine Group and Dexmedetomidine Group. Moreover, Clonidine being more cost effective than Dexmedetomidine can be recommended for maintaining cardiovascular system stability during laparoscopic cholecystectomy.

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ANNEXURE I – CONSENT FORM

CONSENT FOR PARTICIPATION IN RESEARCH STUDY

Mr/Mrs/Miss. _____ we are requesting you to enroll yourself in study conducted by Dr. Jitendra Ladhania, Post Graduate in M.D. Anaesthesiology under the guidance of Dr. Lata Kulkarni M.D DA., Professor, Department of Anaesthesiology, J.N. Medical College, Belgaum under KLE University, Belgaum.

Respected Sir/Madam we request you to enroll yourself to participate in our study as you are eligible for participating in the study. During the study you will be asked some questions regarding your present complaint and you are supposed to answer to the best of your knowledge.

Your participation in research is voluntary. Your decision whether or not to participate in the study will not affect your relationship with J.N. Medical College. If you decide to participate you are free to withdraw at any time.

The purpose of research is **"COMPARISON OF DEXMEDETOMIDINE AND CLONIDINE INFUSIONS ON HAEMODYNAMIC STABILITY IN PATIENTS UNDERGOING LAPAROSCOPIC CHOLECYSTECTOMY – A DOUBLE BLIND RANDOMIZED CONTROLLED TRIAL"**

Procedure Involved:

If you agree to enroll yourself in my study, I will ask your present past and family history. Then you will be clinically examined in detail and routine investigations like Hb, TC, DC, Platelet count, RBS, Blood urea, Serum Creatinine, Urine for Albumin , Sugar, Microscopy And LFT will be done. You will be randomly allocated into either study Group I, II or III. Depending on the study Group randomization, 30 min prior to induction you will be receive either placebo, Clonidine 4mcg/kg/hr or Dexmedetomidine 0.4 mcg/kg/hr. .

Risks:

The risks associated are hypotension and bradycardia.

Benefits:

The benefits of taking part in this research are that, both Clonidine and Dexmedetomidine maintain haemodynamic stability by decreasing blood pressure and heart rate and maintains cardiac output.

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.

Alternative:

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

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 the research are published or discussed, in a conference, no information will be displayed 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.

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 through KLES Hospital and Medical Research Centre, Belgaum. There is no compensation or payment for such medical treatment by law. If you are

injured you may contact Dr. Jitendra Ladhania, at Department of Anaesthesiology, KLES Hospital & MRC or by Ph. No: 8970645826

Questions:

In case you have any questions related to the study, in future or in case of study related injury or illness, you can contact Dr. Jitendra Ladhania, Department of Anaesthesiology, KLES Hospital and MRC, Ph No. 0831-2473777 Extn 1292 or mobile phone number : 8970645826 or Dr. Lata Kulkarni, Professor, Dept Of Anaesthesiology, KLES Hospital and MRC, Belgaum Ph: 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 for participation in research trial

I, _____ 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 language, including the risks and the benefits and having all my questions answered.

Subject Name : _____

Signature or the Left Thumb Print of Subject : _____ Date :

Witness Name : _____ Signature: _____ Date :

Investigators Name: _____ Signature: _____ Date :

Place : _____

ANNEXURE II – PROFOMA

Title: Comparison of Dexmedetomidine and Clonidine infusions on haemodynamic stability in patients undergoing laparoscopic cholecystectomy – A double blind randomized controlled trial.

Patients Name	:	I.P No.	:
Code No:			
Age	:	Weight	:
Height	:	Gender	:
Date of operation	:	Occupation	:
Address	:	Anaesthesiologist:	

Preanaesthetic evaluation

Chief complaints

Past History

- HTN / DM/ IHD / Arrhythmia / LVH / Valvular heart disease
- H/o renal / hepatic dysfunction or use of angiotensin converting enzyme affecting drugs
- H/o drug intake – β-blockers / methyldopa / monoamine oxidase inhibitor / concomitantly on Clonidine

Family History

General physical examination

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

Systemic examination

RS : CNS :

CVS : GIT :

Airway and spine assessment:

Investigations

Hb% : Urine routine :

Blood urea : Serum Creatinine:

FBS : CXR :

LFT :

Diagnosis

Proposed surgery

Preoperative physical status ASA Grade I II III IV V

Observations

Time	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	N1	N2	N3
MAP (mm Hg)															
HR (bpm)															

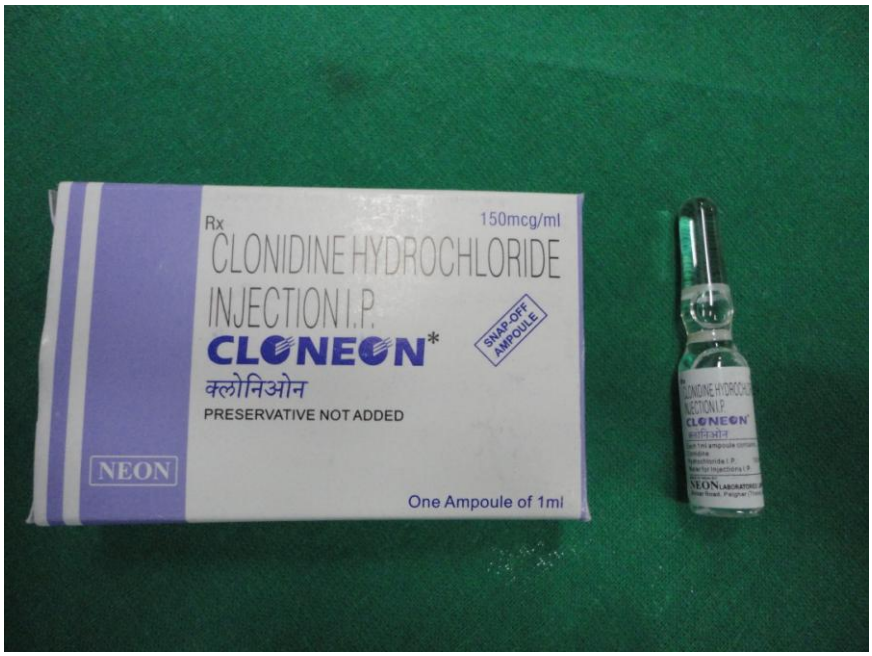
Intraoperative requirement of isoflurane (Percentage)

Anaesthesia (Isoflurane %)		

Recovery Time (min):

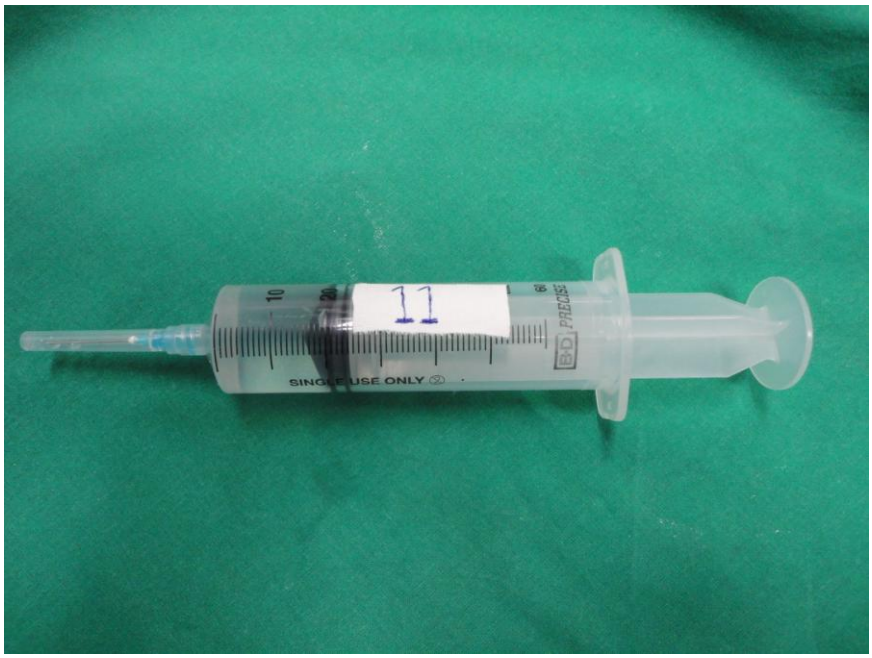
Whether Atropine used:

ANNEXURE III – PHOTOGRAPHS

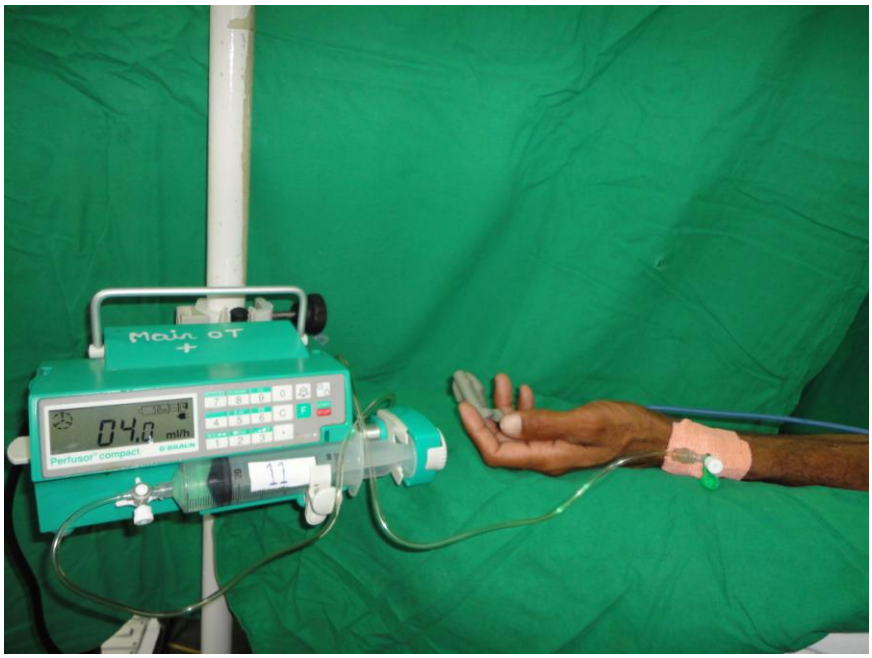


Photograph 1. Clonidine (150 mcg/ml)

Photograph 2. Dexmedetomidine (100 mcg/ml)



Photograph 3. Prefilled coded syringe containing study drug



Photograph 4. Infusion of study drug

MASTER CHART

Serial Number	In Patient Number	Syringe Code Number	Gender	Age (Years)	Weight (Kg)	Date of Operation	ASA Grade	Observations																											
								M1				M2				M3				M4				M5				M6				M7			
								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)
1	399773	1	F	44	50	24-Dec	II	130	80	104	78	134	78	97	80	136	77	102	86	120	72	88	89	113	66	87	84	128	88	101	95	125	85	100	91
2	397649	2	F	53	58	23-Dec	II	155	97	114	116	148	98	111	100	118	87	97	106	121	71	87	94	170	93	122	115	152	110	124	97	153	97	118	120
3	398766	3	M	42	80	24-Dec	II	140	80	100	80	136	80	99	88	120	80	93	80	138	90	112	82	140	100	114	77	130	90	106	68	110	78	88	67
4	397526	4	F	60	65	23-Dec	I	120	70	86	100	130	70	90	93	130	80	97	97	130	90	103	102	113	77	89	88	130	80	97	94	140	88	110	98
5	398886	5	F	39	60	1-Jan	I	160	80	107	84	150	82	105	86	129	88	102	76	153	90	111	79	114	78	87	66	118	61	89	62	122	82	94	65
6	399552	6	M	60	70	7-Jan	I	150	90	110	81	150	90	110	84	140	90	107	93	190	120	143	99	150	95	114	94	148	101	116	89	138	95	109	94
7	398426	7	F	60	55	30-Dec	II	140	90	107	80	142	92	108	83	130	70	120	74	183	87	144	97	103	68	87	72	171	86	140	62	138	76	92	60
8	400517	8	F	28	50	13-Jan	I	125	82	96	110	120	80	93	114	90	60	70	120	150	100	116	130	104	60	75	93	130	90	103	88	130	100	110	90
9	399825	9	F	46	80	8-Jan	I	140	100	113	82	138	90	106	76	113	75	85	74	117	78	90	73	121	86	97	81	115	81	94	74	126	80	94	56
10	400989	10	F	28	50	19-Jan	I	130	80	97	80	134	96	109	94	124	70	88	100	150	110	117	120	140	90	107	110	150	100	117	114	130	86	101	90
11	404164	11	F	38	48	10-Feb	I	110	70	83	110	125	75	97	120	94	68	76	98	106	59	75	106	106	66	84	113	99	58	71	110	100	60	74	114
12	405921	12	M	54	62	24-Feb	I	118	78	91	74	124	82	96	78	98	64	75	74	160	112	128	110	138	98	111	86	142	100	114	88	130	88	102	90
13	405446	13	M	45	54	21-Feb	II	124	80	93	78	120	80	92	74	95	64	76	70	121	83	92	80	90	55	69	59	112	69	84	76	122	78	91	90
14	405731	14	M	53	64	22-Feb	II	150	90	110	81	150	84	106	74	113	74	87	72	123	82	92	72	126	84	94	68	147	96	106	69	136	88	97	66
15	406201	15	M	46	60	25-Feb	I	120	70	87	84	122	74	90	82	110	75	72	84	147	116	128	114	145	100	114	94	132	92	105	78	136	96	109	68
16	406465	16	F	49	54	25-Feb	I	140	80	100	86	140	73	89	89	94	58	67	64	112	62	75	70	117	69	79	62	140	81	95	71	120	70	83	64
17	406702	17	F	32	50	28-Feb	I	120	78	92	110	124	76	92	112	113	82	87	103	123	88	95	75	132	90	104	76	125	91	99	76	124	84	94	72
18	407112	18	M	50	66	3-Mar	I	140	80	100	88	140	90	106	110	110	70	83	111	90	50	66	100	85	63	70	98	138	88	113	75	140	87	110	85
19	404841	19	M	50	52	10-Mar	I	130	80	97	63	140	98	112	76	110	90	80	58	115	87	82	59	150	90	100	68	154	110	106	54	156	110	126	70
20	399664	20	F	36	53	8-Jan	I	124	80	95	84	122	78	93	84	98	64	76	86	154	104	121	110	110	60	77	94	134	94	107	94	140	90	106	110
21	411725	21	M	56	62	9-Jan	II	110	70	86	92	120	78	92	82	124	78	93	84	132	74	93	90	127	84	98	70	150	94	113	80	156	102	120	92
22	411891	22	F	38	44	7-Apr	I	100	80	87	95	120	70	87	85	110	78	89	105	120	60	80	98	124	78	94	70	120	70	87	76	110	80	94	80
23	411418	23	M	32	58	7-Apr	I	128	88	101	84	130	84	99	88	110	74	86	98	168	110	129	126	144	92	109	112	158	106	124	116	136	86	103	98

MASTER CHART

Serial Number	In Patient Number	Observations																												Requirement of isoflurane (%	Recovery Time (MIN)	Atropine Use
		M8				M9				M10				M11				N1				N2				N3						
		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)			
1	399773	104	71	82	100	-	-	-	-	-	-	-	-	-	-	-	-	120	83	95	83	124	70	86	81	110	70	84	68	-	2	-
2	397649	122	82	102	110	-	-	-	-	-	-	-	-	-	-	-	-	150	92	125	93	187	111	146	127	140	90	107	100	1.25	8	-
3	398766	102	67	79	67	119	81	93	58	-	-	-	-	-	-	-	-	126	84	97	63	121	78	97	68	110	70	83	62	1.00	3	-
4	397526	142	90	110	98	140	90	109	96	143	92	111	98	-	-	-	-	144	94	112	98	140	90	107	104	130	84	99	90	1.00	4	-
5	398886	124	80	94	64	120	84	92	54	140	90	107	79	-	-	-	-	125	90	98	62	121	89	96	76	120	82	95	70	-	3	Y
6	399552	134	90	105	95	140	98	112	98	-	-	-	-	-	-	-	-	136	88	104	84	142	92	109	88	154	98	117	101	1.50	6	-
7	398426	150	75	117	64	148	72	115	62	-	-	-	-	-	-	-	-	138	70	112	64	170	110	130	90	160	80	124	70	1.50	8	-
8	400517	130	106	114	94	130	100	110	78	-	-	-	-	-	-	-	-	130	80	97	80	140	90	107	110	140	90	104	88	1.00	10	-
9	399825	122	83	97	58	124	86	97	58	120	80	93	56	130	90	101	70	120	90	96	65	130	94	102	84	117	80	96	62	-	1	Y
10	400989	110	70	83	100	130	80	97	90	110	78	89	80	-	-	-	-	130	76	94	84	140	80	100	90	120	84	96	76	1.00	8	-
11	404164	118	74	92	117	-	-	-	-	-	-	-	-	-	-	-	-	121	64	90	111	128	66	96	112	110	70	83	94	-	3	-
12	405921	132	88	103	96	130	80	97	88	-	-	-	-	-	-	-	-	132	84	100	82	150	96	114	112	130	90	103	92	1.50	8	-
13	405446	130	80	100	92	124	82	94	82	-	-	-	-	-	-	-	-	123	84	96	68	121	78	90	96	110	70	83	64	-	2	-
14	405731	133	79	92	63	128	74	88	54	-	-	-	-	-	-	-	-	136	80	93	52	140	84	102	70	130	80	97	62	1.10	5	-
15	406201	124	87	99	64	126	93	104	68	-	-	-	-	-	-	-	-	128	94	105	70	134	97	109	98	128	90	103	86	1.10	8	-
16	406465	120	68	79	62	97	55	68	58	-	-	-	-	-	-	-	-	116	66	77	60	136	77	89	70	120	80	93	62	-	2	-
17	406702	123	75	86	72	136	80	94	68	137	88	97	64	-	-	-	-	135	83	94	63	140	78	99	72	106	70	82	64	-	3	-
18	407112	146	92	111	83	112	78	86	82	-	-	-	-	-	-	-	-	105	61	79	100	110	80	76	88	118	78	89	86	1.00	4	Y
19	404841	152	100	113	65	-	-	-	-	-	-	-	-	-	-	-	-	156	102	121	70	170	100	123	106	170	100	123	96	1.00	7	-
20	399664	158	96	117	112	144	92	109	100	-	-	-	-	-	-	-	-	134	90	105	88	144	94	111	100	142	96	112	96	1.00	9	-
21	411725	140	88	105	68	136	72	93	72	126	82	98	78	-	-	-	-	144	82	102	90	150	110	123	112	124	70	88	72	1.05	4	-
22	411891	130	80	97	70	126	70	89	72	122	80	94	74	-	-	-	-	140	86	104	97	140	94	109	101	120	74	90	66	1.00	4	-
23	411418	130	84	99	104	132	86	101	98	-	-	-	-	-	-	-	-	130	84	99	86	156	98	118	114	140	86	104	94	1.60	10	-

MASTER CHART

Serial Number	In Patient Number	Syringe Code Number	Gender	Age (Years)	Weight (Kg)	Date of Operation	ASA Grade	Observations																											
								M1				M2				M3				M4				M5				M6				M7			
								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)
24	416293	24	M	60	49	9-May	I	136	84	102	120	144	86	106	110	120	86	97	112	164	98	120	130	160	110	127	108	171	115	135	100	157	87	110	95
25	412397	25	M	58	58	12-Mar	I	140	80	100	90	136	82	100	95	110	78	89	78	124	86	99	82	130	80	100	92	156	92	114	86	138	84	99	88
26	412769	26	F	40	56	15-Apr	I	110	72	85	84	124	88	100	74	118	74	89	76	124	68	87	68	131	78	96	81	124	87	99	93	118	74	89	92
27	414436	27	F	35	50	23-Apr	I	124	84	98	80	128	86	100	82	94	64	74	84	110	72	85	86	120	78	94	85	128	86	100	92	124	80	95	60
28	413143	28	F	35	50	15-Apr	I	126	84	98	90	128	88	101	92	124	80	95	90	140	92	108	135	95	111	82	ECG IRREGULAR INFUSION STOPPED								
29	414724	29	M	42	70	26-Apr	I	117	76	89	65	113	79	90	69	124	80	94	70	120	80	94	65	98	70	79	61	104	76	86	54	118	84	95	66
30	415311	30	M	45	56	4-May	II	126	78	90	79	127	79	91	84	96	59	69	92	117	77	89	101	125	90	100	90	125	86	98	84	128	90	102	77
31	415247	31	F	56	57	7-May	I	110	70	84	82	120	74	90	84	102	64	77	84	110	88	96	90	108	84	92	88	118	86	97	98	108	78	88	94
32	416415	32	F	25	45	7-May	I	108	70	83	100	120	60	70	90	104	62	76	100	90	70	77	110	100	62	75	112	115	85	97	133	103	78	87	125
33	417346	33	M	33	76	13-May	II	140	90	107	90	148	94	112	88	120	88	99	94	174	100	125	116	170	94	120	118	154	100	118	108	150	92	111	106
34	417351	34	M	46	65	13-May	II	134	84	101	79	136	80	99	86	110	70	84	82	122	80	94	80	114	64	81	70	110	60	77	64	108	62	77	64
35	420709	35	F	23	60	3-Jun	I	120	70	87	69	122	72	89	70	92	60	71	66	160	100	120	115	140	98	112	98	142	88	106	100	136	84	101	90
36	417358	36	M	49	68	13-May	I	138	82	101	76	136	80	99	78	102	72	82	80	122	78	93	86	124	80	95	70	120	76	91	70	118	76	90	64
37	416960	37	M	39	80	11-May	I	110	70	84	60	108	68	82	55	106	64	78	54	124	80	95	86	111	74	87	52	132	95	108	52	132	88	103	59
38	416589	38	M	60	59	14-May	II	130	80	97	70	128	78	95	72	116	70	86	68	118	76	90	76	108	68	81	68	106	64	78	66	108	60	73	64
39	417963	39	F	35	50	23-May	I	120	70	87	70	124	72	89	74	110	68	82	72	124	78	94	79	114	70	85	70	118	70	86	66	110	72	85	65
40	419612	40	M	44	74	28-May	II	110	70	83	74	114	78	90	78	92	62	72	72	154	92	112	110	148	88	108	98	140	90	106	89	148	88	108	92
41	417333	41	F	60	63	14-May	II	128	78	95	72	130	80	97	76	110	70	83	68	116	72	86	66	118	76	90	68	115	72	80	66	110	68	82	65
42	419815	42	M	28	60	27-May	I	130	70	90	84	136	84	101	86	110	70	84	76	124	82	96	84	149	99	115	70	121	80	94	68	118	68	84	66
43	417875	43	M	60	62	18-May	II	120	70	87	70	124	74	91	74	94	64	74	69	114	70	84	74	108	68	81	65	106	66	79	62	106	62	77	61
44	421687	44	M	52	45	13-Jun	I	130	80	97	70	117	77	91	66	94	62	74	68	115	79	91	72	147	99	108	68	151	103	115	67	147	99	110	64
45	422044	45	F	48	55	14-Jun	I	128	84	99	82	126	84	98	76	114	80	91	70	116	82	93	70	118	72	87	60	114	76	89	52	130	84	102	92

MASTER CHART

Serial Number	In Patient Number	Observations																												Requirement of isoflurane (%	Recovery Time (MIN)	Atropine Use
		M8				M9				M10				M11				N1				N2				N3						
		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)			
24	416293	142	93	118	110	138	94	114	96	139	96	108	82	-	-	-	-	154	92	120	74	162	94	109	100	140	92	117	84	1.25	6	-
25	412397	132	86	101	88	130	84	99	78	-	-	-	-	-	-	-	-	132	84	100	84	148	92	111	94	124	80	95	78	1.00	4	-
26	412769	128	74	92	98	124	87	99	95	130	78	95	83	-	-	-	-	141	88	106	91	152	98	118	102	130	70	93	81	1.00	3	-
27	414436	110	70	84	74	-	-	-	-	-	-	-	-	-	-	-	-	122	80	94	88	124	74	91	86	120	70	87	64	-	2	-
28	413143	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
29	414724	113	78	90	64	105	75	86	62	97	70	80	61	-	-	-	-	92	63	75	62	114	76	88	84	114	80	89	86	-	3	-
30	415311	133	92	103	74	114	78	90	76	-	-	-	-	-	-	-	-	130	88	103	66	125	84	103	80	124	75	90	82	-	2	-
31	415247	110	84	93	82	112	86	95	80	-	-	-	-	-	-	-	-	108	74	85	84	116	84	96	98	110	70	84	74	-	3	-
32	416415	110	70	84	118	111	87	95	126	-	-	-	-	-	-	-	-	107	74	85	122	117	85	97	136	110	82	92	110	-	3	-
33	417346	150	96	114	109	140	84	103	108	-	-	-	-	-	-	-	-	144	92	110	106	160	98	119	128	130	84	99	100	1.50	6	-
34	417351	112	64	80	62	114	64	81	61	-	-	-	-	-	-	-	-	120	80	94	60	130	86	101	76	110	76	87	65	-	2	-
35	420709	138	88	102	89	128	84	99	84	126	84	98	85	-	-	-	-	130	84	100	82	156	96	116	106	132	84	100	90	1.25	8	-
36	417358	116	70	86	64	118	68	85	62	-	-	-	-	-	-	-	-	116	64	82	62	130	78	95	78	120	70	87	64	-	2	-
37	416960	124	90	100	77	129	89	101	68	-	-	-	-	-	-	-	-	136	90	106	64	145	99	115	94	130	90	103	54	-	3	-
38	416589	102	62	75	64	-	-	-	-	-	-	-	-	-	-	-	-	108	64	79	62	124	78	94	79	110	70	84	64	-	2	-
39	417963	110	74	86	65	-	-	-	-	-	-	-	-	-	-	-	-	110	76	87	64	130	80	97	78	120	70	87	60	-	2	-
40	419612	130	80	97	88	128	82	97	86	-	-	-	-	-	-	-	-	130	80	97	88	150	92	111	106	132	80	98	84	1.25	6	-
41	417333	110	64	79	66	-	-	-	-	-	-	-	-	-	-	-	-	110	60	77	64	134	84	101	86	118	74	89	66	-	2	-
42	419815	116	70	85	64	118	68	84	64	-	-	-	-	-	-	-	-	124	80	94	68	134	90	104	88	121	78	92	66	1.00	3	-
43	417875	104	60	74	62	100	60	73	60	-	-	-	-	-	-	-	-	108	68	81	60	130	74	92	74	110	64	79	60	1.00	2	-
44	421687	133	93	105	63	-	-	-	-	-	-	-	-	-	-	-	-	130	91	104	75	132	97	109	84	130	80	97	62	-	1	Y
45	422044	126	88	101	94	114	78	94	86	-	-	-	-	-	-	-	-	130	80	97	80	140	90	107	94	120	70	87	68	-	-	-

ANNEXURE IV – KEY TO MASTER CHART

ASA	-	American Society of Anaesthesiologist
DBP	-	Diastolic blood pressure
F	-	Female
HR	-	Heart rate
Kg	-	Kilogram
M	-	Male
M1	-	Preoperative Mean arterial pressure and heart rate
M2	-	Mean arterial pressure and heart rate 10 min after starting Study Drug Infusion
M3	-	Mean arterial pressure and heart rate at induction
M4	-	Mean arterial pressure and heart rate after intubation
M5	-	Mean arterial pressure and heart rate before pneumoperitoneum
M6	-	Mean arterial pressure and heart rate 10 minutes after pneumoperitoneum
M7	-	Mean arterial pressure and heart rate 20 minutes after Pneumoperitoneum
M8	-	Mean arterial pressure and heart rate 30 minutes after pneumoperitoneum
M9	-	Mean arterial pressure and heart rate 60 minutes after pneumoperitoneum

M10	-	Mean arterial pressure and heart rate 90 minutes after pneumoperitoneum
M11	-	Mean arterial pressure and heart rate 120 minutes after pneumoperitoneum
MAP	-	Mean arterial blood pressure
Min	-	Minutes
mm Hg	-	Millimeters of mercury
N1	-	Mean arterial pressure and heart rate at end of pneumoperitoneum
N2	-	Mean arterial pressure and heart rate after reversal
N3	-	Mean arterial pressure and heart rate postoperative in recovery
SBP	-	Systolic blood pressure
Y	-	Yes