"TO STUDY THE EFFICACY OF DEXMEDETOMIDINE FOR ATTENUATION OF HEMODYNAMIC RESPONSES IN PATIENTS UNDERGOING LAPAROSCOPIC SURGERIES"

By

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ABBREVIATION

ASA	American Society of Anaesthesiologists
Bpm	Beats per minute
CO	Cardiac Output
CO_2	Carbon Dioxide
CSF	Cerebrospinal Fluid
CVP	Central Venous Pressure
DBP	Diastolic Blood Pressure
Dex	Dexmedetomidine
DS	Diclofenac Sodium
ECG	Electrocardiography
$ETCO_2$	End Tidal Carbon Dioxide
Hg	Mercury
HR	Heart Rate
i.v.	Intravenous
IAP	Intra Abdominal Pressure
kg	kilogram
MAC	Minimum Alveolar Concentration
MAP	Mean Arterial Pressure
mcg	microgram
Min	minute
ml	milliliter
N_2O	Nitrous Oxide
ng	Nanogram
NIBP	Non-Invasive Blood Pressure
O_2	Oxygen
PACU	Post Anaesthesia Care Unit

PNP	Pneumoperitoneum
POD	Post Operative Day
PONV	Post operative Nausea and Vomiting
PVR	Pulmonary Vascular Resistance
rT	reverse Trendelenburg
SBP	Systolic Blood Pressure
SPO_2	Arterial Oxygen Saturation
SVR	Systemic Vascular Resistance
NIH	National Institutes of Health

ABSTRACT

Introduction:

Hemodynamic stability during peri-operative period is of paramount importance. The anaesthesiologist's traditional approach to provide anaesthesia for laparoscopic procedures has been the emphasis on maintaining hemodynamic stability by avoiding hypertension, hypotension and tachycardia.

Key Words:

Dexmedetomidine, Laparoscopy, intubation, pneumoperitoneum, pressor response.

Aims:

To study

- Hemodynamic responses associated with Intubation and Pneumoperitoneum.
- Associated adverse effects like Bradycardia and hypotension.

Methods:

Prospective randomized clinical study was conducted in the department of Anesthesia at B.L.D.E. (DEEMED TO BE UNIVERSITY) Shri B. M. Patil Medical College Hospital and Research Centre, Vijayapur.

Ethical Committee permission- Taken

Informed written consent- Taken

Total of 90 patients scheduled for Laparoscopic surgeries were allotted into two groups.

Group D (Dexmedetomidine)

IV Dexmedetomidine loading dose 1mcg/kg and maintenance dose of IV Dexmedetomidine infusion at 0.4mcg/kg/min.

Group S (Normal saline)

IV Normal saline 0.9% (1ml) loading dose and maintainance IV infusion at 1ml/min.

Test used were Chi square test, unpaired t test and Mann-Whitney test.

Inclusion criteria

- Age 18-60 years of age.
- ASA grade I and II.

Exclusion criteria

- Patients with anticipated difficult airway,
- Morbid obese.

Results:

Time interval	**Group D** MAP in mm of Hg	**Group S** MAP in mm of Hg	**P value**
Baseline	95.4	95.51	0.5643
Intubation	91.13	111.16	<0.0001
Pneumoperitoneum	92.62	109.89	<0.0001
End of Pneumoperitoneum	86.62	101	<0.0001

Conclusion:

Perioperative IV Dexmedetomidine was found to be effective in providing Hemodynamic stability during laparoscopic surgeries without any significant adverse effects.

.TABLE OF CONTENTS

	TOPICS	PAGE NO.
1	INTRODUCTION	1-3
2	AIMS AND OBJECTIVES	4-5
3	REVIEW OF LITERATURE	6-32
4	BASIC SCIENCE	33-64
5	MATERIALS AND METHODS	65-72
6	OBSERVATIONS AND RESULTS	73-93
7	DISCUSSION	94-104
8	SUMMARY	105-107
9	CONCLUSION	108-109
10	BIBILIOGRAPHY	110-130
11	ANNEXURES	
	I. ETHICAL CLEARNACE CERTIFICATE	132
	II. INFORMED CONSENT	133-137
	III. PROFORMA	138-140
12	KEY TO MASTER CHART	141-142
13	MASTER CHART	143

LIST OF TABLES

Table no.	Title	Page no.
1.	Number of patients in both groups.	75
2.	Age distribution in both groups.	76
3.	Mean age distribution in both groups.	77
4.	Sex distribution in both groups.	77
5.	Mean Weight of patients in both groups.	78
6.	ASA status in two groups.	79
7.	Demographic profile of both the groups.	80
8.	Types of surgeries included in the present Study.	80
9.	Mean duration of pneumoperitoneum and duration of surgery in both the groups.	82
10.	Heart Rate in both groups.	83
11.	Systolic Blood Pressure (SBP) changes in both the groups.	85
12.	Changes in the Diastolic Blood Pressure (DBP) in both the groups.	87
13.	Changes in the Mean Arterial Pressure (MAP) in both the groups.	89
14.	Requirement of intra-operative Nitroglycerine (NTG) drip	91
15.	Requirement of intraoperative	92
16.	Post-operative nausea vomiting (PONV).	93

LIST OF GRAPHS

SL. No.	Title	Page No.
1.	Number of patients in both groups.	75
2.	Age Distribution in both the groups	76
3.	Sex distribution in both the groups.	77
4.	Mean weight in both the groups.	78
5.	ASA classification in both groups.	79
6.	Type of surgeries in both groups.	81
7.	Mean duration of PNP and Surgery in both groups.	82
8.	Changes in the Heart Rate (HR) in both the groups.	84
9.	Systolic Blood Pressure (SBP) in both the groups.	86
10.	Diastolic Blood Pressure (DBP) in both the groups.	88
11.	Mean Arterial Pressures (MAP) in both the groups.	90
12.	Graph comparing NTG use in both groups.	91
13.	Graph comparing atropine use in both groups.	92
14.	Graph showing PONV in both groups.	93

LIST OF PHOTOGRAPH

SL. No.	Title	Page No.
1.	Laparoscopic Trolley	15
2.	Inj Dexmedetomidine Hydrochloride	57
3.	Group D drug infusion	70
4.	Group S drug infusion	70
5.	Patient Monitoring	99
6.	Laryngoscopy	102

INTRODUCTION

INTRODUCTION

After almost 30 years of struggle for survival, laparoscopy proved not only its right for existence but is now considered, even by the most persistent sceptics, to be the 'gold standard' for several surgical procedures. The advantages of smaller skin scars, reduced trauma to the patient, lesser post-operative pain and shorter duration of hospital stay have made laparoscopy the procedure of choice for most surgical interventions.

However these advantages of laparoscopic surgeries come at a price. The pneumoperitoneum (PNP) required for laparoscopy results in pathophysiological changes.[1] Pneumoperitoneum is produced by administration of carbon dioxide (CO_2) into the peritoneal cavity during laparoscopic procedures.[2,3] Both pneumoperitoneum and CO_2 cause adverse cardiovascular effects.[4] Immediately after pneumoperitoneum plasma levels of norepinephrine, epinephrine and plasma rennin activity increase.[5] The renin-angiotensin-aldosterone system is also activated by increasing catecholamine levels. All these changes come together to contribute to elevated arterial pressure, increase systemic and pulmonary vascular resistance and reduced cardiac output.[6] Both mechanical and neurohumoral factors contribute to these hemodynamic changes.[7,8]

Hemodynamic stability during peri-operative period is of paramount importance as there are many patients who have a compromised cardiovascular status and are on medications. The anaesthesiologist's traditional approach to provide anaesthesia for laparoscopic procedures has been the emphasis on maintaining hemodynamic stability by avoiding hypertension, hypotension and tachycardia.

To prevent these adverse hemodynamic effects many interventions have been studied. They may be surgical interventions such as abdominal wall lift method

(Laparotensors) providing gasless field for visualization, low intra-abdominal pressure techniques or use of Helium/Argon gas instead of CO_2. Anesthetic interventions to prevent such hemodynamic changes could be the use of various modes of anaesthesia such as epidural or spinal or combined epidural and general anaesthesia techniques for the procedure; or the use of various pharmacological drugs such as opioids, esmolol, sodium nitroprusside, nitroglycerine and alpha-2 adrenergic agonists. But the search for the ideal agent to control this instability in hemodynamics is still on.

Dexmedetomidine is a selective α_2 agonist with 16 times more specificity for alpha-2 receptors compared to clonidine. It has an elimination $t_{1/2}$ of 2-3 hours. Intravenous administration of Dexmedetomidine before induction attenuates sympatho-adrenal response to laryngoscopy and intubation.[9]

This study is attempted to evaluate the efficacy of dexmedetomidine in blunting the neuro-endocrine response and subsequent hemodynamic changes that occur during laparoscopic surgeries.

AIMS AND

OBJECTIVES

AIMS AND OBJECTIVES OF THE STUDY

AIM

To study the efficacy of dexmedetomidine for attenuation of hemodynamic responses in patients undergoing laparoscopic surgeries.

OBJECTIVES

➢ PRIMARY OBJECTIVES

To study the effects of dexmedetomidine in

- Attenuation of hemodynamic responses associated with laryngoscopy and endotracheal intubation.
- Attenuation of hemodynamic responses associated with pneumoperitoneum.

➢ SECONDARY OBJECTIVES

To study the effects of dexmedetomidine on

- Postoperative nausea and vomiting.
- Associated adverse effects like bradycardia and hypotension.

REVIEW OF

LITERATURE

REVIEW OF LITERATURE

Laparoscopy is derived from two Greek words meaning ‘flank’ and ‘insight’. Many have described the advent of operative video-laparoscopy as a change to surgery as “revolutionary to this century as the development of anaesthesia was to the last century.”

History

Hippocrates, the father of Western medicine, detailed the use of a primitive anoscope to examine haemorrhoids in 400 B.C. An Arabian named Abulkasim improved on Hippocrates method around 1000A.D. by reflecting light to examine the cervix.

In 1806, Philip Bozzini produced the first endoscope with a light source, which he termed, the ‘Lichtleiter’ (light conductor) and used it as a cystoscope and vaginoscope. It is considered as the first true endoscope.

The advent of laparoscopy dates back to the beginning of the 20th century. It was in 1901 that Von Ott inspected the abdominal cavity of a pregnant woman. In 1902, Georg Kelling of Dresden in Germany, performed laparoscopic surgery on dogs and called it ‘Coelioscopie’. Eight years later, in 1910, Hans Christian Jacobaeus of Sweden reported the first laparoscopic operation on humans and named it ‘Laparothorakoskopie’.[10]The first large case series on the clinical use of laparoscopy appeared in 1920. B.H. Orndoff from Chicago described 42 cases of diagnostic peritoneoscopy.

A substantial advancement in the field of laparoscopy occurred in 1929 when Heinz Kalk, a German gastroenterologist, developed a 135-degree lens system and described the addition of a working port. In 1934, John Ruddock, claimed laparoscopy to be a diagnostic technique superior to laparotomy. His work produced

an important instrument in modern minimally invasive surgery - forceps with electro coagulation capacity.

Another modern tool of laparoscopy was introduced in 1938 when Hungarian Janos Veress developed a spring - loaded blunt tipped needle for draining ascites and evacuating fluid and air from the chest. Although he did not foresee the application of his tool in minimally invasive surgery, the Veress needle has become an indispensable instrument for many laparoscopic surgeons.

The greatest advance during the middle of the 20th century was not a surgical application but the technological discovery of fiberoptics. Hopkins, an English physicist, produced the first functional fiberoptic prototype in 1954. Overtolt helped develop the first flexible fiberoptic sigmoidoscope colonoscope in 1963.[11]

Few surgeons have had a more influential role in the development of minimally invasive surgery than Kurt Semm of Keil, Germany. He developed electronic carbon dioxide insufflators, producing a clear shift in the previous concept of air pneumoperitoneum. He also developed specific endoscopic tools with a designated function as a uterine manipulator, a high volume irrigation and aspiration device, knot tying instruments and a tubal patency testing device.[12]

Meanwhile, the technical key to Pandora's Box was found in 1982, when real-time, high resolution video camera was developed that could be attached to the endoscope. This development allowed a clear magnified image of the entire operating field that could be shown on a monitor, a recording device or elsewhere.

Five years after this critical innovation, the revolution in minimally invasive surgery began. The first laparoscopic cholecystectomy was reported in 1987 by Philippe Mouret in Lyon, France.

On the surface, it appears that a few advances in the history of surgery have become so widely accepted so quickly. However, given the long struggle against resistance that minimally invasive surgery incurred initially, these early laparoscopic cholecystectomies represent the breaking points that lead to the modern era of minimally invasive surgery. Shortly thereafter, laparoscopy became routinely used for colectomy, splenectomy, nephrectomy, adrenalectomy, appendectomy, small bowel resections, explorations and more.[13]

In September 1992 a NIH consensus conference held in Bethesda concluded that laparoscopic cholecystectomy is the treatment of choice for gall bladder lithiasis.[14] In today's clinical scenario, by far majority of cholecystectomies are done laparoscopically. The range of operations now extends from simple procedures such as herniorhaphy and ovarian cystectomy to complex operations including radical prostatectomy, nephrectomy and adrenalectomy.[15]

Laparoscopic surgery has many advantages over conventional open surgery:

- ✓ Avoiding large open incisions and thus decreasing blood loss, pain and discomfort to the patient
- ✓ Lesser analgesics required thus lesser side effects from the use of analgesics
- ✓ Lesser tissue trauma and blood loss
- ✓ Post operative complications related to the wound such as dehiscence, infection, cellulitis and incisional hernias are much lesser
- ✓ Lower incidence of postoperative peritoneal adhesions with their hazard of later bowel obstruction
- ✓ All these culminate to decreased recovery period, early mobilization leading to lower rates of chest infections and deep vein thrombosis
- ✓ Smaller scars for better cosmetic appearance

But all this comes at a cost. Laparoscopic surgery has several disadvantages as well. As very aptly put 'the size of the incision is inversely proportional to the anaesthetic risk'. Smaller the incision more is the anaesthetic risk.

Laparoscopic surgeries require creation of pneumoperitoneum (PNP), by insufflation of gases like carbon dioxide (CO_2) into the peritoneal cavity. The increase of intra-abdominal pressure (IAP) induced by the PNP and positioning during the procedure may lead to intraoperative hemodynamic instability and respiratory compromise.[16]

Adverse effects of Pneumoperitoneum

Carbon dioxide is insufflated into the peritoneal cavity at a rate of 4 to 6 L/min to a pressure of 10 to 14mm of Hg. The PNP is maintained by a constant flow of 200 to 400m1/min. The raised IAP due to PNP, alteration in the patient's positioning and effects of CO_2 absorption induce pathophysiological changes that complicate anaesthetic management.

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 calculated from measurement of airway flow 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 patient. There were no differences in

frequency and tidal volume dependences of the elastance and resistance before and after abdominal insufflations ($p<0.05$). 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.[17]

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 anaesthesia during laparoscopic cholecystectomy. Before laparoscopy, the patients received an intravenous (i.v.) 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 induction of anaesthesia in the same positions. Measurements were repeated at regular intervals during laparoscopy (IAP at 13 to 16mm of Hg), after deflation of the gas and in the recovery room. It was found that with 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 the systemic vascular resistance increased. With the patient under anaesthesia, SI decreased but CI did not change significantly as a result of the compensatory increase in the 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. Towards the end of

laparoscopy, CI decreased by l5%. 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 levels. The head-up positioning accounts for many of the adverse effects in hemodynamics during laparoscopic cholecystectomy.[18]

In another study, cardiovascular changes associated with insufflation of carbon dioxide and reverse Trendelenburg (rT) position during laparoscopic cholecystectomy were measured using Transesophageal echocardiography in 13 ASA I and II patients. End tidal carbon dioxide was increased 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.[19]

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). Hemodynamic 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 l0 minute anaesthetic induction, 15, 30 and 60 minutes after insufflations (IAP=12mm of 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 SVO2 (+8%) ($p<0.05$), which can be the result of 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 minutes after insufflation (from 33.9 to 38.3 mm of Hg, $p<0.05$) and a further increase after 60 minutes (44.4 mm of Hg) without any sign of extraperitoneal diffusion. There was no change in the intrapulmonary shunt and the end tidal carbon dioxide gradient ($Pa\text{-}ETCO_2$) remained stable (mean 7.2 mm of Hg). It was concluded that gradual intra abdominal insufflation to 12 mm of Hg followed by a limited 10 degree head up tilt is associated with cardiovascular stability in elderly ASA grade III patients.[20]

Hemodynamics (invasive arterial pressure, PAP, RAP, PCWP, HR, CO, SVR and PVR) measured during laparoscopic cholecystectomy under general anaesthesia (isoflurane in N_2O/O_2 (50%)) were investigated in 15 non-obese ASA class I patients by using invasive hemodynamic monitoring including a flow-directed pulmonary artery catheter. During surgery, IAP was maintained automatically at 14 mm of Hg by CO_2 insufflator and minute ventilation was controlled and adjusted to avoid hypercapnia. Hemodynamics were measured before anaesthesia, after the induction of anaesthesia, after tilting into 10 degree head-up position, 5, 10, 15 and 30 minutes

after peritoneal insufflation and 30 minutes after exsufflation. Induction of anaesthesia decreased mean arterial pressure and CI significantly. Tilting the patient to head-up position reduced cardiac preload and caused further reduction of CI. Peritoneal insufflation 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 anaesthesia, 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 hemodynamic changes are mediated both mechanically and humorally. These cardiovascular changes are not hazardous in healthy patients, special care and monitoring is mandatory with impaired cardiac function.[5]

In another study, 4l patients undergoing laparoscopic cholecystectomies were monitored using the SphygmoCor pulse wave analyzing system. Peripheral blood pressures (PBP), central aortic blood pressures (CBP), augmentation index (ALX@HR75) and subendocardial viability ratios were measured at rest (phase1), after anaesthetic induction (Phase 2), after peritoneal inflation (Phase 3) and after peritoneal deflation (Phase 4). Induction of anaesthesia resulted in a statistically significant reduction in both the peripheral blood pressure and central aortic pressures, accompanied by a decrease in augmentation pressure and augmentation index. Peripheral blood pressures did not change along with the peritoneal cavity insufflation, except for a moderate increase in systolic blood pressure. In contrast to this, an increase could be observed in central aortic pressure (106.77±18.78 vs.

118.05±19.85 mmHg, P<0.01) which was accompanied by increased augmentation pressure (18.97±10.80 vs. 31.55±12.01; P<0.001) and augmentation index (7.31±5.59 vs. 12.61±7.56, P<0.001), indicating a rise in peripheral arterial stiffness.[21]

Photograph 1: Laparoscopic Trolley

Peri-operative role of alpha-2 adrenergic agonists

Hemodynamic stability

One of the goals of anaesthesia, in patients who are at risk of cardiac ischemia during surgery, is to maintain myocardial oxygen balance and can be achieved by attenuating sympathetically mediated hyperdynamic responses to stimulation, while maintaining perioperative circulatory function. The ability of alpha-2 agonists to modulate sympathetic tone leads to a desirable hemodynamic profile, which may help to maintain the myocardial oxygen supply/demand ratio.[22]

A meta-analysis was conducted to investigate the effects of alpha-2 adrenergic agonists on peri-operative mortality and cardiovascular complications in adults undergoing surgery. MEDLINE (1966 to May 2002), EMBASE (1980 to May 2002), the Cochrane Clinical Trials Register, the Science Citation Index, and various other articles were searched without language restriction. Randomized trials comparing preoperative, intraoperative, or postoperative (first 48 hours) administration of clonidine, dexmedetomidine, or mivazerol with controls were included. Studies had to report any of the following outcomes: mortality, myocardial infarction, ischemia, or supraventricular tachyarrhythmia. Treatment effects were calculated using the fixed-effects model. Heterogeneity was assessed using the Q test. Twenty-three trials comprising 3395 patients were included. Overall, alpha-2 adrenergic agonists reduced mortality (relative risk [RR]: 0.64; 95% confidence interval [CI]: 0.42 to 0.99; P=0.05) and ischemia (RR=0.76; 95% CI: 0.63 to 0.91; P= 0.003) significantly.

They also reduced mortality (RR = 0.47; 95% CI: 0.25 to 0.90; P=0.02) and myocardial infarction (RR=0.66; 95% CI: 0.46 to 0.94; P=0.02) during vascular surgery. During cardiac surgery, alpha-2 adrenergic agonists reduced ischemia (RR=0.71; 95% CI: 0.54 to 0.92; P=0.01) and were associated with trends toward

lower mortality (RR: 0.49; 95% CI: 0.12 to 1.98; P=0.3) and a reduced risk of myocardial infarction (RR=0.83; 95% CI: 0.35 to 1.96; P=0.7). It was concluded that, alpha-2 adrenergic agonists reduce mortality and myocardial infarction following vascular surgery. During cardiac surgery, they reduce ischemia and may also have effects on mortality and myocardial infarction.[23]

A 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 perioperative ischemia compared with placebo.[24]

Sedation and anxiolysis

Dexmedetomidine administered at an intramuscular dose of 2.5mcg/kg as a premedication produced sedation and anxiolysis comparable with Midazolam dose of 80mcg/kg.

Anaesthetic requirement

Administration of an infusion of dexmedetomidine in patients undergoing abdominal hysterectomy was able to reduce the isoflurane requirements by 90%.[25] Dexmedetomidine has also been reported to be opioid and barbiturate sparing effects.

Analgesia

Alpha-2 adrenoreceptor 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 locus coeruleus and dorsal raphe nucleus and analgesia may be mediated by noradrenaline release. Alpha-2 adrenoreceptors, predominantly the alpha-2A subtype, have been identified in the substantia gelatinosa of the dorsal horn of the spinal cord. Stimulation of these alpha-2 adrenoreceptors by intrathecal

noradrenaline or specific agonists inhibits the firing of nociceptive neurons stimulated by peripheral A-delta and C fibers. Also, intrathecal noradrenaline inhibits the release of 'substance P' by primary afferents of the dorsal horn, and suppresses the activity of wide dynamic range neurons evoked by noxious stimulation.

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

The analgesic effects of intravenous dexmedetomidine (0.2 and 0.4mcg/kg) were demonstrated after laparoscopic tubal ligation. Dexmedetomidine 0.4mcg/kg was reported to provide analgesia requiring significantly less supplementation with morphine compared to analgesia provided by diclofenac 250mcg/kg. There was a high incidence of sedation and bradycardia in the Dexmedetomidine 0.4mcg/kg group, but there is no increase in respiratory depression and the bradycardia responded to atropine.[26]

Peri-operative use of dexmedetomidine

Two alpha-2 agonists, clonidine and dexmedetomidine, were compared to study the metabolic and hemodynamic effects in 30 ASA I patients undergoing plastic surgical procedures under general anaesthesia. Patients were premedicated with clonidine 4 mcg/kg (n=10), dexmedetomidine 2.5 mcg/kg (n=10) or saline (n=10) 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 pressures 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 with the placebo group. After operation, the maximum decrease in systolic arterial pressure

was 11%, diastolic arterial pressure 75% and oxygen consumption 17% in the clonidine and dexmedetomidine groups compared with placebo. Thus concluding that, both clonidine 4mcg/kg and dexmedetomidine 2.5mcg/kg decreased peri-operative oxygen consumption effectively, with a similar hemodynamic profile.[27]

Forty patients undergoing lumbar discectomy were randomly assigned to receive either Dexmedetomidine (a loading dose 1mcg/kg in 10 minutes followed by an infusion rate of 0.2mcg/kg/hr) or saline. In both groups, general anaesthesia was induced with fentanyl, thiopental sodium and rocuronium, and maintained with desflurane in 50% N_2O. Mean arterial blood pressure (MAP), HR, cardiac output (CO), and level of anaesthesia were monitored. Recovery times and analgesic requirements were also recorded. As a response to endotracheal intubation, a significant increase in MAP and HR was observed in the control group compared to the Dex group, but no difference in CO. The recovery times were significantly shorter in the Dex group compared to the control group. Anesthetic and analgesic requirements of the Dex group were lower than controls. Thus the authors concluded, the use of Dex caused no detrimental effects on the hemodynamic variables in prone position.[28]

Volunteers received either placebo or low or high-dose dexmedetomidine (target plasma concentrations 0.3 or 0.6 mg/ml, respectively) infusions in a prospectively randomized, double-blinded crossover study design. 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. Compared 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. During shivering, dexmedetomidine infusion was associated with higher low-frequency and high-frequency heart rate variability power but lower heart rate compared with the sweating threshold and with the control period, suggesting nonreciprocal cardiac autonomic responses. It was concluded that, infusion of dexmedetomidine results in compensated reductions in systemic sympathetic tone without changes in baroreflex sensitivity. Dexmedetomidine blunts heart rate and the systemic sympathetic activation due to sweating, but it is less effective in blunting cardiac sympathetic responses to shivering.[29]

In another double blind study, forty ASA grade I, non-pregnant women scheduled for dilatation and curettage were investigated for vigilance, thiopentone anaesthetic requirement and hemodynamic, catecholamine and hormonal response to surgery. Patients were divided in two groups and received either dexmedetomidine (0.5mcg/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 approximately 30%, which was due to smaller induction doses in the 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 pressures were only moderately increased.[30]

Ten healthy men between 20 to 27 years of age were monitored with electrocardiography (ECG), mean arterial pressure (MAP), central venous pressure (CVP) and pulmonary artery pressure (PAP), cardiac output (CO), oxygen saturation, end-tidal carbon dioxide ($ETCO_2$), respiration, blood gases, and catecholamines. Hemodynamic measurements, blood sampling, and psychometric, cold pressor, and baroreflex tests were performed at rest and during sequential 40min intravenous target infusions of dexmedetomidine (0.5, 0.8, 1.2, 2.0, 3.2, 5.0 and 8.0 ng/ml; 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 l3%, but did not change central venous pressure or pulmonary artery pressure. Subsequent higher doses increased sedation, all pressures, and calculated vascular resistance, and resulted in significant decreases in heart rate, cardiac output, and stroke volume. Recall and recognition decreased at a dose of more than 0.7ng/ml. The pain rating and mean arterial pressure increase to cold pressor test progressively diminished as the dexmedetomidine dose increased. The baroreflex heart rate showing 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. Thus, increasing concentrations of dexmedetomidine in humans resulted in progressive increases in sedation and analgesia, decreases in heart rate, cardiac output and memory. A biphasic (low, then high) dose-response relation for mean arterial pressure, pulmonary arterial pressure,

and vascular resistances and an attenuation of the cold pressor response also were observed.[31]

Fifty patients scheduled for elective minor surgery were randomized into two groups (dexmedetomidine group and placebo group, n=25 in each group). During and after drug administration, the Ramsey sedation scale was applied every 5 minutes. Fentanyl 1mcg/kg was administered to all patients and thiopental was given until lash reflex disappeared. Anaesthesia continuation was maintained with 50%:50%-oxygen: 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. Hemodynamic parameters and adverse effects were recorded every 10 minutes for 1 hour after surgery. It was observed 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±27.041µg in the placebo group ($p<0.05$). At 5 minutes, the Steward scores were >6 in 56% of the dexmedetomidine group and in 4% of the placebo group ($p<0.05$). At 10 minutes, sedation scores were ≥4 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 ($p<0.05$). Thus concluding, preoperative administration of a single dose of dexmedetomidine resulted in progressive increases in sedation, blunted the hemodynamic responses during laryngoscopy, and reduced opioid and anaesthetic requirements. Furthermore,

dexmedetomidine decreased blood pressure and heart rate as well as the recovery time after the operation.[32]

In yet another study, sixty six patients were investigated and randomized to receive 1.0 mcg/kg fentanyl (group F, n=22), 0.5mcg/kg dexmedetomidine (group D0.5, n=22), or 1.0mcg/kg dexmedetomidine (group D1.0, n=22) before induction. Autonomic nervous system balance was assessed by the ratio of low-frequency/high-frequency (LF/HF) power for heart rate variability at baseline (T0), before intubation (T1), and after intubation (T2). QT intervals were corrected by the Bazett's formula (QTc) and compared at baseline, before intubation, and 1, 2 and 3 minutes after intubation. The LF/HF ratio was higher after intubation compared with that at T0 in group F ($P < 0.001$). There were no significant changes in groups D0.5 and D1.0. The LF/HF ratio was significantly higher in group F compared with those in groups D0.5 and Dl.0 after intubation (7.9 vs. 2.1 and 2.5; $P<0.001$). The heart rate was increased for 3 minutes after intubation in group F, whereas only for 1 minute after intubation in groups D0.5 and Dl.0 compared with that at baseline. More patients in group F had QTc greater than 440ms compared with that in group D0.5 or D1.0 (8 vs. 1 and 2; P :0.005) at 1 minute after intubation. In contrast to 1.0 mcg/kg fentanyl, pre-treatment with 0.5 or 1.0 mcg/kg dexmedetomidine suppressed sympathetic hyperactivity and attenuated QTc prolongation during intubation.[33]

Another study was conducted to study the efficacy of intravenous dexmedetomidine for attenuation of cardiovascular responses to laryngoscopy and endotracheal intubation in patients with coronary artery disease. Sixty adult patients scheduled for elective off-pump coronary artery bypass surgery were randomly allocated to receive dexmedetomidine (0.5 mcg/kg) or normal saline 15 min before intubation. Patients were compared for hemodynamic changes (heart rate, arterial

blood pressure and pulmonary artery pressure) at baseline, 5 min after drug infusion, before intubation and 1, 3 and 5 min after intubation. It was observed that, the dexmedetomidine group had a better control of hemodynamics during laryngoscopy and endotracheal intubation. Dexmedetomidine at a dose of 0.5mcg/kg as l0 minutes infusion was administered prior to induction of general anaesthesia attenuates the sympathetic response to laryngoscopy and intubation in patients undergoing myocardial revascularization. The authors suggested its administration even in patients receiving beta blockers.[34]

Dexmedetomidine has anaesthetic sparing effects. In a study the pharmacokinetics and pharmacodynamic interaction between dexmedetomidine and isoflurane was determined in volunteers. Nine male subjects were allocated randomly to receive isoflurane anaesthesia preceded by infusion of dexmedetomidine on three separate occasions, 2 weeks apart. Dexmedetomidine target plasma concentrations were 0.0 (placebo), 0.3 ng/ml (low-dex) and 0.6 ng/ml (high-dex). End-tidal isoflurane concentrations at which gross purposeful movement and response to verbal commands occurred were identified. In the recovery period, sedation scores and digit symbol substitution tests were recorded. Venous blood samples were obtained before, during and after anaesthesia at predetermined intervals for measurement of plasma concentrations of dexmedetomidine and calculation of standard pharmacokinetic indices like area under the curve (AUC), Systemic Clearance (Cl), steady state volume of distribution (Vss) etc. The end-tidal isoflurane concentration at which 50% of subjects first responded to the tetanic stimulus was 1.05% in the placebo group, 0.72% in the low-dex group and 0.52% in the high-dex groups respectively. During anaesthesia the mean values for heart rate, systolic arterial pressures and diastolic arterial pressures were significantly less after both, low dose and high dose

dexmedetomidine infusion groups as compared to placebo. Thus dexmedetomidine decreased isoflurane requirements in a dose-dependent manner. Sedation and slight impairment of cognitive function persisted for several hours after anaesthesia and the end of infusion of dexmedetomidine. Isoflurane did not appear to influence the pharmacokinetics of dexmedetomidine.[35]

Dexmedetomidine was studied for its ability to attenuate stress responses during emergence from anaesthesia after major vascular surgery. Patients scheduled for vascular surgery received either dexmedetomidine (n=22) or placebo (n=19) i.v. beginning 20 min before the induction of anaesthesia and continuing until 48 hr after the end of surgery. Al1 patients received standardized anaesthesia. Heart rate and arterial blood pressure were kept within predetermined limits by varying anaesthetic level and using vasoactive medications. Heart rate, arterial blood pressure, and inhaled anaesthetic concentration were monitored continuously; additional measurements included plasma and urine catecholamines. During emergence from anaesthesia, heart rate was slower with dexmedetomidine (73±11bpm) 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). Thus implicating that dexmedetomidine attenuates increases in heart rate and plasma norepinephrine concentrations during emergence from anesthesia.[36]

Seventy two Patients scheduled for elective craniotomy were randomly assigned to receive either sevoflurane-opioid or sevoflurane-opioid-dexmedetomidine anaesthesia. Bispectral index (BIS) was used to maintain a similar level of hypnosis

in both groups (40-50). Opioids, sevoflurane, and vasoactive medications were titrated in a routine manner, at the discretion of the blinded anaesthesiologist managing the case, to maintain systolic blood pressure (SBP) targeted within 90-130 mm Hg and heart rate (HR) between 50 and 90 bpm. Hemodynamic variables were continuously recorded and stored on a computer for analysis. Efficacy of the anaesthetic technique in controlling SBP or HR is inversely proportional to the area under the curve (AUC) outside the targeted range. Areas under the curves above and below targeted ranges for SBP-time (AUCsbp mmHg*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 post-anaesthesia 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 antiemetics. 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 systolic blood pressure peri-operatively. The use of dexmedetomidine did not increase the incidence of hypotension or bradycardia.[37]

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's sympatholytic effects during that period. Dexmedetomidine was infused postoperatively by CCIP for 60 min to eight women, targeting a plasma concentration (Cp) of 600pg/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 (C[CSF]). Heart rate and arterial blood pressure were measured continuously from 5 min before until 3h 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, C(CSF) was 4%±l% of Cp. Because C (CSF) barely exceeded the assay's limit of quantization, CSF pharmacokinetics was not determined. 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; heart rate decreased from 76±15 to 64±11 bpm; and systolic blood pressure 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 the immediate postoperative period.[38]

A study was designed to define the interaction of intravenous infusion of dexmedetomidine and isoflurane in patients having surgery by using the minimum alveolar concentration (MAC) of isoflurane as the measure of anaesthetic potency.

Forty-nine women scheduled for abdominal hysterectomy were randomly allocated to receive either a placebo infusion (n=16) or a two-stage infusion of dexmedetomidine with target plasma concentration of 0.3 ng/ml (n=17) or 0.6 ng/ml (n=16). The study drug infusion was commenced 15 min before induction of anaesthesia with thiopental 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 min before the patient's response to skin incision was assessed. The MAC of isoflurane was 0.85% end-tidal in the control group, 0.55% end-tidal with the low dose of dexmedetomidine, and 0.45% end-tidal with the high dose of dexmedetomidine. The MAC of isoflurane in the control group was lower than that reported previously in similar patients having surgery, probably due to anaesthesia induction with thiopental and alfentanil. Nevertheless, with the high dose of dexmedetomidine, the MAC of isoflurane was still 47% less than that without dexmedetomidine.[39]

Laparoscopic surgery and dexmedetomidine

Eighty consenting ASA II-III morbidly obese patients, scheduled for laparoscopic bariatric surgery (either gastric banding or gastric bypass), were randomly assigned to 1 of the 4 treatment groups: (1) control group received a saline infusion during surgery, (2) Dex 0.2 group received an infusion of dexmedetomidine 0.2 mcg/kg/h IV (3) Dex 0.4 group received an infusion of dexmedetomidine 0.4 mcg/kg/h IV and (4) Dex 0.8 group received an infusion of dexmedetomidine 0.8 mcg/kg/h IV. Mean arterial blood pressure values were maintained within ±25% of the pre-induction baseline values by varying the inspired desflurane concentration. Peri-operative hemodynamic variables, postoperative pain scores, and the need for "rescue" analgesics and antiemetics were recorded at specific intervals. Follow-up evaluations were performed on postoperative days (PODs) 1, 2 and 7 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. Dex infusion, 0.2, 0.4 and 0.8mcg/kg/h, 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 post anaesthesia care unit (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 1, 2 and 7, 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 (0.2-0.8 mcg/kg/h) decreased fentanyl use, antiemetic therapy, and the length of stay in the PACU. However, it failed to facilitate late recovery (e.g., bowel function) or improve the patient's overall quality of recovery. When used during laparoscopic bariatric surgery, a dexmedetomidine infusion rate of 0.2mcg/kg/h was recommended by the authors to minimize the risk of adverse cardiovascular side effects.[40]

A randomized double blinded prospective clinical study designed to evaluate the efficacy of dexmedetomidine to provide perioperative hemodynamic stability in sixty patients, of either sex (18- 65yrs of age) undergoing elective laparoscopic cholecystectomy was done. Patients were randomly allocated in one of the two parallel groups containing 30 patients each. Group D received dexmedetomidine intravenous infusion at a rate of 0.2mcg/kg/h. Group S received 0.9% saline in the same rate. Mean arterial pressure and heart rate 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. The authors thus concluded that dexmedetomidine improves intra and post-operative hemodynamic stability during laparoscopic surgery without prolongation of recovery.[41]

In an observational study using entropy monitoring, 30 ASA grade I and II patients, aged between 18 to 50 years of either gender undergoing laparoscopic surgeries under general anaesthesia were studied. Loading dose infusion of dexmedetomidine was started at 1 mcg/kg for 15 minutes and patients were premedicated. Routine induction with propofol and fentanyl was carried out, and maintenance infusion of dexmedetomidine 0.2 mcg/kg/hr was given. Patients were monitored with standard monitoring, and in addition, the Depth of Anaesthesia (DOA) was monitored with entropy. A 62.5% reduction (0.75 mg/kg) in the induction dose of Propofol was observed, with a 30% less end-tidal concentration of isoflurane requirement for maintenance of anaesthesia, while maintaining adequate DOA. In other words, dexmedetomidine is an effective anaesthetic adjuvant that can be safely used in laparoscopy without the fear of awareness under anesthesia.[9]

In another study two doses of dexmedetomidine infusion were compared in patients undergoing laparoscopic cholecystectomy to evaluate the effects of low dose dexmedetomidine infusion on hemodynamic response to critical incidences such as laryngoscopy, endotracheal intubation, creation of pneumoperitoneum and extubation in patients undergoing laparoscopic cholecystectomy. Sixty patients of ASA physical grades I and II undergoing laparoscopic cholecystectomy were randomly allocated into three groups of 20 patients each. Group NS patients received normal saline, Group Dex 0.2 and Group Dex 0.4 patients received dexmedetomidine infusion at 0.2mcg/kg/h and 0.4mcg/kg/h respectively, starting 15 min before induction and continued till end of surgery. Parameters noted were pulse rate, mean arterial pressure, oxygen saturation, post-operative sedation and analgesia requirements. The results of the study revealed that, in Group NS significant hemodynamic stress response was seen following laryngoscopy, tracheal intubation, creation of

pneumoperitoneum and extubation. In dexmedetomidine groups, the hemodynamic response was significantly attenuated. The results, however, were statistically better in Dex 0.4 group compared with Dex 0.2 group. Post-operative 24 hour analgesic requirements were much less in dexmedetomidine groups. Thus concluding that Low dose dexmedetomidine infusion in the dose of 0.4mcg/kg/h effectively attenuates hemodynamic stress response during laparoscopic surgery with reduction in postoperative analgesic requirements.

BASIC SCIENCE

BASIC SCIENCE

I. Physiology of Laparoscopy

a) Physiological effects of Pneumoperitoneum

b) Physiological effects of positioning

c) Physiological effects of carbon dioxide absorption

d) Effects of gas insufflation

II. Physiology of alpha-2 adrenoreceptors

III. Pharmacology of Dexmedetomidine

I. Physiology of Laparoscopy

a. Physiological effects of Pneumoperitoneum

Intra-abdominal hypertension is defined as an intra-abdominal pressure above 12 mmHg. Rapid progression of intra-abdominal hypertension will lead to abdominal compartment syndrome, which is defined as an intra-abdominal pressure greater than 20 mmHg with at least one organ failure.[43]

l- Cardiovascular system

Circulatory changes induced by an increased IAP are still controversial. Some authors found a decrease in cardiac output from the very beginning of the increase in IAP[44], whereas others showed that this decrease was preceded by an unchange[45,46] or even a slightly increased cardiac output at low IAP value.[45,46,47]

Conflicting results obtained in these studies might be attributable to at least two factors. First, most of these studies have been performed in patients undergoing abdominal surgery under laparoscopy by using carbon dioxide insufflations. These gas insufflations can induce their own circulatory effects, probably as a result of the activation of a neurohumoral vasomotor system.[49] Second, the measures were usually

performed with a single value of IAP around 15 mm Hg precluding the analysis of the effect of IAP over a wider range of values.

This prompted another group of authors to study the loading conditions during gradually increasing IAP, using echocardiography in an experimental pig model, and examine the effect of the volaemic status. Study documented left ventricular preload and afterload changes in response to a gradual increase in IAP. In normovolaemic conditions, the decrease in abdominal venous capacitance led to a redistribution of abdominal blood volume towards the thoracic compartment at IAP lower than 15 mm Hg, and at its expense at higher values. In hypovolaemia, there was no gain in the thoracic compartment. Whereas the absolute or transmural right atrial pressures were not informative of the direction of this blood shift, a right atrial pressure greater than IAP was associated with an intrathoracic compartment gain.[50]

The increased abdominal pressure will have a biphasic effect on venous return: an initial transient increase due to compression of the abdominal capacitance vessels followed by impedance of venous return from the abdomen (decreased preload) and the lower limbs. In fact, study by **Goodale RL *et al***. shows that during abdominal CO_2 insufflation, the measured pressure in the femoral veins is increased with reduced flow velocity indicating decreased venous return from the lower extremities. [51]

In another study, 10 patients in each group were investigated for the hemodynamic effects of high (15 mmHg) and low (7 mmHg) IAP during laparoscopic cholecystectomy. In the high-pressure group, heart rate (HR) and mean arterial blood pressure (MABP) increased during insufflation. Stroke volume (SV) and cardiac output were depressed by a maximum of 26% and 28%. In the low-pressure group, insufflation produced a rise in MABP and a peak rise in both stroke

volume and cardiac output of 10% and 28% respectively ($p < 0.05$). They concluded that low-pressure pneumoperitoneum laparoscopic cholecystectomy and minimizes hemodynamic effects of peritoneal insufflations.[52]

Ishaizaki *et al*. tried to evaluate the safe intra abdominal pressure during laparoscopic surgery. They observed significant fall in cardiac output at 16 mm Hg, of intra abdominal pressure. Hemodynamic alterations were not observed at 12 mm Hg of intra-abdominal pressure.[53]

Changes in the cardiovascular system are characterized by an increase in arterial pressure and systemic and pulmonary vascular resistances (SVR and PVR) early after the beginning of intra-abdominal insufflation, with no significant changes in the heart rate (HR) with a fall in cardiac output recorded in most of the studies.

Changes in cardiac output:

In a study carried out by **Joris *et al***.[54] cardiac output significantly decreased shortly after the beginning of peritoneal insufflation. The subsequent increase in cardiac output probably resulted from surgical stress, as reflected by increased concentrations of cortisol. Impairment of hemodynamic status occurs mainly at the beginning of peritoneal insufflation probably related to a reduction in preload.

Pneumoperitoneum results in caval compression[55], an increase in venous resistance[56], and pooling of blood in the peripheral circulations[57]. All these effects contribute to decreased venous return. A decline in venous return was confirmed by a reduction in left ventricular end diastolic volume, measured using transesophageal echocardiography.[45]

One must clearly distinguish between the sequential hemodynamic effects of anaesthesia, positioning, (usually 10-20 degrees reverse Trendelenburg), mechanical and neuro-endocrine effects of the pneumoperitoneum and those of absorbed CO_2.

Thus, studies reporting serial rather than single measurements of hemodynamic parameters are most informative. In studies of serial measurements[57,58] , cardiac index mostly followed a biphasic pattern of an early reduction followed by partial recovery of cardiac index. This is supported by studies reporting single measurements of cardiac index during the creation of the pneumoperitoneum.[59,60,6l]

The mechanism:

The initial reduction in cardiac index (CI) is due to the effects of induction of general anaesthesia and positioning. The direct myocardial depressant and the vasodilatory effects of the anaesthetic together with the loss of sympathetic tone cause the initial reduction in CI. This change is followed by the reduction in venous return (preload) due to positioning in reverse Trendelenburg causing a further decrease in CI and pulmonary artery occlusion pressure. The effects of abdominal distension with CO_2 are more complex and it is important to distinguish between the direct mechanical (compressive) effects, the neuro-humoral responses and those of absorbed CO_2.[7]

The cephalad shift of the diaphragm due to abdominal distension will increase pleural pressure, which will, in turn, be partially transmitted to the cardiac chambers causing an increase in cardiac filling pressures (central venous pressure[CVP] and pulmonary artery occlusion pressure[PAOP]). The increased PAOP and reduced CI do not represent cardiac dilatation since ventricular volumes measured by transesophageal echocardiography (TEE) in healthy patients were not increased.[l9] The paradoxical increase in right atrial pressure and pulmonary capillary wedge pressure during insufflation despite decreased venous return[7,8,60] can be explained by the increased intrathoracic pressure associated with PNP. Therefore, during PNP, right atrial pressure and pulmonary capillary occlusion pressure can no longer be

considered reliable indexes of cardiac filling pressures.[54] A 10% to 30% decrease in cardiac output has been reported in most studies.[7,62]

Increase in SVR:

In addition to its effect on venous return, the pneumoperitoneum will directly compress the abdominal arterial tree to a certain extent. This increase in after load (along with other mechanisms) will adversely affect CI. The changes in CI arc closely linked chronologically to the changes in SVR. This may be partially explained by the mathematical coupling which exists between these two measurements:

SVR= (MABP - CVP / CO) * 80 dynes. cm. Sec $^{-3}$

However, one must invoke potent neuro-humoral responses to adequately explain CI recovery and changes in MAP and SVR that occur in all patients during prolonged CO_2 insufflation.[7]

All studies conducted to date describe an increase in SVR during PNP. This increase in afterload cannot be simply considered a reflex sympathetic response to decreased cardiac output. Indeed, SVR also increased in studies where no decrease in cardiac output was reported.[19, 63] Although comparatively better tolerated in healthy patients, they can further lead to decrease in cardiac output in patients with poor cardiac reserve.[64]

The increase in SVR is considered to be mediated by mechanical and neurohumoral factors.[7,8,65] and the role of mechanical factors might not be predominant.

Increase in SVR parallels the increase in PVR in most of the studies. The filling pressures of the heart (pulmonary artery occlusion (wedge) pressure (PAOP) and central venous pressure (CVP), which are markedly reduced by the induction and by positioning in reverse Trendelenburg, increase when CO_2 insufflation starts.[8,60,66-

[68] Same finding of increased SVR along with MAP was also found in other group of studies after PNP creation.[19,57,58]

J. L. Joris *et al*.[7] investigated hemodynamics during laparoscopic cholecystectomy under general anaesthesia {isoflurane in N_2O/O_2 (50%)} in 15 non obese ASA Class I patients by using invasive hemodynamic monitoring including a flow-directed pulmonary artery catheter. Hemodynamics were measured before anaesthesia, after the induction of anaesthesia, after tilting into 10 degrees head-up position, 5 min, 15 min and 30 min after peritoneal insufflation, and 30 min after exsufflation. Peritoneal insufflation 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.

Summary of hemodynamic changes due to mechanical pressure of CO_2 insufflation

- Increased systemic vascular resistance (SVR)
- Increased Mean Arterial pressure (MAP)
- Minimal alternation in heart rate (HR)
- Increased cerebral blood flow (CBF)
- Increased intracranial pressure (ICP)
- Decreased renal blood flow (RBF)
- Decreased portal blood flow
- Decreased splanchnic blood flow
- Decreased pulmonary compliance

Endocrine correlates of hemodynamic changes:

Several mediators like catecholamines,[69,70] prostaglandins,[71] renin,[71] and vasopressin[73,74] have been proposed for their role in hemodynamic changes during laparoscopic surgeries. The plasma concentrations of dopamine,[75] vasopressin,[76,8

adrenaline,[8] noradrenaline,[75,8] renin,[8] and cortisol [70,8] increases considerably. Also it has been found that the plasma concentration - time course profile parallels that of the changes in CI, MABP, and SVR,[75,8] suggesting a probable cause - effect relationship.

The profile of vasopressin release in studies by **Joris *et al***[54] correlated most closely with changes in SVR. Induction of PNP resulted in a rapid and marked release of vasopressin in both studies. Increases in plasma vasopressin levels were correlated with changes in intra-abdominal pressure, intrathoracic pressure and transmural RAP.[74]

Mechanical stimulation of peritoneal receptors also resulted in increase of vasopressin release[77], SVR and arterial pressure[78]. However, whether increasing intra-abdominal pressure to 14 mm Hg is sufficient to stimulate these receptors is unknown.

Plasma concentrations of vasopressin measured in two studies by **Joris *et al***[54] were high, and of a magnitude similar to those reported during acute hemodynamic stimulation (e.g. massive haemorrhage). This is important because vasopressin is a potent vasopressor even at normal physiologic concentrations.[79]

The authors[54] also found that catecholamines, and more particularly norepinephrine, which were also released early during PNP, might contribute to the increase in afterload. Accordingly, clonidine which significantly reduced the release of catecholamines and almost completely blocked norepinephrine release attenuated the increase in SVR. They could not determine the stimulus for catecholamine release during PNP from their studies, but however they suggested that hypercarbia and surgical stress were probably not the cause of the initial increase in epinephrine and nor epinephrine. This is because in their study $PaCO_2$ was kept within physiologic limits and plasma cortisol levels had not yet changed at 5 min of PNP in both studies.

The gradual increase in plasma catecholamine concentrations observed later intra-operatively may be correlated with surgical stress, as reflected by increasing plasma concentrations of cortisol, and may contribute to the intraoperative improvement of cardiac output.

They[54] also found that in their study that the plasma concentration of renin was already increased before insufflation, probably in response to decreased venous return secondary to the head-up position and subsequent hypotension. Five minutes after the beginning of insufflation, even though SVR had reached its peak, no significant further increase was observed. The contribution of renin to the initial increase in after load is therefore questionable.

It has been suggested that during PNP the progressive increase in plasma renin concentration might be related to activation of the sympathetic system and to surgical stress[80]. Furthermore, renin secretion may also result from reduction of glomerular filtration and renal plasma flow induced by PNP.[81,82]

Finally, **Joris *et al***.[54] found that prostacyclin, prostaglandin Thromboxane E_2 and endothelin did not seem to contribute to hemodynamic changes induced by pneumoperitoneum.

Effect of absorbed CO_2:

During prolonged co_2 insufflation, considerable systemic absorption occurs and hypercarbia probably plays an important role in the recovery of CI. The pulmonary elimination of carbon dioxide during laparoscopic cholecystectomy is biphasic. The pattern is characterized by an initial brisk increase in CO_2 elimination (30%)[67] which starts shortly after insufflations begins, followed by a less brisk rate. The initial steep increase reflects the initial rapid peritoneal absorption of CO_2

followed by reduced absorption due the stretch of the peritoneal surface with compression of the perioneal vessels.[83,84]

Intentional hypercarbia increases cardiac output,[85,86]mean arterial blood pressure, plasma epinephrine (E) and norepinephrine (NE) concentrations[85]. The SVR decreasess[85,86], reflecting the direct vasodilatatory effects of CO_2 when that is not countered by activation of the sympathetic nervous system with vasoconstriction of venous capacitance vessels. The net effect of the pneumoperitoneum and hypercarbia during laparoscopic surgery will usually include increases in SVR, CO, CVP[85] and PAOP[86]. Thus, the alteration in cardiovascular dynamics during laparoscopic surgery are probably influenced by increased CO_2, either directly (vasodilatation) or indirectly by stimulating the sympathetic nervous system.

Effect of position on hemodynamics:

The filling pressures of the heart (pulmonary artery occlusion (wedge) pressure (PAOP) and central venous pressure (CVP), are markedly reduced by the induction and by positioning in rT (reverse Trendelenburg).[7]

It has been found that increased intra-abdominal pressure and reverse Trendelenburg positioning may reduce cardiac output and renal blood flow.[72] There is four-fold increase in plasma concentrations of renin and aldosterone after pneumoperitoneum and reverse Trendelenburg positioning.

Data from two groups of patients undergoing laparoscopic surgeries either in the head-up position for cholecystectomy or in the head-down position for hysterectomy were compared in order to determine if there are differences in the stress responses, as reflected by neuroendocrine activation.[69] The two surgical positions differed in their effect on the circulation. In awake patients, head-down tilt was associated with increased concentrations of plasma natriuretic peptide -pro ANP

(atrial natriuretic peptide), indicating increased venous return and atrial stretch. There were no significant differences between groups in cortisol or adrenaline concentrations, or in renin activity. Noradrenaline concentrations increased more in the head-up group suggesting increased sympathetic system activity. In conclusion, abdominal surgical laparoscopy in both the head-up and head-down positions caused marked activation of neuroendocrine responses.

2. <u>Respiratory system</u>

Pneumoperitoneum, which may be as much as 25 to 30L CO_2 in the first 30 min, can have undesirable cardio-respiratory effects, particularly in patients with pulmonary disease in whom severe respiratory acidosis has been reported.[57] If cardiac output is reduced, adverse effects on CO_2 homeostasis and oxygenation can occur. Insufflation of CO_2 is an increased 'load' on ventilation due the volume of CO_2 added by trans-peritoneal absorption. Also, the increased abdominal volume impedes diaphragmatic descent and reduces total compliance, even though the reverse Trendelenburg position may reduce the effects of the increased abdominal volume.[87] Appropriate measures, in particular, increasing minute ventilation must be undertaken to counter the effects of increased CO_2.

During pelvic laparoscopy in the Trendelenburg position, a 20-30% increase in minute volume is necessary to maintain normocarbia.[88]

Changes in the FRC and total compliance (C_{TOT}):

During general anaesthesia, FRC (functional residual capacity) and C_{TOT} (total compliance) arc reduced by about 20% with an increased airway resistance (Paw), as determined by the magnitude of FRC reduction.[89] The FRC is directly related to the body build, and can be reduced by 50% in the obese.[90] cephalad displacement of the diaphragm following induction of anaesthesia causes the reduction in FRC and this

therefore increases the ventilation to perfusion mismatching, which results in the increase in the alveolar-arterial oxygen tension difference ($PA–aO_2$).[89] placing the anaesthetized patient in the reverse Trendelenburg position will increase FRC and presumably compliance, but will not necessarily improve oxygenation.[90]

In a study, the authors found that insufflation of the abdomen with the patient in the supine position, immediately decreased C_{TOT} by 43%[91] and no further changes occurred upon positioning. The distension will prevent the expected passive caudal displacement of the diaphragm that results from reverse Trendelenburg positioning.[90] When insufflation was performed with the patient already in the reverse Trendelenburg position, mean C_{TOT} was reduced by 32%[92] to 48%.[93] The data indicate that insufflation alone leads to a marked reduction in compliance and that subsequent tilting does not further affect the compliance grossly.[91]

Effect on the airway pressures:

After the creation of pneumoperitoneum, end-inspiratory airway pressure increases by 40%, and compliance decreases by 30%.[94] However another author argues that increase in airway pressure (Paw) cannot be used to estimate alterations in compliance because the increase is also due to the augmentation in minute ventilation required to decrease $PetCO_2$.[7]

During laparoscopic cholecystectomy in healthy patients, PaO_2 was stable in spite of the changes in compliance and cardiac output mentioned above.[8]

Morbid obesity significantly decreases respiratory system compliance and increases inspiratory resistance. Increased body weight, and not altered mechanics of breathing, was associated with worse PaO_2 during laparoscopy.

CO_2 homeostasis:

Carbon dioxide homeostasis is a major consideration during laparoscopic cholecystectomy. Hypercarbia occurs because of CO_2 absorption and because compliance is reduced, which impedes adequate pulmonary gas exchange. During the initial 30 minutes, 27+2.5 L CO_2 may be insufflated.[95]

The elimination of the insufflated CO_2 depends on cardiac output, ventilation: perfusion ratios and alveolar ventilation.[87]

Cardiac output is the delivery system of CO_2 to the lungs for elimination and is a determinant of the ventilation: perfusion ratios. As seen already cardiac output either remains same, or decreases in most of the patients during pneumoperitoneum.

The second component in the elimination of CO_2 is the ventilation: perfusion relationship which will be influenced by cardiac output and lung mechanics.

Appropriate increases (12-16%) in minute volume in healthy patients for laparoscopic cholecystectomy could, in most instances, maintain $PaCO_2$ within acceptable limits,[8,87] but did not invariably normalize $PaCO_2$.[87,92] The difference in the amount of minute volume required to achieve end results could be because of the different durations of surgery, and the change in position during surgery.

In another study[61] which dealt with ventilation and $PaCO_2$ during laparoscopic cholecystectomy, the authors concluded that $PEtCO_2$ must be closely monitored and ventilation increased to maintain $PEtCO_2$ below 35 mmHg (4.7 kPa). Also they suggested that the definite, although statistically insignificant, increase in cardiac output is the result of transperitoneal absorption of CO_2.

Postoperative lung function:

Lung function following open upper abdominal surgery is typically restrictive, with more rapid and shallower breathing, reduced vital capacity and FRC with

hypoxemia.[89] A shift from abdominal to rib-cage breathing occurs and is due to the loss of diaphragmatic contribution to tidal volume.[89]

There is also a considerable alteration in the pulmonary defence mechanism. The direction of mucociliary flow is reversed, particularly in the lung zones immediately above the operative site, with retention of secretions.[89]

Two major factors determining the magnitude of these changes are incisional pain and reflex inhibition of diaphragmatic function due to afferent nociceptive signals from the chest wall and/or viscera. Adequate subjective pain relief by epidural analgesia brings about a small increase in FRC and a transient restoration of about 30% of the loss in vital capacity, highlighting the importance of adequate analgesia in post-operative period for adequate lung function.[96] Thus, in examining lung function after laparoscopic surgery, one must consider the changes in vital capacity, FRC, oxygenation and analgesic requirements.

Most authors have examined the reduction in expiratory lung volumes and have come to the conclusion that the magnitude of reduced vital capacity and FEV1 (forced expiratory volume in first second) following laparoscopic cholecystectomy, although quite marked (20 to 40%), was much less than that following 'open' cholecystectomy.[97-100] Reduced PaO_2 was minimal and transient.[99,100]

Two aspects of two reports are noteworthy.

- First, the return to normal function was noted to be twice as fast following in laparoscopic cholecystectomy (5 vs. 10-12 days) compared to open cholecystectomy.[99]
- Secondly, the determination of vital capacity and FEV1 is effort-dependent whereas forced expiratory flow during 25-75% of the vital capacity breath (FEV25-75%) is not, and is, therefore, a better measurement. The reduction in

FEV 25-75% following open cholecystectomy (50%) was almost double that after laparoscopic cholecystectomy (25%) on day 2.[100] On the day of surgery, a transient 20% reduction in FRC following laparoscopic cholecystectomy was reported. This compares very favourably with the 34% reduction after open cholecystectomy.[99]

An important aspect of the report is that marked reductions in FRC occurred in the older, more obese patients and in smokers.

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 anaesthesia because of a variety of factors:

a) Cephalad shift of the diaphragm associated with supine position.[101]
b) Loss of inspiratory muscle tone.
c) Appearance of end expiratory muscle tone in the abdominal expiratory muscles.
d) Changes in intrathoracic blood volume associated with induction of anaesthesia.
e) Influence of muscle relaxants on diaphragmatic excursion.[l02]

Reduced FRC is associated with the development of atelectasis. Sub radiological microatelectasis following surgery occurs normally, detectable only by computerized tomography (CT) scanning. It has been noted in 90% of patients one hour after surgery and can be found in 50% after 24 hr, without clinical evidence of atelectasis[103] or reduced FRC. Radiological atelectasis of varying degrees (micro to lobar) occurred in 40% of patients following laparoscopic cholecystectomy, compared with 90% of patients after open cholecystectomy.[104]

3. <u>Renal system and Metabolism</u>

Marked increased in 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.

Carbon dioxide (CO_2) pneumoperitoneum together with an increased intra-abdominal pressure (IAP) induces a hemodynamic stress response, diminishing urine output and may compromise the splanchnic perfusion.[105]

Head-up position and intra-abdominal pressure greater than l2mmHg should be avoided during laparoscopic surgery because they compromise hepatic and renal blood flow. In respect to insufflation gas effect on intra-abdominal visceral perfusion, it has been found that Argon insufflation impairs liver blood flow. However, helium may be advantageous compared with CO_2 insufflation.[106]

Respiratory acidosis is caused during CO_2 insufflation for laparoscopic cholecystectomy, because of

1. Decreased compliance.
2. Increased CO_2 load.
3. Insufficient ventilation.

Accumulated CO_2 during laparoscopic cholecystectomy increased $PaCO_2$ level in the recovery room.[107]

When ventilatory effects and blood gas changes of prolonged CO_2 pneumoperitoneum in normally ventilated patients undergoing laparoscopic hysterectomy were evaluated, it was found that oxygen consumption decreased with anaesthesia, remained stable to the end of the laparoscopy, increased soon after deflation of the pneumoperitoneum, and reached preanesthetic values during recovery.[108]

4. Gastro-intestinal system

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

5. Nervous system

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

De Cosmo G *et a1*.[109] hypothesized that laparoscopic surgery requires a series of procedures, including intra-peritoneal CO_2 insufflation, which can cause cardiovascular and hemogasanalytic modifications, potentially able to impair cerebral perfusion, however their findings suggested that the cerebrovascular system can undergo adaptive changes during all phases of laparoscopic surgery. However, the extent of cardiovascular and cerebrovascular variation indicates the need for careful preliminary evaluation of cerebral hemodynamics in patients with vascular disorders before laparoscopic surgery. However the extent of cardiovascular and cerebrovascular variation indicates the need for careful preliminary evaluation of cerebral hemodynamics in patients with vascular disorders before laparoscopic surgery.

The blood flow velocity through the middle cerebral artery (an index of CBF) can increase by increase by as much as 50%, probably due to the increase in $PaCO_2$.[110]

Cellular respiration remained intact despite a concomitant increase in $PETCO_2$ and cerebral blood volume during laparoscopy with CO_2 insufflation.[111]

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.

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.

c. Physiological effects of carbon dioxide absorption

Carbon dioxide is the most commonly used gas for insufflations of abdomen as it is colourless, non toxic, non flammable, and has the greatest margin of safety in the 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), effects on the 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.[75]

d. Effects of gas insufflation

Pneumoperitoneum is the essential component for laparoscopic procedures. Even though a gasless approach has been described utilizing an intra-abdominal lift, this approach has never been documented as better than pneumoperitoneum in healthy patients. There are several characteristics which are considered optimal for this gas.[106] Since the surgical procedure may include electrocautery, gases which usually are not able to support combustion are essential. Although oxygen and air would not have significant physiological consequences when absorbed, they assist combustion as well as would have significant deleterious effects with intravascular embolization. Nitrous oxide might have limited physiological effects when absorbed and it is highly soluble, thereby limiting its effects with intravascular embolism, however like air and oxygen, nitrous oxide supports combustion. Although both helium and argon result in little or no change in $PaCO_2$ when compared to CO_2 pneumoperitoneum, and the amount of gas that must definitely be injected intravenously to cause death is markedly less with these inert agents compared to CO_2, availability and cost effectiveness are the concerns with these agents. Due to the issues with some other gases, CO_2 continues to be agent commonly used during laparoscopic procedures.

The perfect gas for insufflation during laparoscopy must have the following characteristics:

- Limited systemic absorption over the peritoneum.
- Limited systemic results when absorbed.
- Rapid removal if absorbed.
- Not supporting combustion.
- High solubility in blood.

- Limited physiological effects with intravascular systemic embolism.
- Cost effective.

Although CO_2 is considered one of the safest gases used for pneumoperitoneum the following adverse effects may be seen during laparoscopic surgery done with CO_2 insufflation:

1. cardiac 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.[112]

2. 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.[113]

3. Venous gas embolism

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.[114]

Although rare, there have been reports of fatal[115] and near fatal CO_2 embolism[116] during laparoscopic cholecystectomy.

6. Trauma

Introduction of trocars may cause damage to underlying organs (e.g. 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.

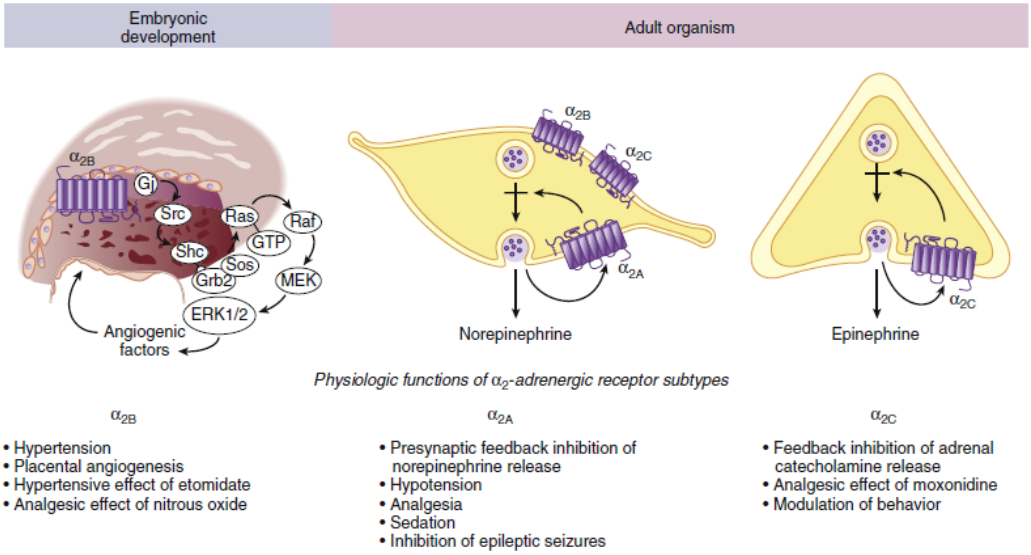
II. Physiology of Alpha 2 Adrenoreceptors

Structure of alpha-2 adrenoreceptors

The alpha-2 adrenoreceptor 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 adrenoreceptor 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. Three subtypes of alpha-2 adrenoreceptors have been described in humans: alpha-2A, alpha-2B, and alpha-2C. 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, counter balancing the 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.[117]

Distribution of alpha-2 adrenoreceptors



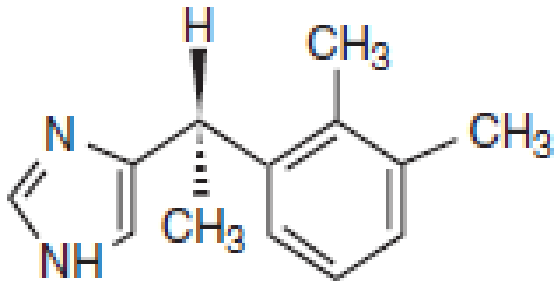
The alpha-2A adrenoceptors are primarily distributed in the periphery, whereas alpha-2B and alpha-2C are in brain and spinal cord.

Presynaptic alpha-2 adrenoceptors are present in sympathetic nerve endings and noradrenergic neurons in the central nervous system where they inhibit the release of noradrenaline. Postsynaptic alpha-2 adrenoreceptors 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. Postsynaptic alpha-2 adrenoreceptors located in peripheral blood vessels produce vasoconstriction; whereas presynaptic alpha-2 adrenoreceptors inhibit the release of norepinephrine and potentially attenuate the vasoconstriction. The overall response to alpha-2 adrenoreceptor antagonists is related to the stimulation of alpha-2 adrenoreceptors located in the CNS and spinal cord.[118] The medullary dorsal motor complex in the brain has a high density of alpha-2 adrenoreceptors and activation of these may be responsible for the hypotensive and bradycardic effects of alpha-2 adrenoreceptor agonists.[119]

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 adrenoreceptor agonists mediated by alpha-2a adrenoceptors located there.[120]

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 the 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 adrenoreceptors 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 adrenoreceptors, while the primary sensory neurons contain both alpha-2B and alpha-2C subtypes of adrenoreceptors.

III. Pharmacology of Dexmedetomidine

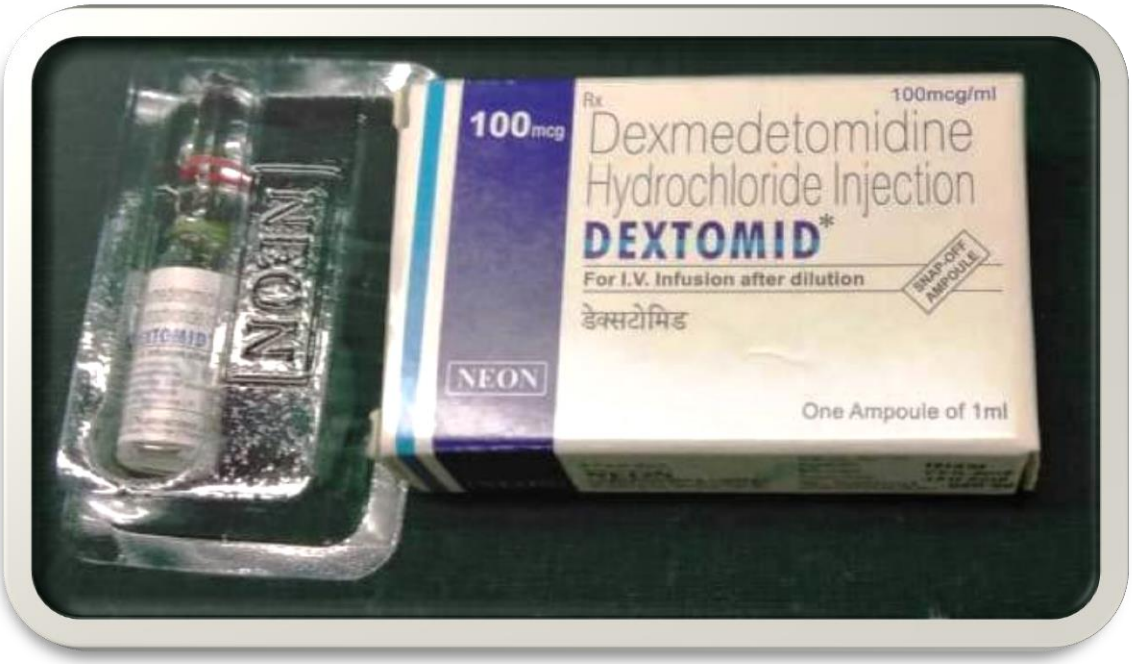


Structure of Dexmedetomidine

Dexmedetomidine belongs to the imidazole subclass of alpha-2 receptor agonist, similar to clonidine. Dexmedetomidine is the S-enantiomer and pharmacologically active component of medetomidine, which has been used for many years in veterinary practice for its hypnotic, sedative and analgesic effects. It shows a high ratio of specificity for the alpha-2 receptor (alpha-2/alpha-1=1600:1) compared with clonidine (alpha-2/alpha-1= 220:1), thus making it a complete alpha-2 agonist.[121] Compared to clonidine, it is seven to ten times more selective for alpha-2 receptors and has a shorter duration of action, than clonidine. Atipamezole is a specific and selective alpha-2 receptor antagonist that rapidly and effectively reverses the sedative and cardiovascular effects of dexmedetomidine. Atipamezole is currently not approved for use in humans.[122]

It is freely soluble in water and is available as a clear isotonic solution containing 100mcg/ml and 9mg sodium chloride per millilitre of water.

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.



Photograph 2: Inj Dexmedetomidine Hydrochloride

Pharmacokinetics and metabolism

Dexmedetomidine undergoes almost complete biotransformation with very little unchanged dexmedetomidine excreted in urine and faeces. Biotransformation involves both direct glucuronidation and cytochrome P450-mediated metabolism. The major metabolic pathways of dexmedetomidine are direct N-glucuronidation to inactive metabolites, hydroxylation (mediated primarily by CYP2A6) and N-methylation.

Dexmedetomidine is 94% protein bound and its concentration ratio between whole blood and plasma is 0.66.

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 intramuscular route probably offers the better predictability as well as reasonably rapid onset, the peak plasma concentration occurring within l5 min.[123]

The pharmacokinetics of dexmedetomidine is not influenced by renal impairment (Creatinine clearance <30 ml/minute) or age. In patients with severe renal disease, the sedative effect may be stronger as a result of a lower degree of plasma protein binding. Clearance is a function of height.[123,124] The elimination half-life of Dexmedetomidine is 2 to 3 hours, with a context sensitive half-time ranging from 4 minutes after a l0-minute infusion to 250 minutes after an 8-hour infusion.

Pharmacodynamics

Dexmedetomidine acts nonselectively on various subtypes of membrane bound G protein-coupled alpha-2 adrenoreceptors. Intracellular pathways include inhibition of adenylate cyclase and modulation of calcium and potassium ion channels.

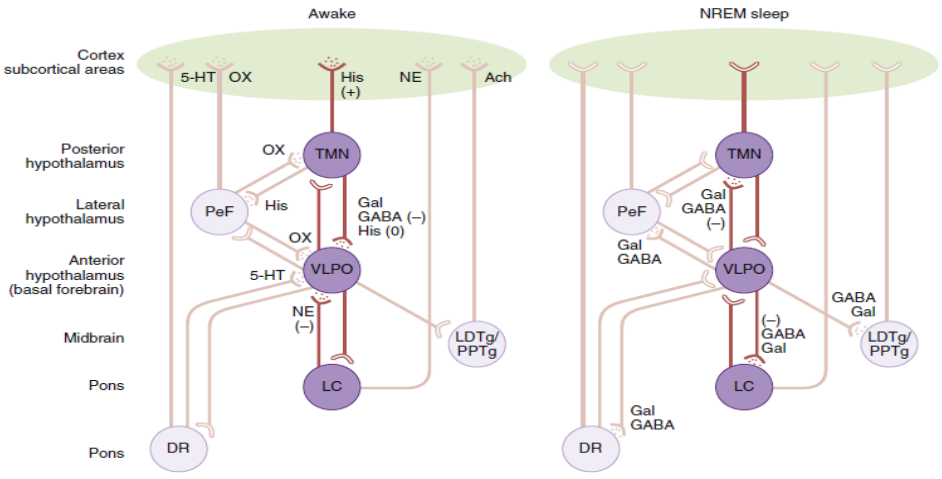
l. Effects on the central nervous system

Sedation

The alpha-2 agonists produce their sedative-hypnotic effect by an action on alpha-2 receptors in the locus coeruleus and by an analgesic action at alpha-2 receptors within the locus coeruleus and within the spinal cord.[125] Dexmedetomidine produces a decrease in activity of the projections of the locus coeruleus to the ventrolateral preoptic nucleus. As a result, gamma aminobutyric acid (GABA) and galanin release in the tuberomammillary nucleus is increased, producing a decrease in histamine release in cortical and subcortical projections.[126] The alpha-2 agonists

inhibit ion conductance through L-type or P-type calcium channels and facilitate conductance through voltage-gated calcium-activated potassium channels. The sedative effect of dexmedetomidine acts through the endogenous sleep-promoting pathways, thus generating natural sleep patterns.[127] Patients have been described as being very easy to wake up and having the ability to follow commands and cooperate while being tracheally intubated. Undisturbed, patients were noted to fall asleep momentarily.[128] This characteristic allows for "daily wake-up" tests to be done in a safe fashion. This critical test, in which ventilated patients in the ICU are taken off all sedatives to assess their mental status and titrate sedation, shortens their ventilated and ICU length of stay.[129,130] The number of patients experiencing delirium in the ICU is significantly lower than dexmedetomidine is used for sedation, compared with propofol or lorazepam[131] or with midazolam.[132]

Mechanism by which dexmedetomidine has been shown to produce NREM sleep pattern



Ach, Acetylcholine; *DR*, dorsal raphae nuclei; *Gal*, galanin; *His*, histamine ; *5-HT*, 5 -hydroxytryptamine (serotonin); *LDTg*, laterodorsal tegmental nuclei; *NE*, norepinephrine; *OX*, orexin (hypocretin); *peF*, perifornical area; *PPTg*, pedunculopontine tegmental nucleus; *TDTg*, laterodorsal tegmental nucleus.

The stimulation of the locus coeruleus (LC) by dexmedetomidine (right) releases the inhibition the LC has over the ventrolateral preoptic nucleus (VLPO). The VLPO subsequently releases gamma aminobutyric acid (GABA) onto the tuberomammillary nucleus (TMN). This inhibits the release of the arousal promoting histamine on the cortex and forebrain, thus inducing the loss of consciousness.[113]

Analgesia

The analgesic effect of the alpha-2 agonists is mediated through stimulation of the alpha-2C and alpha-2A receptor in the dorsal horn, thus directly suppressing pain transmission by reducing the release of pronociceptive transmitters, substance P and glutamate, and hyperpolarisation of interneurons.[134]

Like clonidine, dexmedetomidine is frequently used as an adjuvant in central or peripheral neural blockade. When it is administered caudally, 1 mcg/kg as an adjuvant to bupivacaine 0.25% 1ml/kg, in children undergoing inguinal hernia repair, response to hernial sac traction is reduced and postoperative analgesia is prolonged.[135]

Dexmedetomidine administered as an adjuvant to ropivacaine in ulnar nerve block[136] and tibial nerve block[137] was investigated in volunteers. Both studies showed intensification and foremost prolongation of the sensory blockade. This effect is likely elicited by prolonged hyperpolarisation of the unmyelinated C fibers (sensory), and to a lesser extent the A fibers (motor function).

Central Nervous System Protection and Other Central Nervous System Effects

In animal models of incomplete cerebral ischemia and reperfusion, dexmedetomidine reduced cerebral necrosis and improved neurologic outcome. The prevalent idea is that dexmedetomidine reduces the intracerebral catecholamine outflow during injury. The neuroprotection may be attributed to modulation of

proapoptotic and antiapoptotic proteins.[l38] In addition the reduction of the excitatory neurotransmitter glutamate during injury protective effects.[139]

In other studies, Cerebral Blood Flow (CBF) velocity at the middle cerebral artery, as measured by transcranial Doppler imaging, decreased with increasing concentrations of dexmedetomidine but carbon dioxide responsiveness and autoregulation were preserved.[140,14l]

2. Effects on the Cardiovascular System

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

Intravenous alpha-2 adrenoreceptor agonist administration leads to a decrease in heart rate and a transient increase in arterial blood pressure and systemic vascular resistance, however there is a decrease in cardiac output due to the activation of postjunctional vascular alpha-2 adrenoceptors. The initial increase in arterial blood pressure is probably caused by the vasoconstrictive effects of dexmedetomidine when stimulating peripheral alpha-2 receptors. 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 adrenoreceptor

agonists are yet known. It seems that postsynaptic alpha-2 adrenoreceptors and imidazoline receptors in the brainstem are involved.

The bradycardia commonly seen after administration of alpha-2 adrenoreceptor 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 adrenoreceptor 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.[142]

There are no known directly mediated alpha-2 adrenoreceptor effects on the myocardium. Alpha-2 adrenoreceptor activation causes reduction in sympathetic tone and increase in parasympathetic tone resulting in a reduced heart rate, systemic metabolism, myocardial contractility and systemic vascular resistance. These all result in a decrease in the myocardial oxygen requirements.

3. Effects on the Respiratory System

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.[143]

The locus coeruleus, described earlier, is an important site for the action of alpha-2 adrenoreceptor agonists. The locus coeruleus is involved in arousal reactions; suppression of its activity by alpha-2 adrenoreceptor agonists can result in a state similar to sleep with mild respiratory depression.

Dexmedetomidine-treated patients exhibited a hypercarbic arousal phenomenon, which has been described during normal sleep.

4. Effects on the Renal System

Activation of alpha-l receptors in the kidney results in the redistribution of blood from the cortical to medullary areas due to an increase in renal vascular resistance. Stimulation of alpha-2 adrenoreceptors has a number of effects that promote diuresis and natriuresis. They decrease the secretion of vasopressin and antagonize, its action on renal tubules. Alpha-2 adrenoreceptors are also thought to inhibit the release of renin and increase the release of atrial natriuretic factor.[144]

5. Effects on the Neuroendocrine System

The alpha-2 adrenoreceptor 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 adrenoreceptors located on the beta cells of the islets of Langerhans can temporarily cause direct inhibition of insulin release and clinical hyperglycemia. Alpha-2 receptor agonists also increase the release of growth hormone and inhibit adipose tissue lipolysis.[145]

6. Effects on the Gastrointestinal System

Alpha-2 adrenoreceptors regulate vagally mediated increases in gastric and intestinal motility and secretions. It has been postulated that gastric cholinergic prejunctional alpha-2 adrenoreceptors inhibit gastric secretions during stress. Activation of alpha-2 adrenoreceptors 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 adrenoreceptors is known to reduce salivary secretions and may lead to a dry mouth.[146]

7. Effects on Platelet Function

Selective alpha-2 adrenoreceptor agonists, as well as adrenaline, are known to stimulate platelet aggregation by stimulating alpha-2C receptors on platelets. High concentrations of alpha-2 adrenoreceptor 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.[147]

8. Drug and receptor interactions

Alpha-2 adrenoreceptor 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 adrenoreceptor 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 adrenoreceptor agonists also have a synergistic action with benzodiazepines.[148]

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.

MATERIALS AND METHODS

MATERIALS AND METHODS

A prospective randomized clinical study was conducted in the Department of Anaesthesiology at the **Shri B. M. Patil Medical College, Hospital and Research Centre, Vijayapur** after approval by the Medical Ethical Committee of **BLDE (Deemed to be) University Vijayapur**, The study was carried out on 90 patients belonging to American Society of Anaesthesiology (ASA) classification for physical status I and II of either sex in the age range of 18 to 60 years undergoing laparoscopic procedures under general anaesthesia. They were randomized into two groups of 45 each.

Group D - Dexmedetomidine Group

Group S - Control Group

Inclusion criteria

1. Patients of age between 18 - 60 years
2. ASA Grade I & II patients
3. Type of surgery - elective laparoscopic surgeries
4. Mallampati grade I and II
5. Patients giving valid and informed consent.

Exclusion criteria

1. Patients with anticipated difficult airway
2. Oropharyngeal pathology
3. Patients on beta blockers, patients with conduction defects of the heart (heart blocks)
4. Patients with known allergy to the drug
5. Pregnant women
6. Morbidly obese (body mass index > 35 kg/m^2)

PROCEDURE:-

The ethical clearance for the study was obtained from the Medical Ethical Committee, **Shri B. M. Patil Medical College Hospital and Research Centre, Vijayapur**. Patients undergoing elective laparoscopic procedures, 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 anesthetic procedure in their vernacular language. A written informed consent was obtained from the patient.

A preanesthetic evaluation with detailed medical history and systemic examination was done and relevant investigations were advised and reviewed on the previous day and on the day of surgery. Patients were randomized into two groups:

- Group D patients received intravenous Dexmedetomidine Perioperatively. (Study group)
- Group S patients received intravenous normal saline 0.9% Perioperatively. (Placebo)

The study drug was provided as prefilled identical lml syringes for the loading dose and 50 ml syringes for the infusion dose containing study drugs, as per the randomization protocol, in dilutions of;

For loading dose:

1. Dexmedetomidine - 1ml (100mcg/ml)
2. Normal saline 0.9% - lml

For infusion:

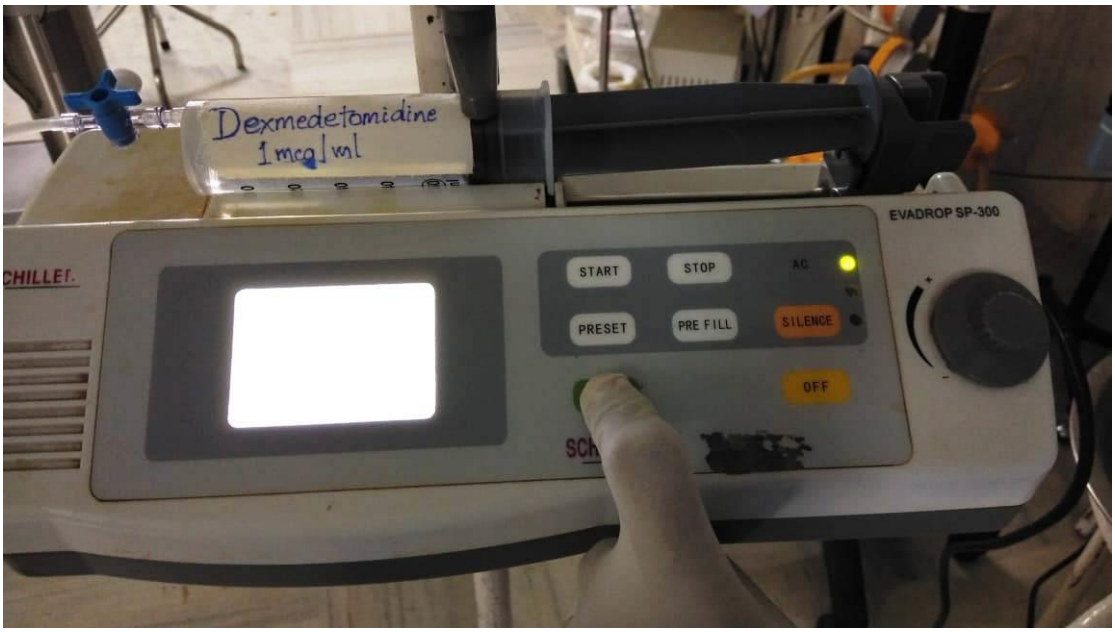
1. Dexmedetomidine - 50m1 (1mcg/ml)
2. Normal saline 0.9% - 50ml

Patients were explained about the study, but did not know which drug was used. Two intravenous lines were secured, one 20 G intravenous i.v cannula in the right hand for infusion of the study drug and another 18G i.v cannula in the left hand for intravenous fluids and drug administration.

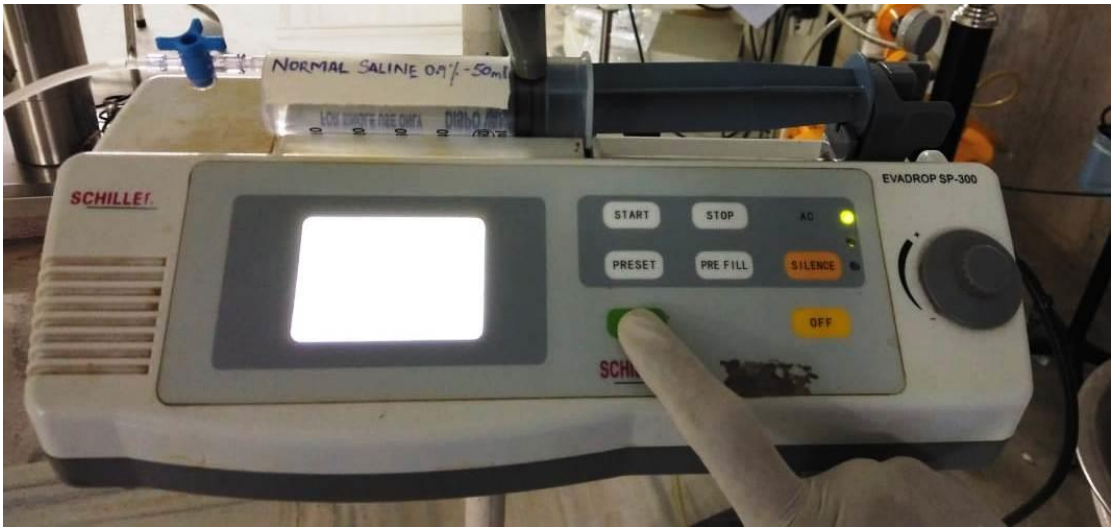
After securing intravenous access, all patients were premedicated with inj. ranitidine 1mg/kg i.v and inj. Ondensetron 0.08mg/kg i.v, 500ml of crystalloids (Ringer Lactate) i.v was started. On arrival in the operation theater baseline monitors like ECG, Pulse-Oximeter and Non - Invasive Blood Pressure (NIBP) were attached. Baseline values of Heart rate (HR), Oxygen Saturation (SPO_2), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP) and Mean Arterial Pressure (MAP) were noted. All patients received inj. Midazolam 0.04mg/kg i.v and inj. Glycopyrrolate 4 micrograms/kg i.v. The study drug was started 20 minutes prior to induction. Patients belonging to group D received a loading dose of dexmedetomidine at 1mcg/kg over 10minutes, followed by maintenance infusion of dexmedetomidine at the rate of 0.4mcg/kg/hr. Patients belonging to the Group S received normal Saline 0.9% at a similar rate as dexmedetomidine infusion.

All patients received inj. Fentanyl l.5mcg/kg i.v 5minutes prior to induction of general anaesthesia. Patients were pre-oxygenated with 100% FiO_2 for 5minutes. General anaesthesia was induced with inj. Propofol 2mg/kg i.v Inj. Succinylcholine 2mg/kg i.v was administered to Facilitate intubation. All patients were intubated with appropriate size cuffed Endotracheal Tubes. End - Tidal Carbon dioxide ($ETCO_2$) was monitored throughout the surgery and maintained between 35-40 mm of Hg by adjusting the minute ventilation. General anaesthesia was maintained on O_2, N_2O, Isoflurane and inj. Vecuronium bromide 0.08mg/kg. The maximum concentration of Isoflurane used was 1.5% Pneumoperitoneum was created slowly, starting at 2

litre/min, using CO_2 and the Intra Abdominal Pressure (IAP) was maintained between 12-14mm of Hg. Fall in MAP of more than 20% of basal MAP was treated with iv fluids and iv ionotropes. For rise in MAP more than 20% of baseline MAP and not being maintained within this limit with an isoflurane concentration of 1.5%, an NTG infusion was started to maintain the MAP. Heart rate less than 50 beats per minute (bmp) was treated with inj. Atropine 0.6mg i.v. On completion of surgery patients neuromuscular blockade was reversed using inj. Neostigmine 0.05mg/kg and inj Glycopyrrolate 0.008mg/kg. Patients were extubated and transferred to post operative recovery room and observed for the next one hour for any evidence of complications or adverse events in the first 24 hours were assessed.



Photograph 3: Group D drug infusion



Photograph 4: Group S drug infusion

Hemodynamic Parameters including HR, $SPO_{2,}$ SBP, DBP and MAP were noted at:

1. Preoperatively (Ml)
2. 10 minutes After starting the Study Drug (M2)
3. At Induction (M3)
4. During Intubation (M4)
5. Before Pneumoperitoneum (M5)
6. 10 minutes after Pneumoperitoneum (M6)
7. 20 after Pneumoperitoneum (M7)
8. 30 after Pneumoperitoneum (M8)

   Every 30 minutes till the end of Pneumoperitoneum
9. At the end of Pneumoperitoneum (M9)
10. 10 minutes after reversal (N1)
11. Post operatively after 30minutes (N2)

    Study Drug infusion was stopped 5 minutes before reversal.

METHOD OF STATISTICAL ANALYSIS

Data obtained was decoded and entered into a Microsoft excel spreadsheet. The categorical data was expressed in terms of ratios and percentage; and continuous data expressed in terms of mean ± standard deviation. Data analysis was carried out using SPSS v:17 software. Students unpaired "t"/ Mann Whitney U test was used to compare quantitative variables in both groups. The categorical data was compared using chi square test. The probability value (p-value) less than 0.05 ($p<0.05$) was considered to be statistically significant.

OBSERVATIONS

AND RESULTS

OBSERVATIONS AND RESULTS

This study entitled “To study the efficacy of dexmedetomidine for attenuation of hemodynarnic responses in patients undergoing laparoscopic surgeries” was carried out in the department of Anesthesiology at BLDEU’s Shri B M Patil medical college, hospital and research centre, Vijayapur after the approval of the institutional ethical committee's approval.

Our study comprised of 90 ASA I and II grading, undergoing elective laparoscopic surgeries, which were randomly divided into two groups: Group D and Group S comprising 45 patients each.

The patients belonging to Group D (dexmedetomidine) received inj, Dexmedetomidine intravenously in the perioperative period and the patients belonging to Group S (placebo) received normal saline in the perioperative period, predesigned variables were recorded and analyzed.

Table 1: Table showing the number of patients in both groups.

GROUP	DRUG USED	NUMBER OF PATIENTS
Group D	INJ. DEXMEDETOMIDINE	45
Group S	NORMAL SALINE	45
TOTAL		90

GROUP D, n: 45, received inj. Dexmedetomidine i.v., in the perioperative period.

GROUP S, n: 45, received normal saline 0.9%, in the perioperative period.

Graph 1: Graph Showing number of patients in both groups.

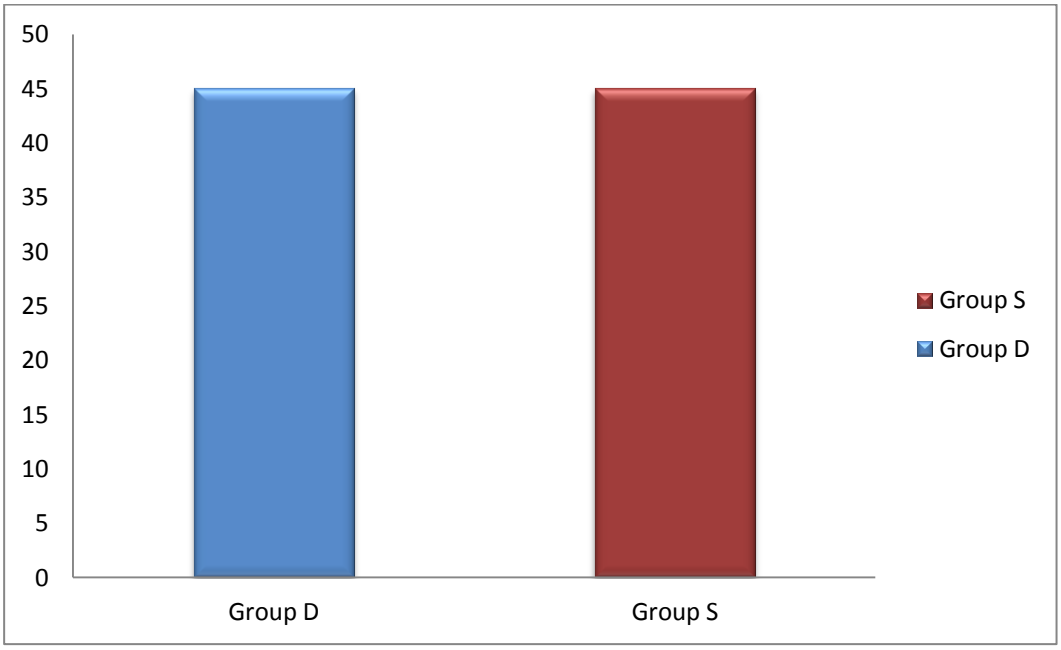


Table 2: Table showing the age distribution in both groups.

AGE(YEARS)	GROUP D	GROUP S	TOTAL
<18	0	0	0
19-39	28(62.2%)	22(49%)	50(56%)
40-60	17(37.8%)	23(51%)	40(44%)
>60	0	0	0
Total	45(100%)	45(100%)	90
Mean ± SD Age (Yrs)	37.06±11.56	37.77±11.78	P=0.773 NS

In group D, maximum number of patients i.e.28 (62.2%) were in the age group of 19-39 years, whereas 22 (49%) were in the age group of 40-60 years. In Group S, maximum number of patients i.e. 23 (51%) were in the age group of 40-60 years, whereas 17 (37.8%) were in the age group of 19-39 years. The mean age of all patients in group D was 37.06±11.56 years while that in group S was 37.77±11.78 (p=0.773, p>0.05). Thus both groups were statistically comparable as far as age was concerned.

Graph 2: Graph Showing Age Distribution in both the groups

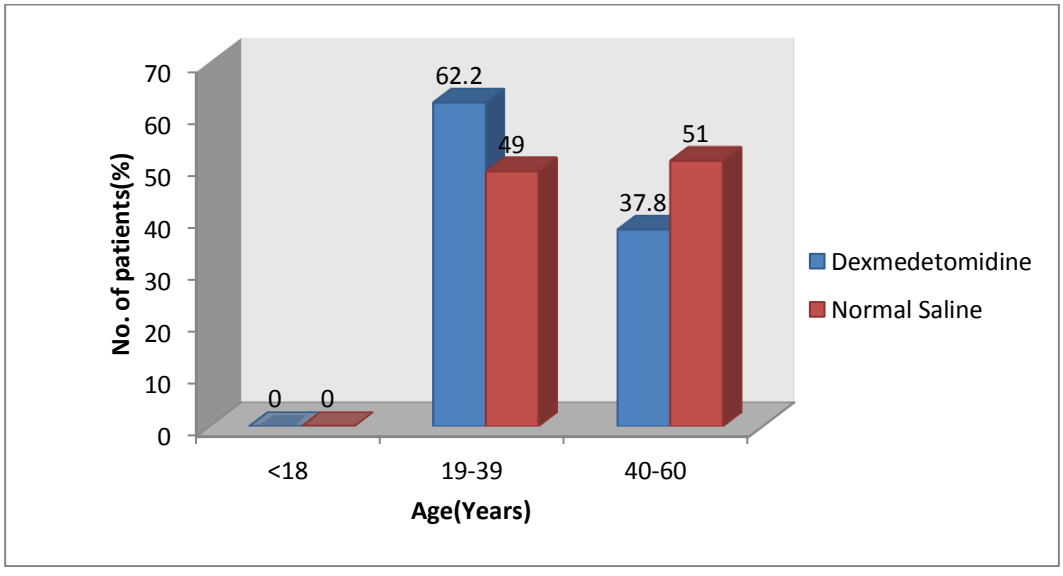


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Table 3: Table showing mean age distribution in both groups.

AGE(YEARS)	MEAN	STD. DEVIATION	UNPAIRED T TEST
Dexmedetomidine	37.0667	11.55894	
Normal Saline	37.7778	11.77997	P=0.773 NS

NS - Not Significant

Table 4: Table showing sex distribution in both groups.

GENDER	GROUP D	GROUP S	TOTAL	CHI SQUARE TEST
Male	26(58%)	20(49%)	46 (51%)	P=0.2058 NS
Female	19(42%)	25(56%)	44(49%)	
Total	45	45	90	

NS - Not Significant

The number of females in group D was 19 and in group S was 25. The number of males in group D was 26 and in group S was 20 (P: 0.2058, P>0.05), thus the both groups were comparable statistically as far as sex is concerned.

Graph 3: Graph showing sex distribution in both the groups.

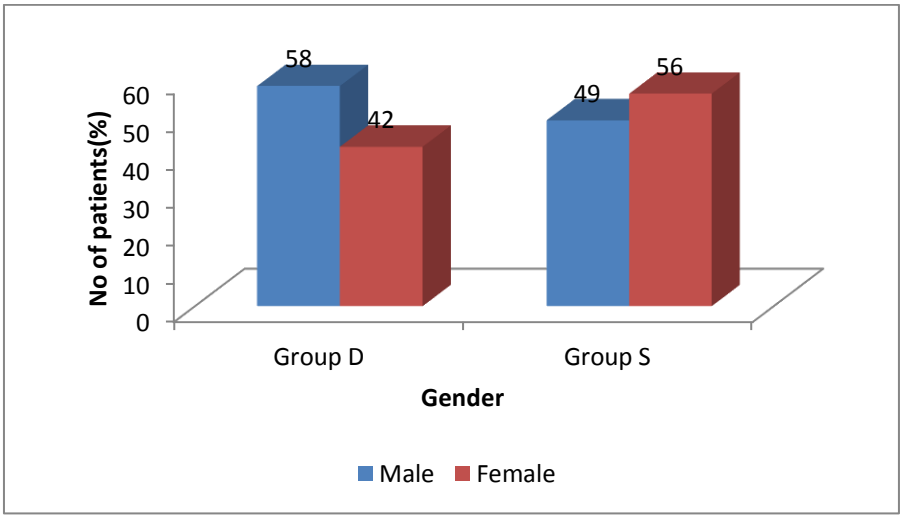


Table 5: Table showing Mean Weight of patients in both groups.

BODY WEIGHT(KG)	MEAN	STD. DEVIATION	MANN-WHITNEY TEST
Group D	66.1556	7.04839	P=0.903 NS
Group S	66.0222	6.12554	

NS - Not Significant

The mean weight of patients in group D was 66.15±7.05 kg where as in group S it was 66.02±6.12 kg. (P: 0.903, P>0.05), thus the both groups were statistically comparable as far as body weight is concerned.

Graph 4: Graph showing mean weight in both the groups.

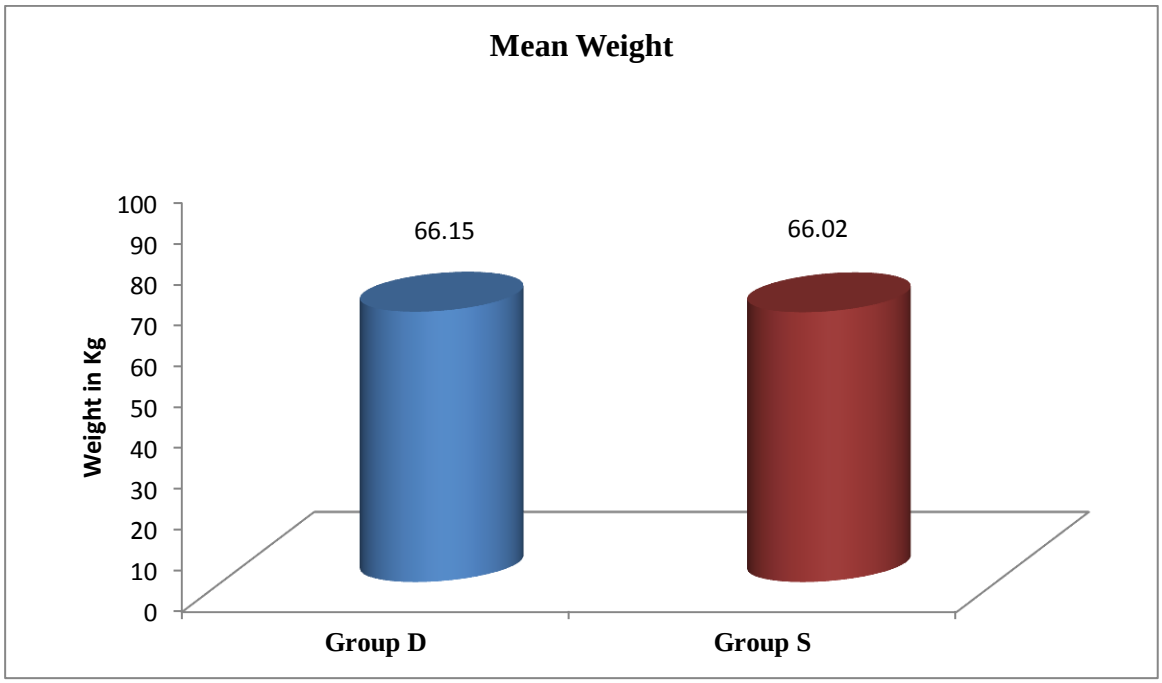


Table 6: Table showing Distribution of patients according to ASA status in two groups.

ASA STATUS	GROUP D	GROUP S	TOTAL	CHI SQUARE TEST
ASA I	32(71%)	37(82%)	69(77%)	P=0.2127 NS (p>0.05)
ASA II	13(30%)	8(18%)	21(23%)	
Total	45	45	90	

NS - Not Significant

The number of ASA grade I patients in group D were 32 and in group S were 37.The number of ASA grade II patients in group D was 13 and in group S were 8. Both groups were comparable as far as the ASA grading was concerned as the p value is 0.2127, (p value>0.05).

Graph 5: Graph showing distribution of patients as per ASA classification in both groups.

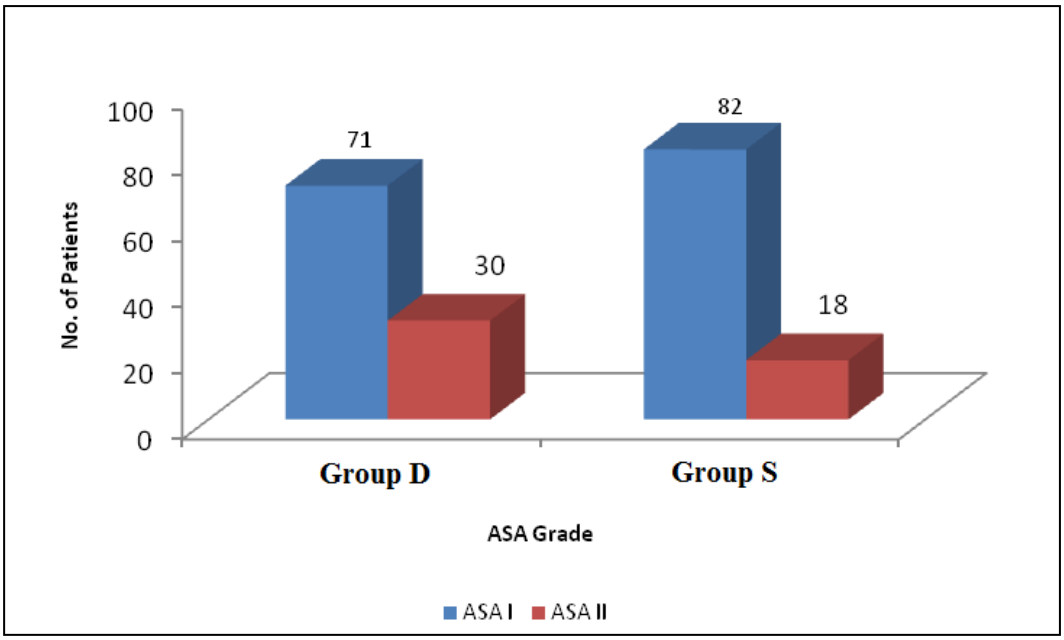


Table 7: Demographic profile of both the groups.

DEMOGRAPHIC PROFILE	GROUP D	GROUP S	P VALUE	SIGNIFICANCE
Age(Years)	37.06±11.56	37.77±11.78	0.773	NS
Gender(F:M)	19:26	25:20	0.206	NS
Weight(Kg)	66.15±7.05	66.02±6.13	0.903	NS
ASA Grades	32:13	37:8	0.213	NS

NS - Not Significant

Table 8: Table showing types of surgeries included in the present Study.

TYPE OF SURGERY	GROUP D	GROUP S	TOTAL	CHI SQUARE TEST
LA	22(49%)	23(51%)	45(50%)	P=0.7923 NS
LC	14(31%)	13(29%)	27(30%)	
LU	9(20%)	9(20%)	18(20%)	
Total	45	45	90	

LA- Laparoscopic Appendectomy.

LC- Laparoscopic Cholecystectomy.

LU- Laparoscopic Umbilical Hernia Repair.

NS- Not Significant.

Patients undergoing three types of laparoscopic surgeries were included in the present study- laparoscopic appendectomy, laparoscopic cholecystectomy and laparoscopic umbilical hernia repair. 22(49%) patients in group D and 23(51%) patients in the group S underwent laparoscopic appendectomy. 14(31%) patients in group D and 13(29%) patients in group S underwent Laparoscopic cholecystectomy.

9(20%) patients in group D and 9(20%) patients in group S underwent laparoscopic umbilical hernia repair. P value was 0.7923 (p>0.05), which indicates that the three groups were comparable in terms of type of surgery the patients underwent.

Graph 6: Graph showing type of surgeries in both groups.

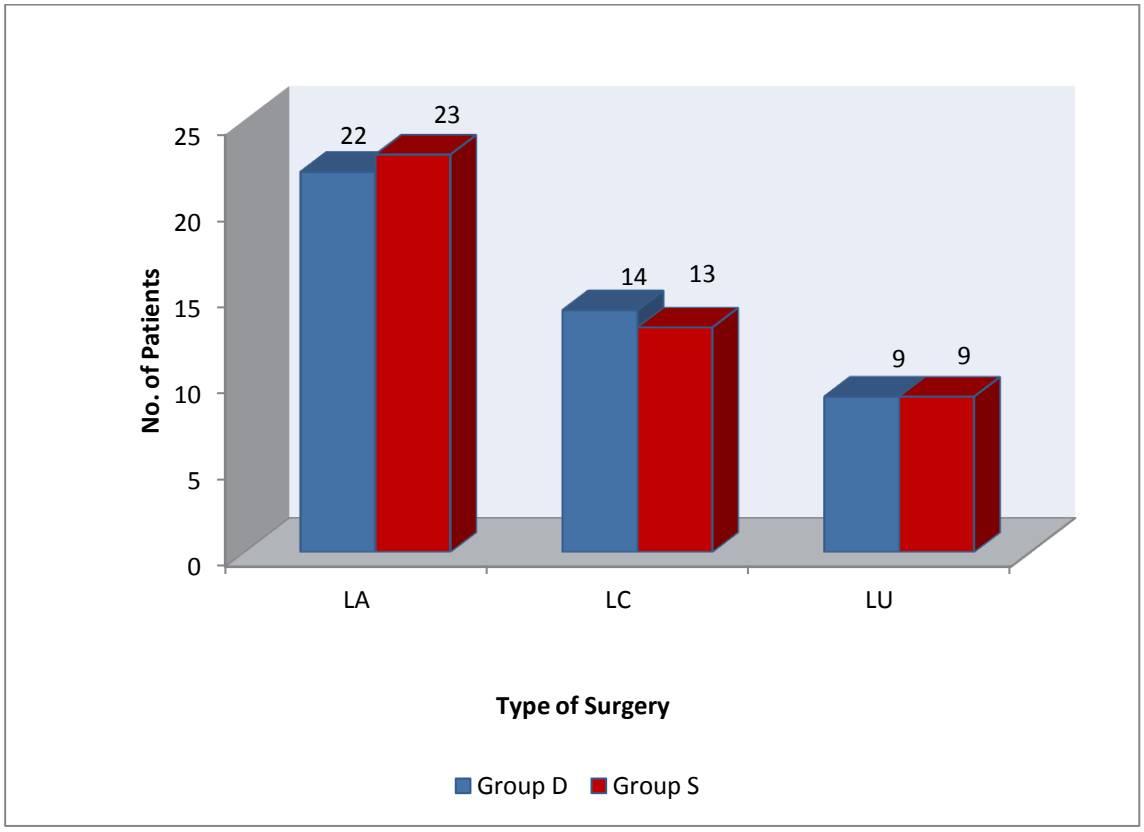


Table 9: Table showing mean duration of pneumoperitoneum and duration of surgery in both the groups.

DURATION	GROUP D		GROUP S		MANN-WHITNEY TEST
	MEAN	STD. DEVIATION	MEAN	STD. DEVIATION	
Duration of Pneumoperitoneum	58.18	24.27	56.42	56.42	P=0.903 NS
Duration of Surgery	88.69	25.78	88.20	22.96	P=0.799 NS

NS – (Not Significant)

The average duration of PNP in group D was 58.18±24.27 min whereas in group S it was 56.42±56.42 min with a p value of 0.903 (p>0.05). The average duration of surgery (Sx) was 88.69±25.78 min and in group S it was 88.20±22.96 min, with a p value of 0.799 (p>0.05). Thus the duration of surgery and that of PNP were not significant in both the groups, making the groups comparable with respect to duration of surgery and PNP.

Graph 7: Graph showing mean duration of PNP and Surgery in both Groups.

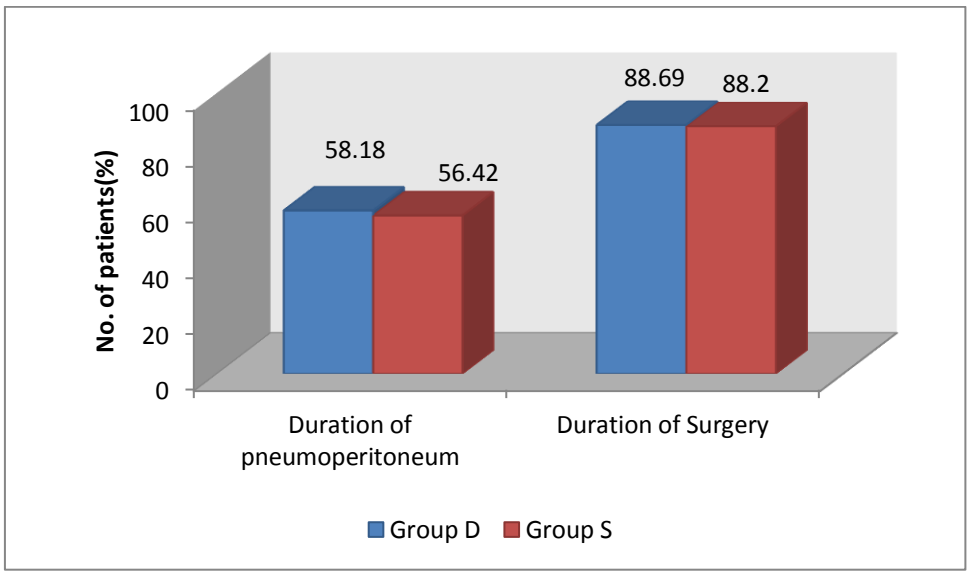


Table 10: Table showing Heart Rate in both groups.

TIME INTERVAL	GROUP D		GROUP S		MANN-WHITNEY TEST/UNPAIRED T TEST
	MEAN	STD. DEVIATION	MEAN	STD. DEVIATION	
M1	82.57	12.513	82.73	13.30	P=0.865 NS
M2	81.89	13.85	84.16	12.48	P=0.616 NS
M3	80.24	13.97	85.71	12.76	P=0.047 S
M4	85.71	12.76	101.91	13.57	P=0.001 S
M5	76.96	14.89	89.42	13.64	P=0.001 S
M6	73.00	12.43	93.62	12.016	P=0.001 S
M7	71.67	11.22	95.49	9.19	P=0.001 S
M8	70.24	10.43	94.56	11.91	P=0.001 S
M9	69.42	10.52	87.87	10.74	P=0.001 S
N1	71.67	11.67	93.36	14.70	P=0.001 S
N2	78.71	10.38	90.0	8.86	P=0.001 S

S - Significant, NS - Not Significant

Heart rate in Group S increased significantly when compared to Group D, after intubation (M4), before pneumoperitoneum (M5), 10 minutes after pneumoperitoneum (M6), 20 minutes after pneumoperitoneum (M7), 30 minutes after pneumoperitoneum (M8), at the end of pneumoperitoneum (M9), l0 minutes after reversal of neuromuscular blockade (N1) and 30 minutes postoperatively (N2) ($p<0.05$).

Graph 8: Graph showing changes in the Heart Rate (HR) in both the groups.

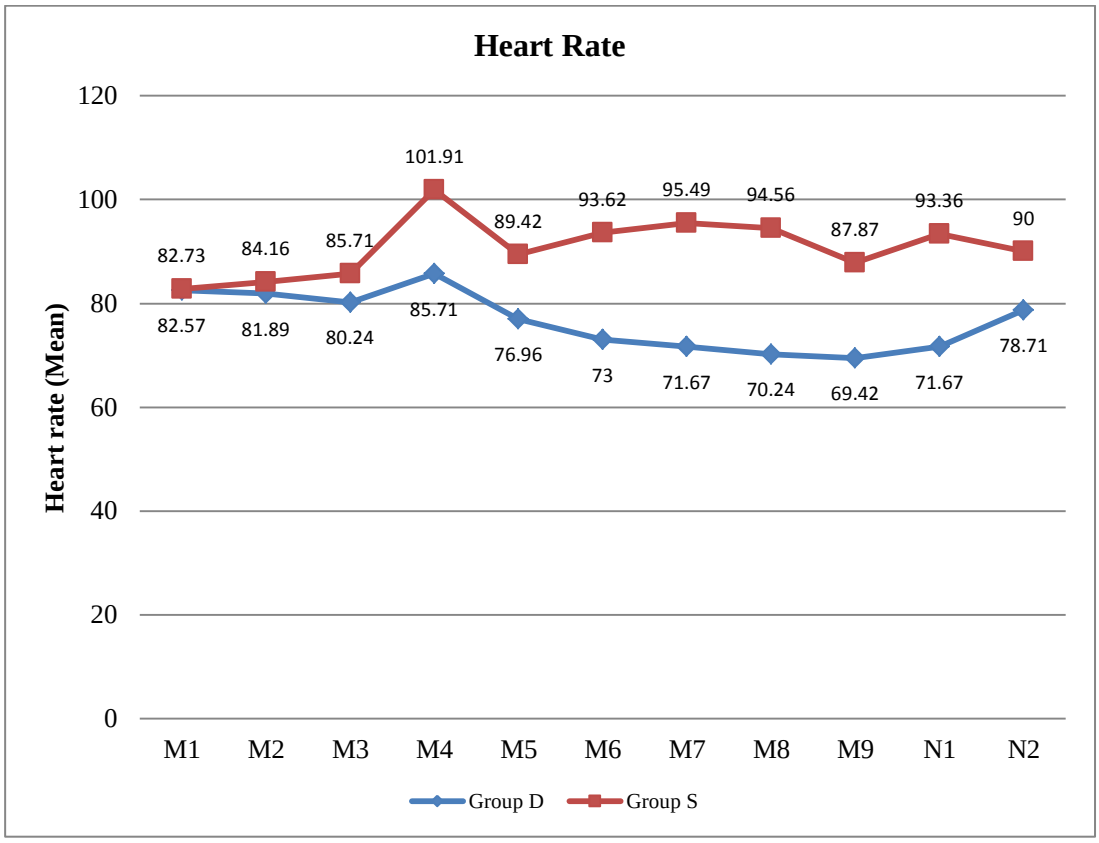


Table 11: Table showing Systolic Blood Pressure (SBP) changes in both the groups.

TIME INTERVAL	GROUP D		GROUP S		MANN-WHITNEY TEST/UNPAIRED T TEST
	Mean	Std. Deviation	Mean	Std. Deviation	
M1	126.93	15.05	126.62	13.19	P=0. 997 NS
M2	127.09	11.28	128.98	12.21	P=0.354 NS
M3	109.09	15.29	121.44	14.31	P=0.001 S
M4	121.16	15.43	147.69	21.07	P=0.001 S
M5	112.49	12.43	130.04	18.12	P=0.001 S
M6	117.49	13.55	144.20	12.67	P=0.001 S
M7	116.60	12.03	139.69	10.20	P=0.001 S
M8	114.29	9.14	139.31	10.07	P=0.001 S
M9	113.71	10.24	131.98	10.35	P=0.001 S
N1	120.27	10.72	137.56	10.72	P=0.001 S
N2	122.02	8.97	132.91	10.56	P=0.001 S

NS - Not Significant, S - Significant

Systolic Blood Pressure (SBP) in Group S increased significantly when compared to Group D, at induction (M3), after intubation (M4), before pneumoperitoneum (M5), l0 minutes after pneumoperitoneum (M6), 20 minutes after pneumoperitoneum (M7), 30 minutes after pneumoperitoneum (M8), at the end of pneumoperitoneum (M9), 10 minutes after reversal of neuromuscular blockade (N1) and 30 minutes postoperatively (N2) ($p<0.05$).

Graph 9: Graph showing changes in the Systolic Blood Pressure (SBP) in both the groups.

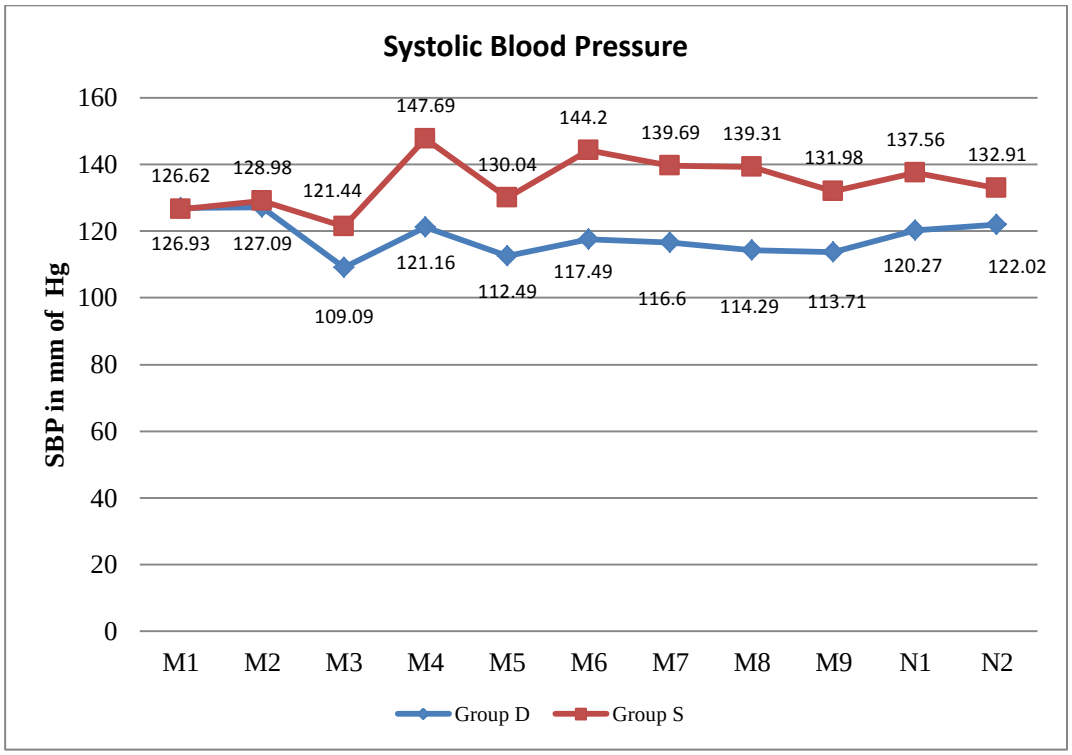


Table 12: Table showing changes in the Diastolic Blood Pressure (DBP) in both the groups.

TIME INTERVAL	GROUP D		GROUP S		MANN-WHITNEY TEST/UNPAIRED T TEST
	MEAN	STD. DEVIATION	MEAN	STD. DEVIATION	
M1	79.02	7.59	79.18	8.92	P=0.777 NS
M2	78.49	7.49	81.69	9.619	P=0.082 NS
M3	70.16	8.12	77.24	9.54	P=0.001 S
M4	77.62	11.31	93.24	12.71	P=0.001 S
M5	71.73	10.75	85.69	10.39	P=0.001 S
M6	75.11	10.00	93.20	8.88	P=0.001 S
M7	75.09	9.66	89.87	6.69	P=0.001 S
M8	72.63	7.71	88.20	5.72	P=0.001 S
M9	73.64	8.54	84.44	8.120	P=0.001 S
N1	76.84	9.57	85.84	6.78	P=0.001 S
N2	77.27	7.57	82.42	7.67	P=0.001 S

NS - Not Significant, S - Significant

Systolic Blood Pressure (SBP) in Group S increased significantly when compared to Group D, at induction (M3), after intubation (M4), before pneumoperitoneum (M5), l0 minutes after pneumoperitoneum (M6), 20 minutes after pneumoperitoneum (M7), 30 minutes after pneumoperitoneum (M8), at the end of pneumoperitoneum (M9), 10 minutes after reversal of neuromuscular blockade (N1) and 30 minutes postoperatively (N2) ($p<0.05$).

Graph 10: Graph showing changes in the Diastolic Blood Pressure (DBP) in both the groups.

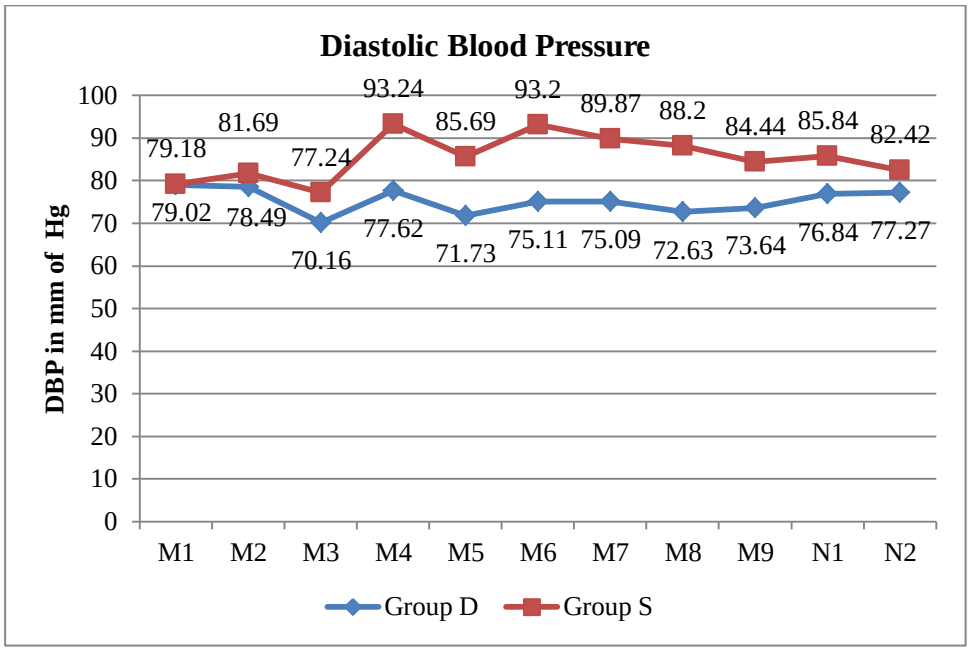


Table 13: Table showing changes in the Mean Arterial Pressure (MAP) in both the groups.

TIME INTERVAL	GROUP D		GROUP S		MANN-WHITNEY TEST/UNPAIRED T TEST
	MEAN	STD. DEVIATION	MEAN	STD. DEVIATION	
M1	95.4	9.28	95.51	9.81	P=0.956 NS
M2	94.71	8.99	97.22	9.42	P=0.199 NS
M3	83.02	10.32	91.56	11.39	P=0.001 S
M4	92.62	12.41	111.16	14.82	P=0.001 S
M5	85.18	10.369	101.47	10.39	P=0.001 S
M6	91.13	9.60	109.89	8.81	P=0.001 S
M7	88.91	9.61	106.69	7.483	P=0.001 S
M8	86.84	8.11	106	5.72	P=0.001 S
M9	86.62	6.59	101	8.12	P=0.001 S
N1	91.56	9.15	103.69	8.78	P=0.001 S
N2	92.13	6.89	99.4	7.83	P=0.001 S

NS - Not Significant, S – Significant

Systolic Blood Pressure (SBP) in Group S increased significantly when compared to Group D, at induction (M3), after intubation (M4), before pneumoperitoneum (M5), l0 minutes after pneumoperitoneum (M6), 20 minutes after pneumoperitoneum (M7), 30 minutes after pneumoperitoneum (M8), at the end of pneumoperitoneum (M9), 10 minutes after reversal of neuromuscular blockade (N1) and 30 minutes postoperatively (N2) ($p<0.05$).

Graph 11: Graph showing changes in the Mean Arterial Pressures (MAP) in both the groups.

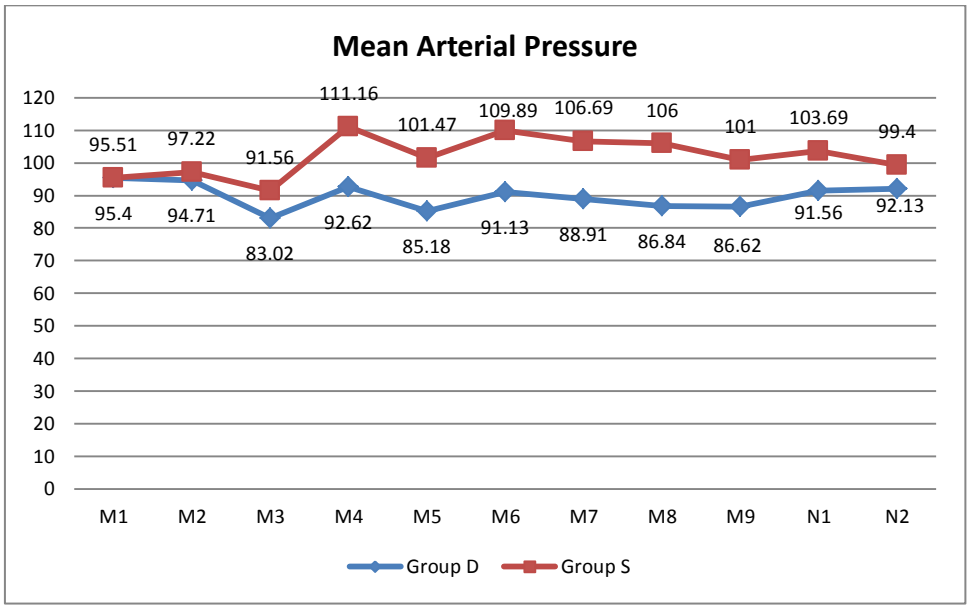


Table 14: Table showing requirement of intra-operative Nitroglycerine (NTG) drip for control of hypertension in both the group.

NTG USED	GROUP D	GROUP S	TOTAL	CHI SQUARE TEST
Yes	0	10(22%)	10(11%)	
No	45(100%)	35(78%)	80(89%)	P=0.0008 S
Total	45	45	90	(p<0.05)

S = Significant

Ten out of 45 patients (22%) required intra-operative NTG drip for control of hypertension in group S (placebo), whereas none of the patients in group D required NTG drip. p value was 0.0008 (p<0.05) and thus the difference is statistically significant.

Graph 12: Graph comparing NTG use in both groups.

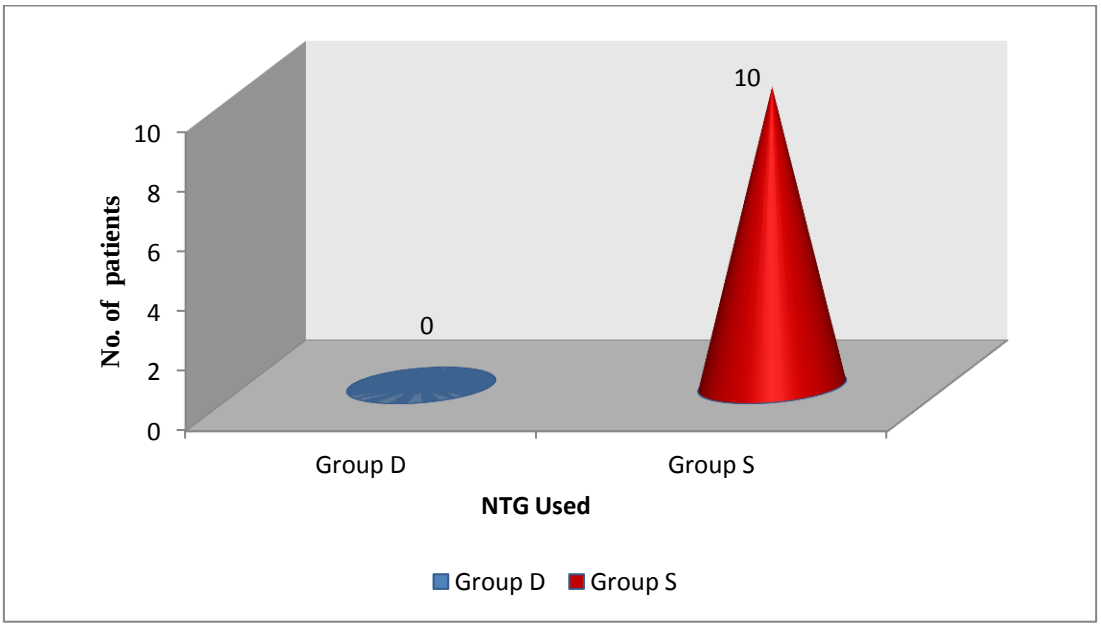


Table 15: Table showing requirement of intraoperative atropine to treat bradycardia in both the groups.

ATROPINE USED	GROUP D	GROUP S	TOTAL	CHI SQUARE TEST
Yes	4(9%)	0	4(4%)	P=0.0408 S (p<0.05)
No	41(91%)	45(100%)	86(96%)	
Total	45	45	90	

S -Significant

Four out of 45 (9%) patients in group D required inj. Atropine for the treatment of bradycardia (HR<50bmp). On the other hand none of the patients in the group S (placebo) required the use of atropine intraoperatively. p value was 0.0408 i.e. p>0.05, thus it is statistically significant.

Graph 13: Graph comparing atropine use in both groups.

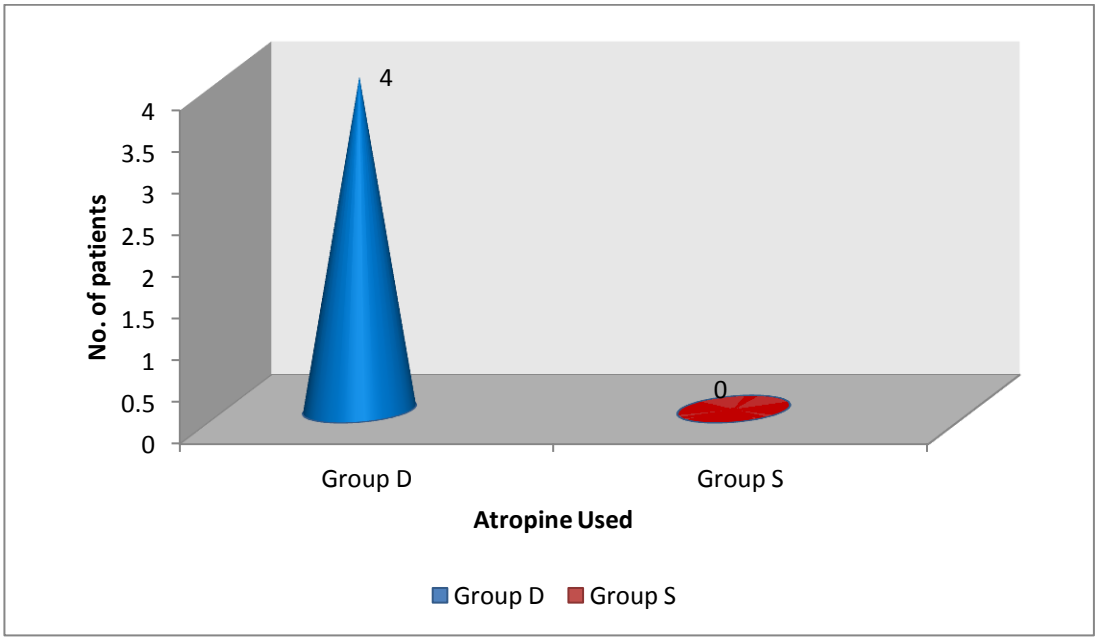


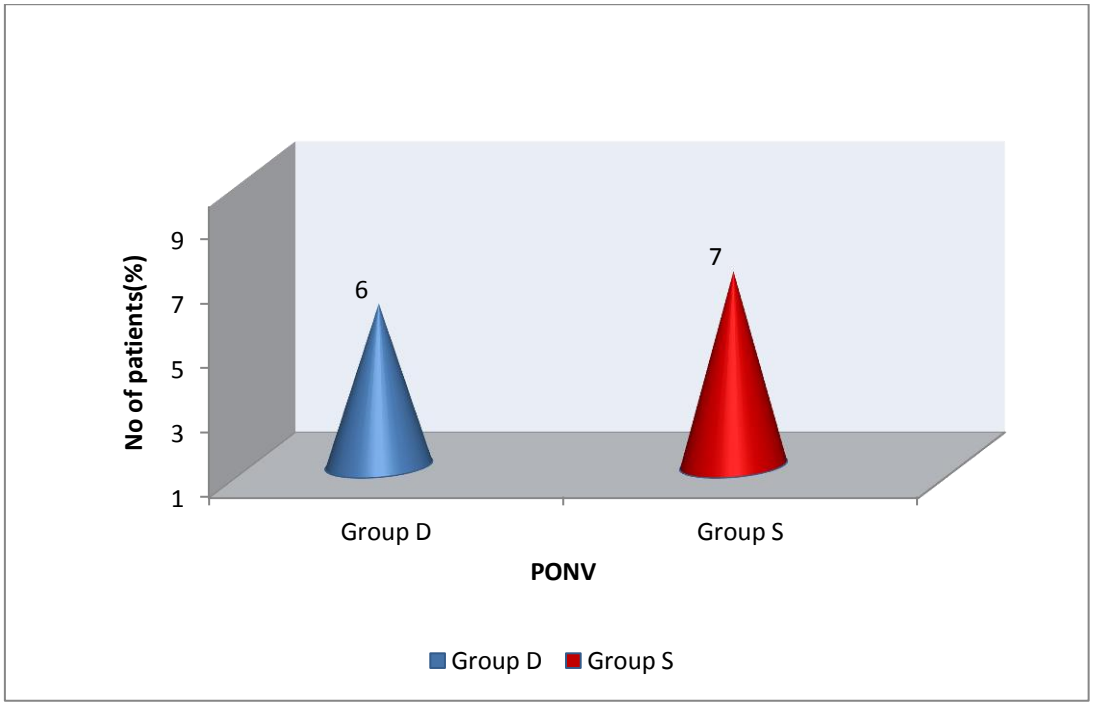
Table 16: Table showing post-operative nausea vomiting (PONV) in both groups.

PONV	GROUP D	GROUP S	TOTAL	CHI SQUARE TEST
Yes	6(13%)	7(16%)	13(14%)	P=0. 7643 NS (p>0.05)
No	39(87%)	38(84%)	77(86%)	
	45	45	90	

NS= Not significant

Six patients out of 45 (13%) of the group D experienced Post-Operative Nausea and Vomiting (PONV), while in Group S (placebo) 7 out of 45 patients (16%) experienced PONV. p value for PONV was 0.7643 which means (p>0.05), thus it is statistically not significant.

Graph 14: Graph showing PONV in both groups.



DISCUSSION

DISCUSSION

Laparoscopic surgeries have become the gold standard for many surgical procedures, like laparoscopic cholecystectomy for gall bladder diseases. But laparoscopic surgery requires creation of Pneumoperitoneum by insufflation of carbon dioxide (CO_2) into the peritoneal cavity. Pneumoperitoneum has its own adverse effects due to raised intra-abdominal pressure (IAP), patient positioning and absorption of CO_2, in addition to release of vasopressin and catecholamines. These pathophysiological changes are because of combination of mechanical and neurohumoral factors. These changes are particularly more pronounced in the cardiovascular system. Intraoperative hypertension and tachycardia are the most common hemodynamic disturbances in patients undergoing laparoscopic surgeries.

Many methods have been proposed to attenuate these hemodynamic responses during laparoscopic surgeries. Modifications in surgical techniques have been proposed. Some of them include using abdominal wall lift methods (Laparotensors), use of low pressure pneumoperitoneum, and use of other gases in place or in combination with CO_2 for creation of pneumoperitoneum. Various anaesthetics techniques have also been used. Epidural, segmental spinal anaesthesia and epidural analgesia combined with general anaesthesia have been successfully used to attenuate the hemodynamic responses during laparoscopic procedures. Various drugs like esmolol, nitroglycerine, magnesium sulphate and alpha-2 adrenergic agonists like clonidine and dexmedetomidine have been used with varying degrees of success. Use of high doses of remifentanil almost completely prevents the hemodynamic changes. The alpha-2 adrenoreceptor agonists have several beneficial actions during the perioperative period. They exert a central sympatholytic action, improving hemodynamic stability in response to endotracheal intubation and surgical stress,

reducing the anesthetic and opioid requirements and causing sedation, anxiolysis and analgesia.

Furthermore, alpha-2 adrenoreceptor agonists may offer benefits in the prophylaxis and treatment of perioperative myocardial ischemia. The alpha-2 adrenoreceptor agonists have an analgesic action at several sites of the peripheral and central nervous system. It also causes prolongation of epidurally or intrathecally administered local anaesthetics and opioids. Perioperative i.v. dexmedetomidine infusion has been used in various doses (from 0.2 to 0.8mcg/kg/hr) to attenuate hemodynamic responses in patients undergoing laparoscopic surgeries.

Tufanogullari B *et al*.[40] used 0.2 to 0.8 mcg/kg/hr dexmedetomidine i.v. infusion. **Bhattacharjee DP et al**.[41] used perioperative i.v. dexmedetomidine in the dose of 0.2mcg/kg/hr. **Ghodki PS *et al*.**[9] used a loading dose infusion of dexmedetomidine starting 1mcg/kg for 15 minutes and a maintenance infusion of dexmedetomidine at 0.2 mcg/kg/hr.

While **Gourishankar RM *et al*.**[42] compared two doses of perioperative dexmedetomidine infusion, 0.2mcg/kg/hr and 0.4mcg/kg/hr in patients undergoing laparoscopic surgeries. They found that dexmedetomidine provided good hemodynamic stability at these doses without adverse effects. **Gourishankar RM *et al*.**[42] in their study they concluded that a dexmedetomidine infusion of 0.4mcg/kg/hr provided better hemodynamic stability as compared to an infusion rate of 0.2mcg/kg/hr.

Therefore in our study, we used dexmedetomidine in a loading dose of 1mcg/kg over 10 minutes, before induction of general anaesthesia, followed by a maintenance infusion of dexmedetomidine at the rate of 0.4mcg/kg/hr. We studied the effects of dexmedetomidine on the stress response during laryngoscopy and

endotracheal intubation, the hemodynamic response during pneumoperitoneum and intraoperative period.

In the present study 90 adult patients were randomly allocated to two groups of 45 each. Group D patients received inj. Dexmedetomidine as a loading dose of 1mcg/kg/hr iv, followed by an infusion of inj. Dexmedetomidine at the rate of 0.4mcg/kg/hr i.v. While patients of group S (placebo) received, 0.9% normal saline at a similar rate.

Demographic data:

In the present study there was no statistically significant difference with respect to the demographic characteristic (Age, Sex, Weight and ASA grading) of both the groups.

Hemodynamic Variables:

Heart Rate:

In the present study the mean heart rate of patients before receiving premedication, which was considered as the baseline heart rate, was 82.57±12.513 beats per minute (bpm) in group D, whereas it was 82.73±13.30 bpm in group S. The mean heart rate varied from 69.42±10.52 to 85.71±l2.76 bpm in group D whereas it varied from 82.73±13.30 bpm to 101.91±13.57 bpm in group S.

Bhattacharjee DP *et al*.[41] and **Gourishankar RM *et al*.**[42] found that the heart rate significantly increased after laryngoscopy and endotracheal intubation and after creation of pneumoperitoneum. Studies by both the above authors found that perioperative inj dexmedetomidine infusion significantly reduced the heart rate after endotracheal intubation and pneumoperitoneum and remained lower throughout the period of pneumoperitoneum in comparison to placebo.

In the present study we found significant decrease in the heart rate in Group D (dexmedetomidine) after laryngoscopy and endotracheal intubation and with the onset of pneumoperitoneum and throughout the period of pneumoperitoneum in comparison to group S (placebo).

Ghodki PS *et al*.[9] also found similar results in their study wherein there was a transient yet significant fall in the heart rate at the beginning of the dexmedetomidine infusion and that the heart rate was sustained for the entire duration of the infusion.

Dexmedetomidine is a centrally acting highly selective alpha-2 agonist. Activation of receptors in the brain and spinal cord level inhibits neuronal firing, leading to sympatholysis and thereby causing hypotension and bradycardia. The initial increase in arterial blood pressure is probably caused by the vasoconstrictive effects of dexmedetomidine when stimulating peripheral alpha-2 receptors. The incidence of hypotension and bradycardia may be related to the administration of a large i.v loading dose. Omitting the loading dose or not giving more than 0.4mcg/kg/hr reduces the incidence of hypotension or makes it less pronounced.[149]

In the present study 4 out of the 45 patients (9%) who received dexmedetomidine developed bradycardia (HR<50bpm), but responded well to treatment with anticholinergics (inj. Atropine sulphate 0.6 mg i.v). In several studies after IM and IV administration, in a small percentage of patients, dexmedetomidine caused profound bradycardia (<40 bpm) and occasionally sinus arrest or pause. Generally, these episodes resolved spontaneously or were readily treated without adverse outcome by anticholinergics.[150]

Photograph 5: Patient monitoring

Blood Pressure changes:

In the present study the systolic blood pressure (SBP), the diastolic blood pressure (DBP) and the mean arterial pressure (MAP) in group S (placebo) were significantly higher than the baseline values during laryngoscopy, endotracheal intubation and throughout the period of pneumoperitoneum. Whereas in group D (dexmedetomidine) these values showed minimal variability from the baseline values during intubation and during the period of pneumoperitoneum.

In group D there was a significant fall in the MAP values before induction, before pneumoperitoneum and after release of pneumoperitoneum. There was slight increase in values (<5%) after intubation, 15 and 30 minutes after pneumoperitoneum and after extubation. The values were significantly higher at all points of time in group S.

Upon statistical comparison of the two groups, there was a significant difference in values of both the groups (for SBP, DBP and MAP) at all points of time except before premedication where the values were comparable. There was a

significant fall in the SBP, DBP and MAP in patients of group D before induction. It confirmed that 10 minutes is adequate for i.v. loading dose of dexmedetomidine to act.

Ghodki PS *et al*.[9] in their study confirmed that after the loading dose of dexmedetomidine infusion there was a significant fall in the SBP. After which minimal change was observed for the entire duration of pneumoperitoneum.

Bhattacharjee DP *et al*.[41] found that the MAP was significantly lower in the patients receiving dexmedetomidine infusion, in comparison to the placebo group, after induction, after intubation and pneumoperitoneum; and remained lower throughout the pneumoperitoneum and in the post-operative period.

Gourishankar RM *et al*.[42] when comparing two doses of dexmedetomidine infusion found that the MAP decreased significantly in the Dex 0.2 group and highly significantly in the dex 0.4 group below the pre-infusion levels. The increase in the MAP was significantly lower after intubation and extubation in the dex 0.2 group compared to the placebo group. MAP in the dex 0.4 group remained below pre-infusion levels after intubation and extubation, which is similar to the present study. Pneumoperitoneum did not produce a significant effect in both the dex groups.

Tufanogullari *et al*.[40] compared three infusion doses of Dexmedetomidine 0.2, 0.4 and 0.8mcg/kg/hr with saline in morbidly obese patients undergoing Laparoscopic Bariatric surgery. Although the intraoperative hemodynamic values were similar in the four groups, MAP 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). In our study also, the mean arterial pressure in Dexmedetomidine group was significantly less in PACU.

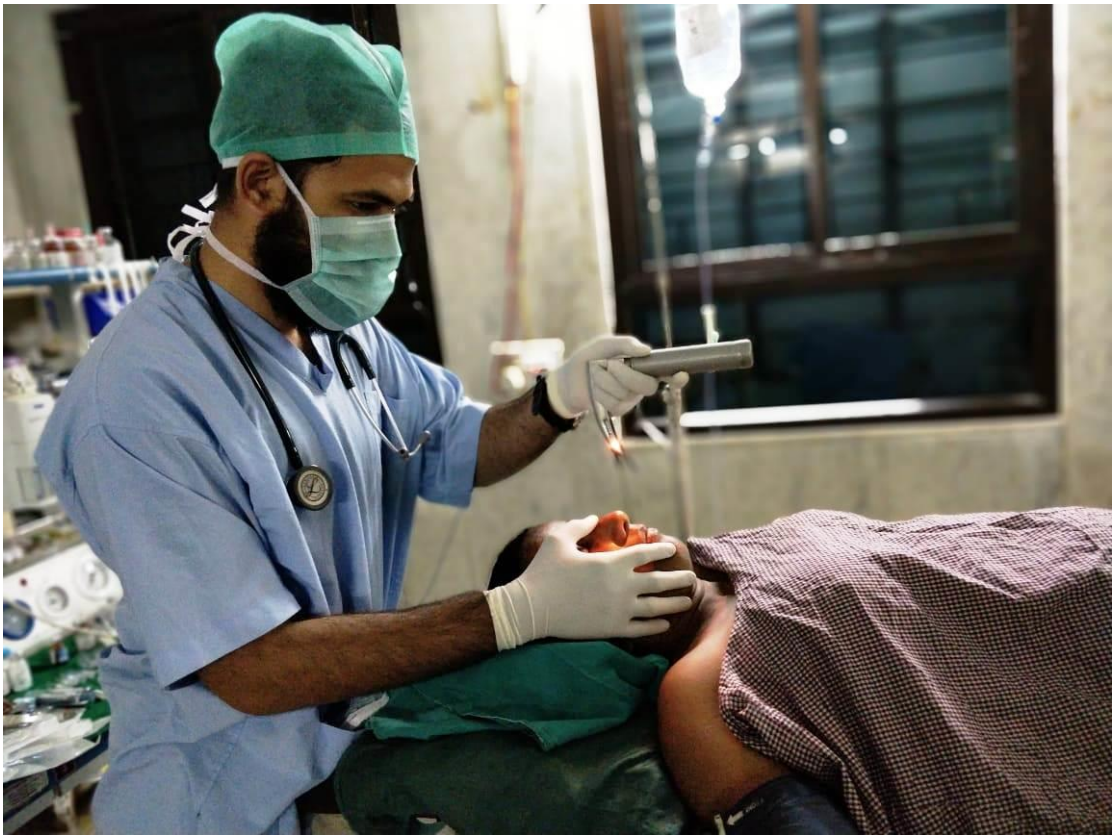
In spite of maintaining normocapnia, keeping intra-abdominal pressure below 14 mmHg and providing good potent analgesia with fentanyl, there was a significant rise in heart rate, systolic, diastolic, and mean arterial pressure from baseline in group S at all points during surgery.

In group S, out of the 45 patients, 10 (22%) patients required intra-operative drip of inj. Nitroglycerine (NTG) for control of hypertension (defined as an increase of more than 20% in the MAP from the baseline not controlled by an isoflurane concentration of 1.5%). On the other hand none of the patients in group D required a NTG drip.

Direct laryngoscopy and endotracheal intubation following induction of anaesthesia is associated with hemodynamic changes due to reflex sympathetic discharge caused by epipharyngeal and laryngopharyngeal stimulation. This increased sympatho-adrenal activity may result in hypertension, tachycardia and arrhythmias.[151,l52]

This increase in blood pressure and heart rate are usually transient, variable and unpredictable. The magnitude of the response is greater with increasing force and duration of laryngoscopy.[152] The elevation in arterial pressure typically starts within five seconds of laryngoscopy, peaks in 14 min and returns to control levels within 5 minutes.

Dexmedetomidine, being a central sympatholytic, has been used in various doses to attenuate the hemodynamic responses due to laryngoscopy and endotracheal intubation. In our study, we confirmed that dexmedetomidine infusion given 20 minutes prior to induction of general anaesthesia, effectively blunted the reflex tachycardia and hypertension caused due to laryngoscopy and intubation.



Photograph 6: Laryngoscopy

Yildiz *et al*.[32] evaluated the effect of a single pre-induction i.v. dose of dexmedetomidine 1mcg/kg on the cardiovascular response resulting from laryngoscopy and endotracheal intubation. They found that in the dexmedetomidine group the increase in blood pressure and heart rate after tracheal intubation was significantly lower as compared to the placebo group.

Sulaiman *et al*.[34] studied the efficacy of i.v. dexmedetomidine (0.5mcg/kg given 10 minutes prior to induction) for attenuation of cardiovascular responses to laryngoscopy and endotracheal intubation in patients with coronary artery disease. They too found that dexmedetomidine at a dose of 0.5mcg/kg as l0 minute infusion, administered prior to induction of general anaesthesia, attenuates the sympathetic response to laryngoscopy and intubation in patients undergoing myocardial revascularization.

Cho JS *et al*.[33] also had similar findings when using i.v. dexmedetomidine pre-treatment in the doses of 0.5mcg/kg or 1.0mcg/kg. Dexmedetomidine suppressed sympathetic hyperactivity and attenuated QTc prolongation during intubation.

Jaakola *et al*.[33] found decreased BP and heart rate during intubations following the administration of 0.6 pg/kg bolus of dexmedetomidine preoperatively.

Lawrence *et al*.[154] found decreased hemodynamic response to tracheal intubation or extubation following a single high dose of dexmedetomidine (2mcg/kg).

Isoflurane requirement was found to be significantly less in Group D as compared to Group S. The requirement of isoflurane was significantly higher in Group S.

Khan ZP *et al*.[35] studied the effects of dexmedetomidine on isoflurane requirements in healthy volunteers. They concluded that dexmedetomidine decreased isoflurane requirements in a dose dependent manner.

Tufanogullari B *et al*.[40] also found reduced average end-tidal desflurane concentrations with dexmedetomidine infusions.

Ghodki PS *et al*.[9] in their study found that dexmedetomidine infusion reduced the end-tidal concentration of isoflurane requirement for maintenance of anaesthesia by 30%, while maintaining adequate depth of anaesthesia.

Post-operative nausea and vomiting (PONV):

Post-operative nausea vomiting occurred in 6 out of 45 patients (13%) in group D, whereas it occurred in 7 out of 45 (16%) patients in group S. P value was 0.764 (P >0.05), and thus the difference was statistically not significant.

Our findings did not correlate with the study by **Tufanogullari B *et al*.**[40] in which 70% of the patients in the placebo group suffered from PONV while only 30% patients in the dex 0.2 and dex 0.4 group suffered from PONV. Only 10% of the

patients of the dex 0.8 group suffered from PONV. This may be because all our patients already received inj. Ondensetron and inj. Ranitidine as premedication.

SUMMARY

SUMMARY

Laparoscopic surgeries continue to evolve day by day to reduce trauma to the patient, morbidity, mortality and hospital stay; with consequent reduction in health care costs. Laparoscopic procedures are being performed for the most complex of surgical procedures including cholecystectomies, appendectomies, adrenalectomies, nephrectomies and even bariatric surgeries. But these laparoscopic procedures require insufflation of a gas, CO_2 being the most commonly used, for the creation of pneumoperitoneum. Pneumoperitoneum and patient positioning required for laparoscopy induce pathophysiologic changes in almost every system of the body that complicate anesthetic management.

Intraoperative hypertension and tachycardia caused by neurohumoral effects of laparotomy are the most common hemodynamic changes seen during laparoscopic procedures. Opioids, volatile anesthetic agents like isoflurane, sevoflurane, nitroglycerine, beta blockers, etc. have been used with varying degrees of success to control the hemodynamic changes occurring during laparoscopy.

Dexmedetomidine has been recently added to the anaesthesia armamentarium for its sedative, analgesic and opioid sparing effects. The present study has been undertaken to study the efficacy of this new alpha-2 agonist in attenuation of the hemodynamic effects seen during laparoscopic surgeries.

A single blinded randomized control study was conducted in the Department of Anaesthesia, Shri B. M. Patil medical college, Hospital and Research Centre, Vijayapur during the period of November 2016 to July 2018. A total of 90 patients randomly allocated in two group of 45 each, Group D (dexmedetomidine group) and Group S (placebo group) undergoing elective laparoscopic procedures under general anaesthesia were studied. The patients received a loading dose of 1mcg/kg over

10mins i.v followed by an i.v infusion at the rate of 0.4mcg/kg/hr of either inj. Dexmedetomidine or normal saline depending on the group. Sex, age, weight and ASA physical grading were comparable in both the groups. Dexmedetomidine maintained cardiovascular stability during laryngoscopy and laparoscopy. There was a significant rise in the heart rate and systolic, diastolic & mean arterial blood pressures in the patients of group S; in comparison to group D, during laryngoscopy and intubation, throughout the period of pneumoperitoneum, after extubation and 30 minutes postoperatively.

A significant number of patients in the placebo group required the use of nitroglycerine drip intraoperatively to control the increase in blood pressure whereas none of the patients in the dexmedetomidine group required nitroglycerine intraoperatively. There were no significant side effects in the dexmedetomidine group except bradycardia which responded well to inj. Atropine 0.6mg i.v.

Perioperative intravenous Dexmedetomidine can be recommended for maintaining cardiovascular stability during laparoscopic surgeries.

CONCLUSION

CONCLUSION

In the present study effects of CO_2 pneumoperitoneum on hemodynamics and the efficacy of intravenous dexmedetomidine infusion to prevent the same were assessed. The conclusions drawn from the study are:

- CO_2 pneumoperitoneum causes activation of the sympathetic autonomic nervous system leading to hemodynamic perturbations.
- Perioperative intravenous dexmedetomidine as a loading dose of 1mcg/kg/hr over 10mins prior to induction, followed by an infusion of 0.4mcg/kg/hr in ASA I and II patients was found to be effective in providing intraoperative hemodynamic stability during laparoscopic surgeries without any significant adverse effects.
- In addition, dexmedetomidine also blunted the stress responses to laryngoscopy & endotracheal intubation and extubation.
- The intraoperative requirement of NTG was decreased by administration of i.v. dexmedetomidine.

Hence dexmedetomidine can be safely used to attenuate the hemodynamic responses during laparoscopic surgeries with the added advantage of it being an adjuvant to general anaesthesia.

However additional studies are necessary to ascertain the efficacy and safety of dexmedetomidine in elderly and ASA III and IV patients, particularly in those with compromised cardiovascular function.

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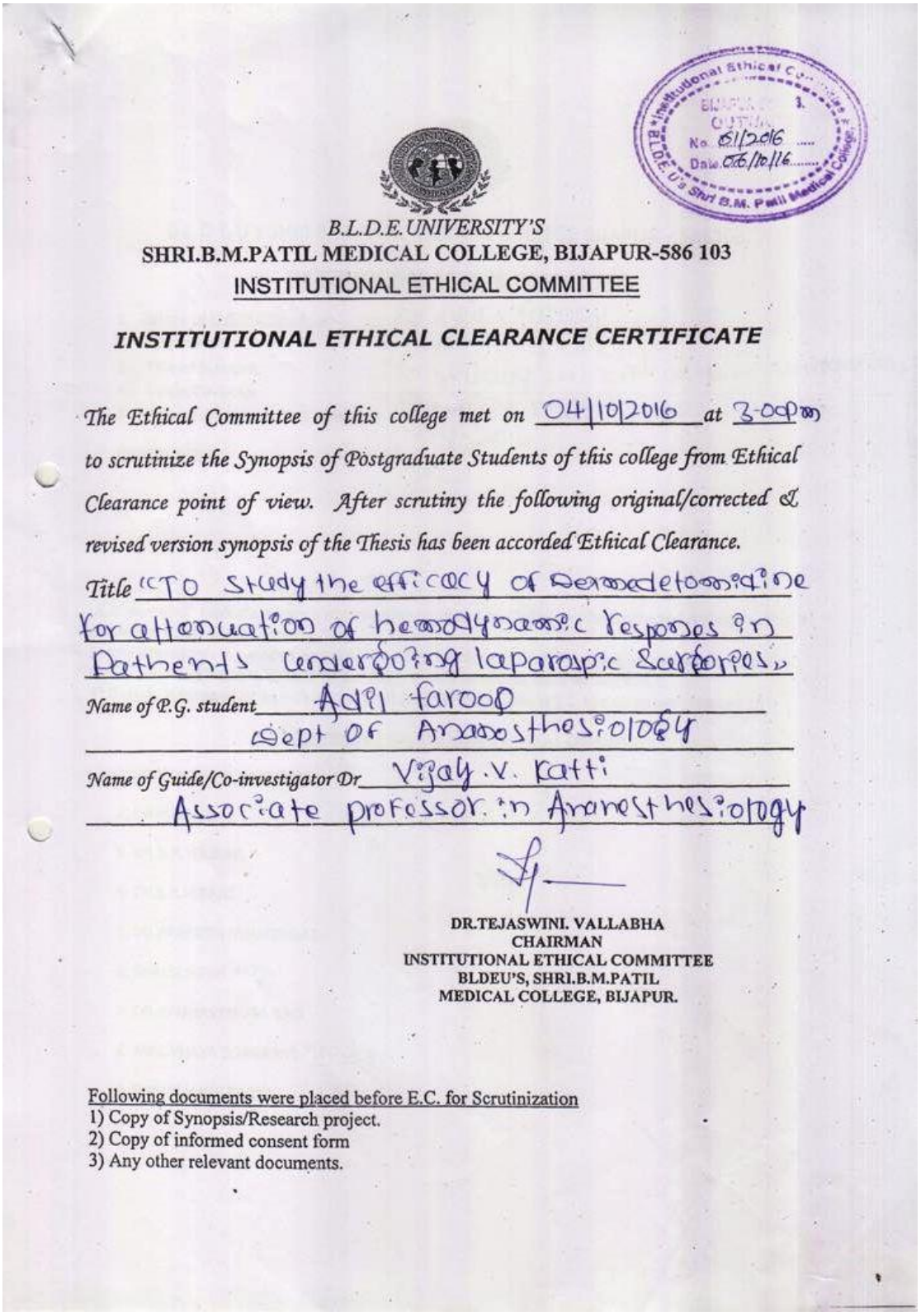
ANNEXURES

ANNEXURE-I

ETHICAL CLEARANCE CERTIFICATE



B.L.D.E. UNIVERSITY'S
SHRI.B.M.PATIL MEDICAL COLLEGE, BIJAPUR-586 103
INSTITUTIONAL ETHICAL COMMITTEE

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this college met on 04/10/2016 *at* 3-00pm *to scrutinize the Synopsis of Postgraduate Students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected & revised version synopsis of the Thesis has been accorded Ethical Clearance.*

Title "To study the efficacy of Dexmedetomidine for attenuation of hemodynamic responses in Pathents undergoing laparoscopic surgeries"

Name of P.G. student Adil farooq
Dept of Anaesthesiology

Name of Guide/Co-investigator Dr Vijay. V. Katti
Associate professor in Anaesthesiology

DR.TEJASWINI. VALLABHA
CHAIRMAN
INSTITUTIONAL ETHICAL COMMITTEE
BLDEU'S, SHRI.B.M.PATIL
MEDICAL COLLEGE, BIJAPUR.

Following documents were placed before E.C. for Scrutinization
1) Copy of Synopsis/Research project.
2) Copy of informed consent form
3) Any other relevant documents.

ANNEXURE-II

CONSENT FORM

B.L.D.E. (Deemed To Be University) SHRI B.M. PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE, VIJAYAPUR – 586103, KARNATAKA

TITLE OF THE PROJECT : "To Study the Efficacy of Dexmedetomidine for Attenuation of Hemodynamic Responses in Patients undergoing Laparoscopic Surgeries"

PRINCIPAL INVESTIGATOR: **Dr. ADIL FAROOQ**

Department of Anaesthesiology

BLDE (Deemed to be) University's

Shri B.M. Patil Medical College Hospital and

Research Centre, Sholapur Road Vijayapur-03

Email: adilfarooqgalaxy@gmail.com

PG GUIDE : **Dr. VIJAY V KATTI**

Associate Professor,

Department of Anaesthesiology

BLDE (Deemed to be) University's

Shri B.M. Patil Medical College Hospital and

Research Centre, Sholapur Road Vijayapur-03

Email: drvijaykatti@gmail.com

PURPOSE OF RESEARCH:

I have been informed that this study **"To Study The Efficacy of Dexmedetomidine For Attenuation of Hemodynamic Responses In Patients Undergoing Laparoscopic Surgeries"**

I have been explained about the reason for doing this study and selecting me/my ward as a subject for this study. I have also been given free choice for either being included or not in the study.

PROCEDURE:

I understand that I will be participating in the study: **"To Study The Efficacy of Dexmedetomidine For Attenuation of Hemodynamic Responses In Patients Undergoing Laparoscopic Surgeries"**

BENEFITS:

I understand that my wards participation in this study will help in finding out: is **"To Study The Efficacy of Dexmedetomidine For Attenuation of Hemodynamic Responses In Patients Undergoing Laparoscopic Surgeries"**

CONFIDENTIALITY:

I understand that medical information produced by this study will become a part of this Hospital records and will be subjected to the confidentiality and privacy regulation of this hospital.

If the data are used for publication in the medical literature or for teaching purpose, no names will be used and other identifiers such as photographs and audio or video tapes will be used only with my special written permission. I understand that I may see the photograph and videotapes and hear audiotapes before giving this permission.

REQUEST FOR MORE INFORMATION:

I understand that I may ask more questions about the study at any time. **Dr. ADIL FAROOQ** is available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during the course of this study, which might influence my continued participation.

If during this study, or later, I wish to discuss my participation in or concerns regarding this study with a person not directly involved, I am aware that the social worker of the hospital is available to talk with me.

And that a copy of this consent form will be given to me for keep for careful reading.

REFUSAL OR WITHDRAWL OF PARTICIPATION:

I understand that my participation is voluntary and I may refuse to participate or may withdraw consent and discontinue participation in the study at any time without prejudice to my present or future care at this hospital.

I also understand that **Dr. ADIL FAROOQ** will terminate my participation in this study at any time after he has explained the reasons for doing so and has helped arrange for my continued care by my own physician or therapist, if this is appropriate.

INJURY STATEMENT:

I understand that in the unlikely event of injury to me/my ward, resulting directly due to my participation in this study, such injury will be reported promptly, then medical treatment would be available to me, but no further compensation will be provided.

I understand that by my agreement to participate in this study, I am not waiving any of my legal rights.

I have explained to _____ the purpose of this research, the procedures required and the possible risks and benefits, to the best of my ability in patient's own language.

Date: **Dr. ADIL FAROOQ**

(Investigator)

Patient's signature Witness to above signature

STUDY SUBJECT CONSENT STATEMENT:

I confirm that **Dr. ADIL FAROOQ** has explained to me the purpose of this research, the study procedure that I will undergo and the possible discomforts and benefits that I may experience, in my own language.

I have been explained all the above in detail in my own language and I understand the same. Therefore I agree to give my consent to participate as a subject in this research project.

_____ _____

(Participant) Date

_____ _____

(Witness to above signature) Date

ANNEXURE-III

PROFORMA

STUDY: "To Study The Efficacy of Dexmedetomidine For Attenuation of Hemodynamic Responses In Patients Undergoing Laparoscopic Surgeries"

PATIENT DETAILS: DATE:

I. Name: Age/ Sex: I.P No: Ward:

Group allotted by randomization: Group D / Group S

II. 1. Type of the surgery:

Duration of surgery:_____ (min)

2. Indication:

III. Significant History:

IV. General Physical Examination:

Pallor: Icterus: Cyanosis: Clubbing:

Koilonychia: Lymphadenopathy: Oedema:

Teeth: Dentures:

V. Vital Parameters

Pulse: Blood Pressure: Respiratory Rate: Temperature:

VI. Systemic Examination

1. CVS 2.RS:

3. CNS 4.Per Abdomen:

VII. Airway Assessment:

MP Grade: Cervical Spine:

Mouth opening: Neck Movement:

VIII. ASA Grade:

IX. Investigation:

Hemoglobulin: TLC:

S. Urea: S. Creatinine:

LFT's: Platelet count:

Urine Routine:

Chest X-ray: ECG:

X. Perioperative Hemodynamic parameters:

Parameters	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**N1**	**N2**
HR (/min)											
SPO_2 (%)											
SBP(mmHg)											
DBP(mmHg)											
MAP(mmHg)											

Other parameters noted in both groups:

a) Intra operative requirement of atropine and NTG.
b) Post operative Nausea and vomiting.

Hemodynamic Parameters including HR, SPO_2, SBP, DBP and MAP were noted at:

1. Preoperatively (Ml)
2. 10 minutes After starting the Study Drug (M2)
3. At Induction (M3)
4. During Intubation (M4)
5. Before Pneumoperitoneum (M5)
6. 10 minutes after Pneumoperitoneum (M6)
7. 20 after Pneumoperitoneum (M7)
8. 30 after Pneumoperitoneum (M8)

   Every 30 minutes till the end of Pneumoperitoneum
9. At the end of Pneumoperitoneum (M9)
10. 10 minutes after reversal (N1)
11. Post operatively after 30minutes (N2)

    Study Drug infusion will be stopped 5 minutes before reversal.

Date:-

Place:- Vijayapur Investigator:- **Dr. ADIL FAROOQ**

Guide:- **Dr. VIJAY V. KATTI**

Key to Master Chart

Sr No	Serial Number
D	Dexmedetomidine Group
S	Saline Group
IP Number	In Patient Hospital Number
F	Female
M	Male
LC	Laparoscopic Cholecystectomy
LA	Laparoscopic Appendectomy
LU	Laparoscopic Umbilical Hernia
ASA	American Society of Anaesthesiologists
M1	Preoperatively
M2	10 minutes after starting the Study Drug
M3	At Induction
M4	During Intubation
M5	Before Pneumoperitoneum
M6	10 minutes after pneumoperitoneum
M7	20 after pneumoperitoneum
M8	30 after pneumoperitoneum
M9	At the end of pneumoperitoneum
N1	10 minutes after reversal
N2	Post operatively after 30minutes
HR (bmp)	Heart Rate in beats per minute
SPO2(%)	Arterial Oxygen Saturation
SBP(mm Hg)	Systolic Blood Pressure in mm of mercury

DBP(mm Hg)	Diastolic Blood Pressure in mm of mercury
MAP(mm Hg)	Mean Arterial Pressure in mm of mercury
PNP Duration	Duration of pneumoperitoneum
Surgery Duration	Duration of Surgery
NTG	Nitroglycerine
PONV	Post operative Nausea and Vomiting

MASTER CHART

GROUP D (Dexmedetomidine group)

										M1					M2					M3					M4					M5					M6						
Sr No	Group	IP Number	Date of Surgery	Name	Age	Sex	Body Weight (kg)	Surgery	ASA	HR (bpm)	SPO2 (%)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	HR (bpm)	SPO2 (%)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	HR (bpm)	SPO2 (%)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	HR (bpm)	SPO2 (%)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	HR (bpm)	SPO2 (%)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	HR (bpm)	SPO2 (%)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	HR (bpm)	SPO2 (%)
1	D	39599	12/2/2016	Farzana	32	F	55	LA	I	110	100	110	70	83	102	100	125	75	97	98	100	94	68	76	106	99	106	59	75	100	100	106	66	84	98	100	99	58	91	90	100
2	D	39720	12/3/2016	Neelamma	30	F	58	LA	I	78	100	124	80	93	74	100	120	80	92	70	100	95	64	76	80	100	121	83	92	59	100	90	55	69	76	100	112	69	84	82	99
3	D	40494	12/9/2016	Sudhir	30	M	68	LA	I	80	100	140	80	100	88	100	136	80	99	97	100	120	80	93	82	98	138	90	112	77	99	140	100	114	68	99	130	90	106	67	99
4	D	41601	12/15/2016	Malsiddappa	54	M	67	LC	II	84	100	160	80	107	86	100	150	82	105	76	100	129	88	102	79	99	153	90	111	66	99	114	78	87	62	100	118	61	89	65	100
5	D	42102	12/24/2016	Nagraj	31	M	70	LA	I	110	100	125	82	96	114	100	120	80	93	110	100	90	60	70	112	99	150	100	116	106	100	104	60	75	88	100	130	90	103	84	100
6	D	42512	12/28/2016	Revangouda	42	M	72	LA	II	82	100	140	100	113	76	100	138	90	106	74	100	113	75	85	73	99	117	78	90	81	100	121	86	87	74	100	115	81	94	58	100
7	D	42765	12/30/2016	Soujanya	41	F	60	LU	I	110	100	110	70	83	102	100	125	75	97	98	100	94	68	76	106	99	106	59	75	100	100	106	66	84	98	100	99	58	91	90	100
8	D	410	1/7/2017	Ramappa	36	M	74	LA	I	78	100	124	80	93	74	100	120	80	92	70	100	95	64	76	80	100	121	83	92	59	100	90	55	69	76	100	112	69	84	82	99
9	D	719	1/9/2017	Rachappa	29	M	72	LC	I	81	100	150	90	110	84	100	150	84	106	72	100	113	74	87	72	100	123	82	92	68	100	126	84	94	68	100	147	96	106	66	100
10	D	602	1/10/2017	Ramesh	48	M	78	LU	I	86	100	140	80	100	89	100	140	73	89	64	100	94	58	67	70	100	112	62	75	62	100	117	69	79	71	99	132	81	98	64	100
11	D	1782	1/19/2017	Kashinath	55	M	72	LC	II	88	100	140	80	100	92	100	140	90	106	94	100	110	70	83	94	100	90	50	66	90	99	85	63	70	75	100	92	64	73	72	100
12	D	2863	1/27/2017	Sudhir	40	M	76	LU	I	85	100	100	80	87	85	100	120	70	87	90	100	110	78	89	92	100	120	60	80	70	99	124	78	94	76	100	120	70	87	80	99
13	D	2904	1/28/2017	Navya	54	F	64	LC	II	84	100	110	72	85	74	100	124	88	100	76	100	118	74	89	68	100	124	68	87	72	100	131	78	96	84	100	124	87	99	80	100
14	D	3559	2/3/2017	Ganesh	20	M	74	LA	I	64	100	114	78	92	58	100	113	74	89	74	100	120	82	97	80	100	114	60	80	68	100	108	68	83	74	100	112	72	86	64	100
15	D	3396	2/9/2017	Shilpa	23	F	60	LA	I	110	100	134	77	99	109	100	122	73	91	105	100	146	94	115	102	100	127	90	101	80	100	95	50	67	76	100	113	77	91	96	100
16	D	4425	2/10/2017	Parmanand	41	M	75	LU	II	80	100	114	70	87	90	100	118	73	90	68	100	110	67	84	89	100	118	75	92	68	100	84	54	64	54	100	111	72	86	56	100
17	D	4468	2/11/2017	Kavitha	37	F	65	LA	I	72	100	112	75	88	54	100	104	65	79	63	100	94	54	69	84	100	124	74	93	52	100	116	70	89	52	100	121	79	93	52	100
18	D	4089	2/15/2017	Bharathi	38	F	62	LC	I	86	100	127	82	99	84	100	140	91	110	93	100	156	72	103	107	100	149	92	115	88	100	123	73	93	70	100	154	78	111	76	100
19	D	5239	2/17/2017	Vedant	22	M	70	LA	I	94	100	154	91	114	97	100	120	81	96	100	100	103	69	81	96	100	131	88	104	108	100	115	71	82	92	100	92	67	76	88	100
20	D	6065	2/25/2017	Shilpa	25	F	55	LA	I	80	100	124	84	98	82	100	128	86	100	84	100	94	64	74	86	100	110	72	85	85	100	120	78	94	72	99	128	86	100	64	100
21	D	6500	3/8/2017	Neelabai	55	F	60	LC	II	68	100	117	76	89	69	100	113	79	90	70	100	102	70	81	84	100	113	74	87	85	100	104	66	79	78	100	108	72	84	74	100
22	D	7804	3/13/2017	Kamalabai	26	F	55	LA	I	82	100	110	70	84	84	100	120	74	90	80	100	102	64	77	90	100	110	88	96	88	100	108	84	92	98	100	118	86	97	84	100
23	D	10702	4/1/2017	Prabhagya	35	M	65	LA	I	90	100	108	70	83	80	100	120	60	70	84	100	104	62	76	83	100	90	70	77	78	100	100	62	75	74	100	115	85	97	74	100
24	D	10927	4/8/2017	Sharnamma	35	F	58	LC	I	79	99	134	84	101	86	100	136	80	99	82	100	110	70	84	80	100	122	80	94	70	100	114	64	81	64	100	110	60	77	64	100
25	D	11449	4/19/2017	Iramma	25	F	66	LC	I	76	100	138	82	101	72	100	136	80	99	68	100	102	72	82	84	100	122	78	93	70	100	124	80	95	70	100	120	76	91	64	100
26	D	12393	4/27/2017	Yallawwa	58	F	64	LC	II	60	99	110	70	84	56	99	108	68	82	55	100	106	64	78	62	100	114	70	85	52	100	111	74	87	52	99	121	74	90	56	100
27	D	14613	5/10/2017	Yallappa	59	M	74	LU	II	70	100	130	80	97	72	100	128	76	93	68	100	116	70	86	76	100	118	76	90	68	99	108	68	81	66	100	106	64	78	64	100
28	D	14772	5/11/2017	Manikanthan	33	M	76	LA	I	70	99	120	70	87	66	99	124	72	89	72	100	110	68	82	72	100	124	78	94	70	100	114	70	85	67	100	118	70	86	65	99
29	D	16396	5/24/2017	Jayashree	31	F	60	LA	I	72	100	128	78	95	76	100	130	80	97	68	100	110	70	84	66	100	116	72	86	68	99	118	76	90	66	100	115	72	86	68	100
30	D	16668	5/25/2017	Guthappa	32	M	76	LA	I	84	100	130	70	90	86	100	136	84	101	76	100	110	70	84	84	100	120	70	87	76	100	122	66	85	70	99	116	68	84	67	100
31	D	18077	6/7/2017	Naveen	35	M	78	LA	I	70	99	120	70	87	74	99	124	74	91	69	100	94	64	74	74	100	114	70	88	65	100	108	68	81	62	100	106	66	79	61	100
32	D	19501	6/10/2017	Shivanand	58	M	65	LU	II	82	100	128	84	99	76	100	126	84	98	70	99	114	80	70	70	100	116	82	93	60	100	118	72	87	52	100	114	76	89	90	99
33	D	22977	7/15/2017	Shruthi	21	F	55	LA	I	94	99	154	91	114	97	100	120	81	96	100	100	103	69	81	96	100	131	88	104	108	100	115	71	82	92	100	92	67	76	88	100
34	D	23099	7/17/2017	Renuka	45	F	56	LA	II	80	100	124	84	98	82	99	128	86	100	84	99	94	64	74	86	100	110	72	85	85	100	120	78	94	72	100	128	86	100	64	100
35	D	23770	7/22/2017	Afrin	25	F	58	LA	I	68	99	117	76	89	69	99	113	79	90	70	99	102	70	81	84	100	113	74	87	85	100	104	66	79	78	100	108	72	84	74	100
36	D	24235	7/26/2017	Sarapa	44	M	75	LU	II	82	99	110	70	84	84	99	120	74	90	80	100	102	64	77	90	100	110	88	96	88	100	108	84	92	98	100	118	86	97	84	100
37	D	24429	7/27/2017	Sunil vittal	30	M	68	LC	I	90	100	108	70	83	80	99	120	60	70	84	100	104	62	76	83	100	90	70	77	78	100	100	62	75	74	99	115	85	97	74	99
38	D	24413	7/27/2017	Ramdev	20	M	60	LU	I	79	99	134	84	101	86	100	136	80	99	82	99	110	70	84	80	100	122	80	94	70	100	114	64	81	64	100	110	60	77	64	99
39	D	25282	8/3/2017	Laxmibai T	50	M	66	LA	II	76	100	138	82	101	72	99	136	80	99	68	99	102	72	82	84	100	122	78	93	70	99	124	80	95	70	100	120	76	91	64	100
40	D	25477	8/4/2017	Ramesh	47	M	68	LU	I	60	99	110	70	84	56	99	108	68	82	55	99	106	64	78	62	100	114	70	85	52	100	111	74	87	52	100	121	74	90	56	100
41	D	25511	8/11/2017	Sujata	30	F	65	LC	I	86	99	127	82	99	84	100	140	91	110	93	100	156	72	103	107	100	149	92	115	88	100	123	73	93	70	100	154	78	111	76	100
42	D	26566	8/14/2017	Shiraj	26	M	64	LC	I	80	99	140	80	100	88	99	136	80	99	97	100	120	80	93	82	98	138	90	112	77	99	140	100	114	68	99	130	90	106	67	99
43	D	29586	9/6/2017	Yallawwa	30	F	64	LC	I	84	100	160	80	107	86	99	150	82	105	76	99	129	88	102	79	99	153	90	111	66	99	114	78	87	62	100	118	61	89	65	100
44	D	31779	9/22/2017	Ramesh	35	M	60	LA	I	110	99	125	82	96	114	99	120	80	93	110	99	90	60	70	112	99	150	100	116	106	100	104	60	75	88	100	130	90	103	84	100
45	D	33473	10/5/2017	Basagond R	55	M	74	LC	II	82	99	140	100	113	76	100	138	90	106	74	99	113	75	85	73	99	117	78	90	81	100	121	86	87	74	100	115	81	94	58	100

M7			M8					M9					N1					N2									
SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	HR (bpm)	SPO2 (%)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	HR (bpm)	SPO2 (%)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	HR (bpm)	SPO2 (%)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	HR (bpm)	SPO2 (%)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	PNP Duration	Surgery Duration	Atropine Use	NTG Use	PONV
100	60	74	82	100	102	60	74	84	100	96	64	75	106	100	121	64	90	110	100	128	66	96	48	79	0	0	0
122	78	91	88	100	120	82	95	82	100	124	82	94	68	100	123	84	96	92	100	121	78	90	55	83	0	0	0
110	78	88	-	-	-	-	-	66	99	104	71	82	63	100	126	84	97	68	99	121	78	97	27	55	0	0	0
122	82	94	64	100	124	80	94	54	100	120	84	92	62	100	125	90	98	76	99	121	89	96	28	60	0	0	0
130	100	110	84	100	120	76	91	84	100	122	76	91	80	100	130	80	97	86	99	134	78	97	57	87	0	0	0
126	80	94	58	100	122	83	97	54	100	124	86	97	65	100	120	90	96	84	100	130	94	102	26	58	0	0	0
100	60	74	82	100	102	60	74	84	100	96	64	75	106	100	121	64	90	110	100	128	66	96	48	79	0	0	0
122	78	91	88	100	120	82	95	82	99	124	82	94	68	100	123	84	96	92	100	121	78	90	55	83	0	0	0
136	88	97	63	100	133	79	92	54	99	128	74	88	62	100	136	80	93	70	99	140	84	102	53	79	0	0	0
120	70	83	62	100	120	68	79	58	99	97	55	68	60	100	116	66	77	70	99	136	77	89	57	78	0	0	1
98	66	77	76	100	104	71	82	82	99	112	78	86	66	100	105	61	79	74	99	110	80	76	60	88	0	0	0
110	80	94	70	100	106	72	83	74	100	102	73	83	90	100	110	64	79	84	100	104	62	76	59	95	0	0	0
118	74	89	82	100	128	74	98	82	100	124	87	99	86	99	126	88	101	82	100	114	79	91	55	83	0	0	0
134	89	106	62	100	122	76	94	60	100	114	78	90	54	99	117	77	93	52	100	104	71	80	29	66	0	0	0
142	93	113	88	100	136	86	106	80	100	132	84	103	82	100	135	78	98	84	100	128	82	97	53	74	0	0	0
108	71	85	64	100	119	80	99	75	100	132	85	103	75	100	114	75	91	70	100	126	74	90	27	54	0	0	0
119	72	89	52	100	115	78	91	50	99	111	70	86	54	100	119	67	88	82	99	116	64	82	29	62	0	0	0
145	70	98	-	-	-	-	-	80	99	133	83	102	70	100	149	93	114	68	99	138	80	100	27	58	0	0	1
111	71	85	84	100	102	72	82	76	100	114	72	88	81	100	135	90	108	69	100	112	72	88	59	88	0	0	0
124	80	95	62	100	114	73	87	64	100	110	70	84	68	100	122	80	94	74	100	124	74	91	84	117	0	0	0
102	68	79	68	100	98	65	76	74	100	100	64	76	80	100	108	72	84	80	100	114	73	87	58	87	0	0	0
108	78	88	82	100	110	84	93	80	100	112	86	95	84	100	108	74	85	88	99	116	84	96	88	140	1	0	0
103	78	87	70	99	110	70	84	64	100	105	75	86	76	100	107	74	85	80	100	117	85	97	108	132	0	0	0
108	62	77	62	99	112	64	80	61	100	114	64	81	60	100	120	80	94	76	99	130	86	101	84	117	0	0	1
118	76	90	64	100	116	70	86	62	100	118	68	85	62	100	116	64	82	78	100	130	78	95	65	93	0	0	0
113	68	83	62	100	115	62	80	66	100	109	64	79	72	100	112	68	83	82	100	118	70	86	49	74	1	0	0
108	60	73	-	-	-	-	-	64	100	102	62	75	62	100	108	64	79	74	100	110	70	84	88	120	0	0	0
110	72	85	-	-	-	-	-	65	99	110	74	86	64	100	110	76	87	76	100	126	78	94	54	83	0	0	0
110	68	82	66	100	110	64	79	68	99	111	70	86	64	100	110	60	77	84	100	118	74	89	95	124	0	0	0
118	68	84	64	100	116	70	85	64	100	118	68	84	68	100	124	80	94	66	100	121	78	92	115	147	0	0	1
106	62	77	60	100	104	60	74	60	100	100	60	73	64	100	108	68	81	70	99	110	64	79	60	88	0	0	0
126	88	101	-	-	-	-	-	86	99	114	78	74	80	100	130	80	97	82	100	120	70	87	58	94	0	0	0
111	71	85	84	100	102	72	82	76	99	114	72	88	81	100	135	90	108	69	100	112	72	88	59	88	0	0	0
124	80	95	62	100	114	73	87	64	100	110	70	84	68	100	122	80	94	74	100	124	74	91	84	117	0	0	0
102	68	79	68	99	98	65	76	74	100	100	64	76	80	100	108	72	84	80	100	114	73	87	58	87	0	0	0
108	78	88	82	99	110	84	93	80	100	112	86	95	84	99	108	74	85	88	100	116	84	96	88	140	1	0	0
103	78	87	70	100	110	70	84	64	100	105	75	86	76	99	107	74	85	80	100	117	85	97	108	132	0	0	0
108	62	77	62	100	112	64	80	61	100	114	64	81	60	99	120	80	94	76	100	130	86	101	84	117	0	0	1
118	76	90	64	99	116	70	86	62	100	118	68	85	62	100	116	64	82	78	100	130	78	95	65	93	0	0	0
113	68	83	62	100	115	62	80	66	100	109	64	79	72	100	112	68	83	82	100	118	70	86	49	74	1	0	0
145	70	98	-	-	-	-	-	80	100	133	83	102	70	100	149	93	114	68	100	138	80	100	27	58	0	0	1
110	78	88	-	-	-	-	-	66	99	104	71	82	63	100	126	84	97	68	99	121	78	97	27	55	0	0	0
122	82	94	64	100	124	80	94	54	100	120	84	92	62	100	125	90	98	76	99	121	89	96	28	60	0	0	0
130	100	110	84	100	120	76	91	84	100	122	76	91	80	100	130	80	97	86	99	134	78	97	57	87	0	0	0
126	80	94	58	99	122	83	97	54	100	124	86	97	65	100	120	90	96	84	100	130	94	102	26	58	0	0	0

MASTER CHART

GROUP S (Normal Saline Group)

										M1					M2					M3					M4					M5					M6						
Sr No	Group	IP Number	Date of Surgery	Name	Age	Sex	Body Weight (kg)	Surgery	ASA	HR (bpm)	SPO2 (%)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	HR (bpm)	SPO2 (%)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	HR (bpm)	SPO2 (%)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	HR (bpm)	SPO2 (%)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	HR (bpm)	SPO2 (%)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	HR (bpm)	SPO2 (%)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	HR (bpm)	SPO2 (%)
1	S	41026	12/14/2016	Aneesh	27	M	65	LA	I	92	100	110	70	86	82	100	120	78	92	84	99	124	78	93	90	100	132	74	93	78	100	127	84	98	78	100	150	94	113	86	100
2	S	40960	12/21/2016	Vidyashree	25	F	55	LA	I	68	100	140	90	107	74	100	138	86	103	76	100	144	92	110	85	100	160	96	119	77	100	128	89	103	94	100	156	96	117	82	100
3	S	42122	12/24/2016	Malappa	25	M	66	LA	I	78	99	130	80	104	80	100	134	78	97	86	100	136	77	102	89	99	120	72	88	84	100	113	66	87	95	100	128	88	101	91	100
4	S	42688	12/24/2016	Bhairai	57	F	60	LA	II	108	99	155	97	114	110	99	148	98	111	106	100	118	87	97	94	100	121	71	87	115	99	170	93	122	97	100	152	110	124	109	100
5	S	304	1/4/2017	Shankarling	50	M	70	LC	II	96	99	120	70	86	93	100	130	70	90	97	100	130	80	97	102	100	130	90	103	88	100	113	77	89	94	99	130	80	97	98	99
6	S	381	1/6/2017	Vani	40	F	68	LU	I	81	100	150	90	110	84	99	150	90	110	93	100	140	90	107	99	100	190	120	143	94	100	150	95	114	89	100	148	101	116	94	100
7	S	1230	1/13/2017	Akash	47	M	58	LU	I	80	100	140	90	107	83	100	142	92	108	74	100	130	70	90	97	100	183	87	119	76	100	103	68	87	86	100	171	86	114	94	100
8	S	2005	1/20/2017	Parvati	55	F	68	LC	II	80	99	130	80	97	92	100	134	96	109	96	100	124	70	88	108	99	150	110	123	110	100	140	90	107	106	100	150	100	117	100	100
9	S	1991	1/20/2017	Bhimashankar	50	M	70	LC	II	74	99	118	78	91	78	100	124	82	96	74	100	98	64	75	110	100	160	112	128	86	100	138	98	111	88	99	142	100	114	90	100
10	S	2678	2/26/2017	Kavyashree	20	F	55	LA	I	84	99	120	70	87	82	100	122	74	90	84	100	110	75	72	114	100	147	102	117	94	100	145	96	112	78	100	132	92	105	84	99
11	S	2998	1/30/2017	Asha	37	F	64	LU	I	110	100	120	78	92	112	100	124	76	92	103	99	113	82	87	96	100	123	88	95	97	99	132	90	104	94	100	125	91	99	98	100
12	S	4219	2/8/2017	Vijayalaxmi	42	F	65	LA	I	64	99	130	80	97	76	100	140	98	110	72	100	132	94	107	66	100	115	87	82	74	100	120	78	92	78	100	154	110	106	84	100
13	S	4226	2/9/2017	Sandeesh	27	M	68	LA	I	84	98	124	80	95	84	100	122	82	95	86	100	98	64	76	84	100	126	88	101	94	100	110	60	77	94	100	134	94	107	99	100
14	S	5168	2/17/2017	Akshay	30	M	70	LA	I	92	100	110	70	86	82	100	120	78	92	84	100	124	78	93	90	100	132	74	93	78	100	127	84	98	78	100	150	94	113	86	100
15	S	5848	2/22/2017	Nagveni	29	F	58	LA	I	68	100	140	90	107	74	100	138	86	103	76	100	144	92	110	85	100	160	96	119	77	100	128	89	103	94	100	156	96	117	82	100
16	S	6638	3/1/2017	Vijayalaxmi	21	F	58	LA	I	71	100	108	66	80	66	100	104	62	76	65	99	113	65	81	100	100	140	90	108	72	100	105	78	89	80	100	137	81	100	88	100
17	S	6720	3/3/2017	Chandrabhaga	40	F	60	LC	I	62	99	112	78	89	62	98	116	76	89	65	100	120	80	95	90	100	119	86	98	65	100	102	75	84	78	100	121	85	98	84	100
18	S	9956	3/31/2017	Ramesh	40	M	78	LU	I	74	98	118	88	99	70	100	122	88	99	77	100	124	89	101	80	100	160	94	116	82	100	121	87	99	84	100	157	94	116	104	100
19	S	10068	4/3/2017	Parvati	36	F	66	LC	I	83	100	150	94	113	80	100	142	90	107	81	100	150	90	110	102	100	186	94	127	78	100	137	92	107	81	100	156	94	115	92	100
20	S	11443	4/17/2017	Shankramma	35	F	68	LC	I	65	100	110	80	90	68	100	104	78	87	68	100	116	84	95	78	99	130	90	105	62	100	120	90	100	101	99	140	88	107	86	100
21	S	12790	4/24/2017	Geetha	35	F	62	LC	I	73	100	130	78	97	71	100	136	84	101	77	99	134	86	103	107	100	146	89	109	81	100	119	86	98	86	100	140	85	105	92	100
22	S	12118	4/24/2017	Naveen	40	M	78	LA	I	76	100	116	82	95	70	99	114	84	94	79	100	120	80	95	121	100	160	90	115	86	100	128	84	99	80	100	150	90	110	108	100
23	S	13309	4/24/2017	Sasubai	45	F	70	LA	I	97	100	140	80	100	92	100	136	76	96	99	100	144	82	104	121	100	170	95	120	95	100	134	85	102	88	100	160	94	116	118	99
24	S	13166	5/4/2017	Laxmibai	35	F	66	LC	I	87	100	126	68	88	84	100	124	74	91	89	100	130	70	90	123	100	130	86	101	93	100	116	79	92	110	100	130	86	101	113	100
25	S	14750	5/13/2017	Geetha	22	F	58	LA	I	81	100	107	62	77	82	100	113	66	82	84	100	110	65	80	107	100	140	86	105	77	99	116	76	90	119	100	134	87	103	102	100
26	S	15948	5/25/2017	Hanumanth	26	M	66	LA	I	93	100	125	70	90	94	100	123	74	90	104	100	120	72	90	132	100	140	82	104	89	100	118	80	94	116	99	137	78	100	119	100
27	S	17330	6/1/2017	Shivraj	42	M	74	LA	I	84	100	128	88	101	88	100	130	84	99	98	99	110	74	86	114	100	168	110	129	112	100	144	92	109	105	100	158	106	124	98	100
28	S	17142	6/7/2017	Renuka	42	F	70	LU	I	112	100	136	84	102	110	100	144	86	106	112	100	120	76	97	124	100	164	98	120	104	100	160	110	127	123	100	171	115	135	95	100
29	S	21619	7/5/2017	Dayanand	31	M	68	LA	I	90	100	140	90	107	88	100	148	94	112	94	100	120	86	99	116	99	174	100	125	118	100	170	94	120	116	100	154	100	118	106	100
30	S	22898	7/14/2017	Malamma	53	F	70	LU	II	69	100	120	70	87	70	100	122	72	89	66	100	92	88	71	115	100	160	100	120	98	100	140	98	112	100	100	142	88	106	90	100
31	S	22890	7/14/2017	Sharnappa	45	F	66	LC	I	74	100	110	70	83	78	100	114	78	90	72	100	92	60	72	110	100	154	92	112	98	100	148	88	108	108	100	140	90	106	92	100
32	S	22989	7/15/2017	Sainath	25	M	68	LC	I	61	100	126	75	92	85	99	126	80	95	91	100	121	62	91	108	100	152	93	113	92	100	130	89	103	100	99	147	92	110	99	100
33	S	23136	7/17/2017	Laxmi	23	F	56	LA	I	96	99	120	70	86	93	100	130	70	90	97	100	130	80	97	102	100	130	90	103	88	99	113	77	89	94	100	130	80	97	98	100
34	S	25369	8/4/2017	Jyothi	22	F	55	LA	I	81	100	150	90	110	84	99	150	90	110	93	100	140	90	107	99	100	190	120	143	94	100	150	95	114	89	100	148	101	116	94	99
35	S	25395	8/4/2017	Rekha	44	F	68	LU	I	80	100	140	90	107	83	100	142	92	108	74	100	130	70	90	97	100	183	87	119	76	100	103	68	87	86	99	171	86	114	94	100
36	S	26079	8/9/2017	Hardik	42	M	76	LU	I	80	99	130	80	97	92	100	134	96	109	96	100	124	70	88	108	100	150	110	123	110	100	140	90	107	106	100	150	100	117	100	100
37	S	25683	8/9/2017	Mallamma	60	F	66	LC	II	74	99	118	78	91	78	100	124	82	96	74	100	98	64	75	110	100	160	112	128	86	100	138	98	111	88	100	142	100	114	90	100
38	S	25613	8/12/2017	Siddangaudappa	58	M	75	LC	II	71	100	108	66	80	66	100	104	62	76	65	100	113	65	81	100	100	140	90	108	72	100	105	78	89	80	100	137	81	100	88	100
39	S	26002	8/14/2017	Akshay	50	M	70	LA	I	78	99	130	80	104	80	100	134	78	97	86	100	136	77	102	89	99	120	72	88	84	100	113	66	87	95	100	128	88	101	91	100
40	S	26951	8/16/2017	Iranna	45	M	68	LU	I	108	99	155	97	114	110	99	148	98	111	106	100	118	87	97	94	100	121	71	87	115	99	170	93	122	97	100	152	110	124	109	100
41	S	29087	9/2/2017	Fayaz	49	M	70	LC	I	96	99	120	70	86	93	100	130	70	90	97	100	130	80	97	102	100	130	90	103	88	100	113	77	89	94	99	130	80	97	98	99
42	S	29260	9/4/2017	Ameera	20	F	55	LA	I	80	99	130	80	97	92	100	134	96	109	96	100	124	70	88	108	99	150	110	123	110	100	140	90	107	106	100	150	100	117	100	100
43	S	30006	9/9/2017	Baswaraj	21	M	68	LA	I	74	99	118	78	91	78	100	124	82	96	74	99	98	64	75	110	100	160	112	128	86	100	138	98	111	88	100	142	100	114	90	100
44	S	31319	9/20/2017	Gangamma	57	F	68	LC	II	84	99	120	70	87	82	100	122	74	90	84	100	110	75	72	114	100	147	102	117	94	100	145	96	112	78	100	132	92	105	84	100
45	S	31779	9/22/2017	Ramesh	35	M	70	LA	I	110	100	120	78	92	112	100	124	76	92	103	100	113	82	87	96	100	123	88	95	97	100	132	90	104	94	100	125	91	99	98	99

M7			M8					M9					N1					N2									
SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	HR (bpm)	SPO2 (%)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	HR (bpm)	SPO2 (%)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	HR (bpm)	SPO2 (%)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	HR (bpm)	SPO2 (%)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	PNP Duration	Surgery Duration	Atropine Use	NTG Use	PONV
156	102	120	78	99	140	88	105	72	99	136	72	93	90	99	144	82	102	74	100	124	70	88	59	95	0	0	1
152	98	116	76	98	150	90	110	73	100	134	87	103	88	100	165	96	119	82	100	152	90	111	57	77	0	1	0
125	85	100	100	100	128	92	104	96	100	130	96	101	83	100	120	83	95	81	100	124	70	86	29	60	0	0	0
153	97	118	110	100	146	94	111	106	100	142	88	106	93	99	150	92	125	100	99	140	90	107	58	87	0	0	0
140	88	110	96	100	143	92	111	98	100	140	90	109	98	100	144	94	112	90	100	130	84	99	88	140	0	0	0
138	95	109	95	100	143	90	105	98	100	140	98	112	84	100	136	88	104	88	100	142	92	109	84	117	0	0	1
138	76	92	88	100	150	75	117	84	100	148	72	115	90	100	138	70	93	82	100	160	80	107	27	58	0	1	0
130	86	101	90	100	134	84	101	84	100	138	78	98	84	100	130	76	94	90	100	140	80	100	65	93	0	0	0
130	88	102	96	100	132	88	103	88	100	130	80	97	82	100	132	84	100	92	100	130	90	103	84	111	0	0	0
136	96	109	88	100	134	98	110	87	100	126	93	104	76	100	128	94	105	86	100	128	90	103	27	55	0	0	0
128	94	105	92	100	136	80	94	88	100	137	88	97	80	100	135	83	94	78	100	124	78	93	57	86	0	0	0
156	110	126	82	100	152	100	113	92	100	148	96	113	70	100	142	96	111	78	100	136	92	107	60	88	0	1	0
140	90	106	108	100	158	96	117	100	100	144	92	109	88	100	134	90	105	96	100	142	96	112	28	57	0	0	0
156	102	120	78	99	140	88	105	72	99	136	72	93	90	100	144	82	102	74	100	124	70	88	59	95	0	0	1
152	98	116	76	98	150	90	110	73	100	134	87	103	88	100	165	96	119	82	100	152	90	111	57	77	0	1	0
136	84	101	81	100	130	81	98	71	100	108	68	83	98	100	126	78	94	98	100	120	72	88	60	84	0	0	0
122	83	96	79	100	119	84	96	81	100	109	80	90	121	100	130	90	104	116	99	132	80	97	90	110	0	0	0
155	94	114	100	100	160	92	115	68	100	130	90	104	117	100	160	90	114	108	100	142	84	103	27	60	0	1	0
153	93	113	84	100	160	90	113	87	98	138	87	107	87	100	140	90	107	104	100	126	78	94	53	84	0	1	0
138	92	107	82	100	130	90	105	63	100	121	88	100	97	100	130	90	103	88	100	118	74	89	59	87	0	0	1
134	88	103	84	100	139	87	105	95	99	116	84	98	123	100	140	80	100	103	100	128	80	96	65	93	0	0	0
142	86	105	109	100	145	90	109	78	100	130	86	100	120	100	140	90	108	96	100	119	82	94	28	67	0	0	0
157	92	114	115	100	158	89	112	89	100	134	70	103	123	100	150	87	108	92	100	136	80	99	88	124	0	1	0
126	88	101	112	100	120	85	97	99	100	118	82	87	121	100	124	85	98	84	100	116	70	85	48	81	0	0	1
136	84	101	104	100	130	86	102	84	100	112	78	93	119	100	126	84	95	92	100	116	84	95	29	62	0	0	0
135	80	98	121	100	130	83	99	96	100	121	86	91	117	100	145	79	103	96	99	138	75	96	52	94	0	0	0
136	86	103	104	100	130	84	99	98	100	132	94	101	86	99	130	84	99	94	100	140	86	104	48	86	0	0	0
157	87	110	121	100	142	93	118	96	100	138	84	114	74	98	154	92	120	84	100	140	92	117	54	79	0	1	1
150	92	111	109	99	150	96	114	108	100	140	84	103	106	100	144	92	110	100	99	130	84	99	49	84	0	1	0
136	84	101	89	98	138	88	102	84	100	128	84	99	82	100	130	84	100	90	100	132	84	100	27	58	0	0	0
148	88	108	88	100	130	80	97	86	100	128	82	97	88	100	130	80	97	84	100	132	80	98	50	93	0	0	0
141	87	105	102	100	137	88	104	90	99	126	85	99	106	99	139	86	104	91	100	130	82	98	57	92	0	0	0
140	88	110	96	100	143	92	111	98	100	140	90	109	98	100	144	94	112	90	100	130	84	99	88	140	0	0	0
138	95	109	95	100	143	90	105	98	100	140	98	112	84	100	136	88	104	88	100	142	92	109	84	117	0	0	1
138	76	92	88	100	150	75	117	84	100	148	72	115	90	100	138	70	93	82	99	160	80	107	27	58	0	1	0
130	86	101	90	100	134	84	101	84	100	138	78	98	84	100	130	76	94	90	100	140	80	100	65	93	0	0	0
130	88	102	96	100	132	88	103	88	100	130	80	97	82	100	132	84	100	92	100	130	90	103	84	111	0	0	0
136	84	101	81	100	130	81	98	71	100	108	68	83	98	100	126	78	94	98	100	120	72	88	60	84	0	0	0
125	85	100	100	100	128	92	104	96	100	130	96	101	83	100	120	83	95	81	100	124	70	86	29	60	0	0	0
153	97	118	110	100	146	94	111	106	100	142	88	106	93	99	150	92	125	100	99	140	90	107	58	87	0	0	0
140	88	110	96	100	143	92	111	98	100	140	90	109	98	100	144	94	112	90	100	130	84	99	88	140	0	0	0
130	86	101	90	100	134	84	101	84	100	138	78	98	84	100	130	76	94	90	100	140	80	100	65	93	0	0	0
130	88	102	96	99	132	88	103	88	100	130	80	97	82	100	132	84	100	92	100	130	90	103	84	111	0	0	0
136	96	109	88	100	134	98	110	87	99	126	93	104	76	100	128	94	105	86	100	128	90	103	27	55	0	0	0
128	94	105	92	100	136	80	94	88	100	137	88	97	80	100	135	83	94	78	100	124	78	93	57	86	0	0	0