COMPARATIVE STUDY OF INTRAVENOUSLY ADMINISTERED CLONIDINE AND MAGNESIUM SULFATE ON HEMODYNAMIC RESPONSES DURING LAPAROSCOPIC SURGERIES

Dissertation submitted to

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In partial fulfilment of the regulations for

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ANAESTHESIOLOGY

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CERTIFICATE

This is to certify that this dissertation entitled **"COMPARATIVE STUDY OF INTRAVENOUSLY ADMINISTERED CLONIDINE AND MAGNESIUM SULFATE ON HEMODYNAMIC RESPONSES DURING LAPAROSCOPIC SURGERIES"** is a bonafide original work of **Dr. KABILAN R** in partial fulfilment of the requirements for M.D Branch -X (Anaesthesiology) Examination of the Tamilnadu Dr. M.G.R. Medical University to be held in APRIL - 2016. The period of study was from JUNE 2014 - JULY 2015

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DECLARATION

I, **Dr. KABILAN R**, solemnly declare that the dissertation titled **"COMPARATIVE STUDY OF INTRAVENOUSLY ADMINISTERED CLONIDINE AND MAGNESIUM SULFATE ON HEMODYNAMIC RESPONSES DURING LAPAROSCOPIC SURGERIES"** is a bonafide work done by me at Thanjavur Medical College, Thanjavur during June 2014 to July 2015 under the guidance and supervision of **Dr. SHANTHI PAULRAJ M.D.,** Department of Anaesthesiology, Thanjavur Medical College, and Thanjavur.

This dissertation is submitted to Tamilnadu Dr. M.G.R Medical University towards partial fulfilment of requirement for the award of **M.D degree (Branch -X) in Anaesthesiology.**

Place: Thanjavur

Date: **(Dr. KABILAN R)**

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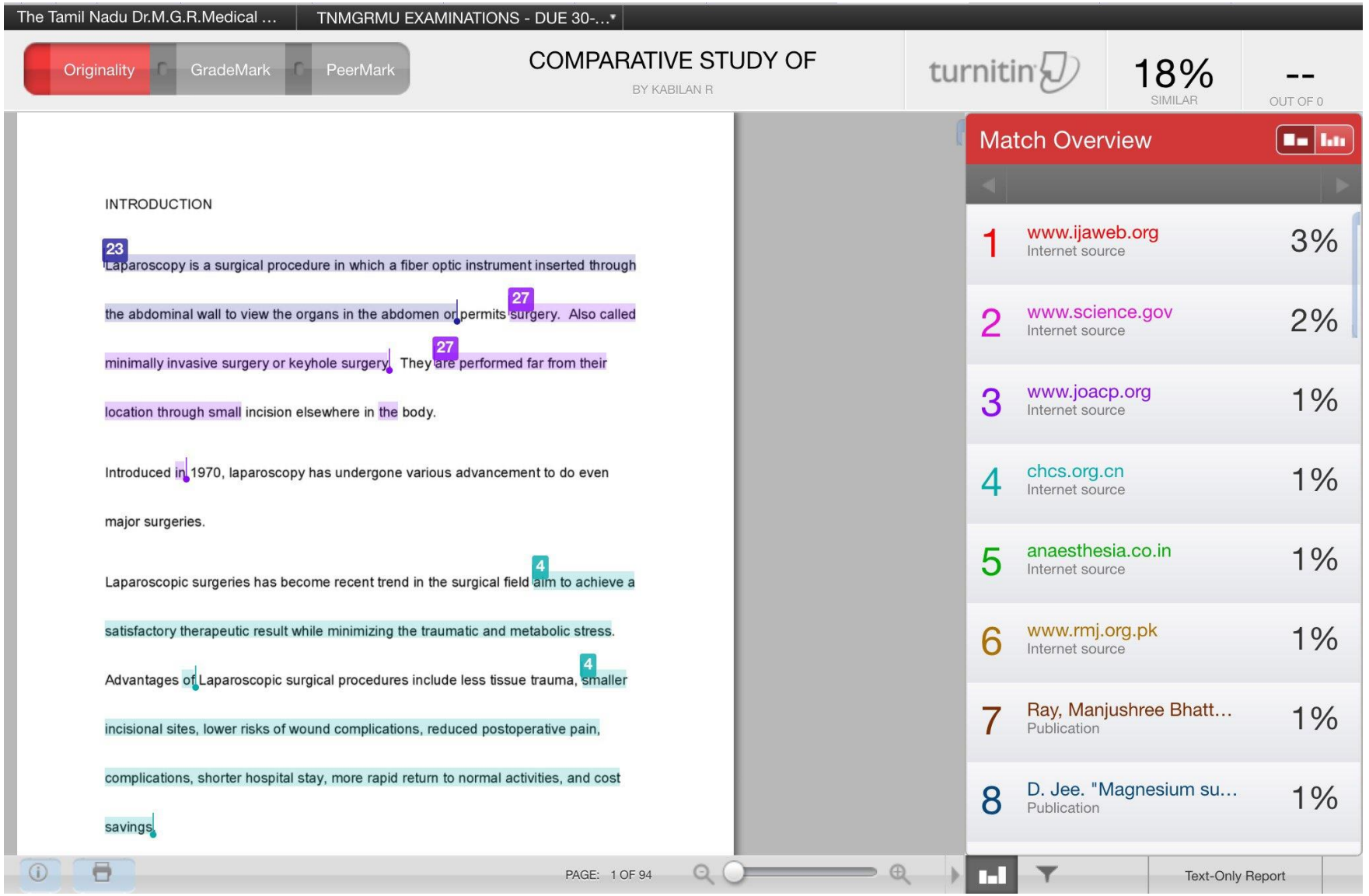
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INTRODUCTION
Laparoscopy is a surgical procedure in which a fiber optic instrument inserted through the abdominal wall to view the organs in the abdomen or permits surgery. Also called minimally invasive surgery or keyhole surgery. They are performed far from their location through small incision elsewhere in the body.
Introduced in 1970, laparoscopy has undergone various advancement to do even major surgeries.
Laparoscopic surgeries has become recent trend in the surgical field aim to achieve a satisfactory therapeutic result while minimizing the traumatic and metabolic stress.
Advantages of Laparoscopic surgical procedures include less tissue trauma, smaller incisional sites, lower risks of wound complications, reduced postoperative pain, complications, shorter hospital stay, more rapid return to normal activities, and cost savings.
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INTRODUCTION

Laparoscopy is a surgical procedure in which a fiber optic instrument inserted through the abdominal wall to view the organs in the abdomen or permits surgery. Also called minimally invasive surgery or keyhole surgery. They are performed far from their location through small incision elsewhere in the body.

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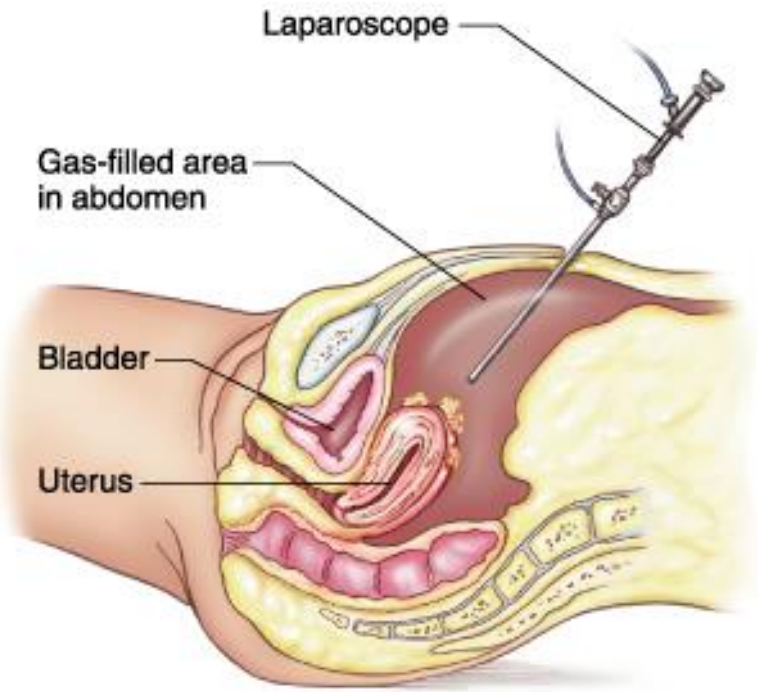
Laparoscopic surgeries has become recent trend in the surgical field aim to achieve a satisfactory therapeutic result while minimizing the traumatic and metabolic stress. Advantages of Laparoscopic surgical procedures include less tissue trauma, smaller incisional sites, lower risks of wound complications, reduced postoperative pain, complications, shorter hospital stay, more rapid return to normal activities, and cost savings.

Laparoscopy requeires the establishment of pnemoperitoneum in order to provoide adequate surgical exposure and maintain operative freedom. This insufflation of carbon dioxide can lead to various physiological changes. An emerging body of data adresses the hemodynamic, respiratory, immunological and stress response related to the pnemoperitoneum.


Laparoscope
Gas-filled area
in abdomen
Bladder
Uterus

The physiologic changes associated with laparoscopy include those associated with tilting the patient to facilitate instrumentation, surgical exposure, the pressure effects of instilled gas into a closed cavity, and the systemic effects of the gas, almost universally, CO_2 instilled (absorbed or embolized).

Cardiovascular changes include increase in mean arterial pressure with no significant change in heart rate, decrease in cardiac output (10% to 30%), and increase in systemic vascular resistance. These vasopressor responses are due to hypercarbia-induced release of catecholamines, vasopressin, or both.

The pneumoperitoneum and its consequent hemodynamic changes can be attenuated by pharmacological agents such as nitroglycerine, β blocker, and opioids, to provide hemodynamic stability during pneumoperitoneum, but they have their own disadvantages.

Clonidine, a selective α-2 adrenergic receptor agonist, has shown promising results for attenuation of hemodynamic response associated with laparoscopic surgery. Clonidine causes a fall in the heart rate and blood pressure along with decreased systemic vascular resistance and cardiac output.

Magnesium blocks release of catecholamines from both adrenergic nerve terminals and adrenal gland. Magnesium also produces vasodilation by

acting directly on blood vessels. In high doses, it attenuates vasopressin-mediated vasoconstriction.

This study was designed in a prospective, randomized, double-blinded fashion to compare the efficacy of intravenously administered clonidine and magnesium sulfate on hemodynamic stress response during laparoscopic surgeries.

AIM OF THE STUDY

The aim of this study was to compare the intravenously administered clonidine and magnesium sulfate on hemodynamic responses during laparoscopic surgeries in terms of

1. Heart rate
2. Systolic blood pressure
3. Diastolic blood pressure
4. Mean arterial pressure
5. Level of sedation on recovery
6. Adverse effects

PHYSIOLOGICAL EFFECTS IN LAPAROSCOPIC SURGERIES

The physiologic effects of carbon dioxide insufflation into an endocavity combined with various positioning causes a major impact on cardiopulmonary function that complicates anesthetic management.

In earlier days higher intra-abdominal pressure (>20 mm Hg) were used and they observed many serious complications. After 1990 pneumoperitoneum using low intra-abdominal pressure (<15 mm Hg) was used in modern anesthesia techniques.

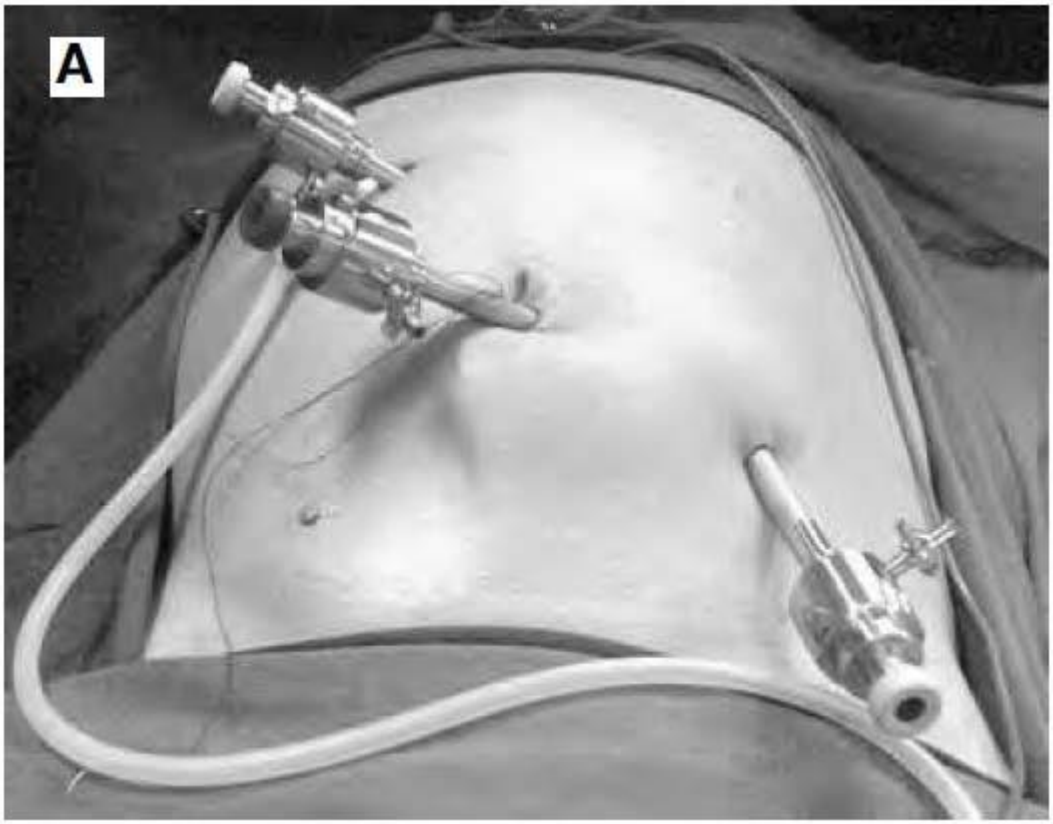
PNEUMOPERITONEUM

Hemodynamic Problems during Laparoscopy

Hemodynamic changes observed during laparoscopy result from the combined effects of pneumoperitoneum, patient position, anesthesia, and hypercapnia from the absorbed CO_2. In addition to these pathophysiologic changes, reflex increases of vagal tone and arrhythmias can also develop.

Hemodynamic Repercussions of Pneumoperitoneum in Healthy Patients

Normal intra-abdominal pressure ranges from zero to 5 mm Hg, but for better visualization of the operating field intra-abdominal pressure should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be maintained around 15 to 20 mm Hg. Increases in intra-abdominal pressure above 10 mm Hg are clinically significant, and above 15 mm Hg can result in an abdominal compartment syndrome, which affects multiple organ systems. The cardiovascular manifestations understood via the following simple relationship, which expresses the determinants of blood pressure:

Mean Arterial Pressure (MAP) = Cardiac Output (CO) x Systemic Vascular Resistance (SVR)

Peritoneal insufflation to intra-abdominal pressure higher than 10 mm Hg induces significant alterations of hemodynamics. These disturbances characterized by decreases in cardiac output, increased arterial pressures, and elevation of systemic and pulmonary vascular resistance. Heart rates remain unchanged or increased only slightly. The decrease in cardiac output is proportional to the increase in intra-abdominal pressure. Cardiac output also been reported to be increased or unchanged during pneumoperitoneum. These discrepancies caused by differences in rates of CO_2 insufflation, intra-abdominal pressure, steepness of patient tilt, time intervals between insufflation and collection of data, techniques used to assess hemodynamics, and anesthetic techniques. However, the cardiac output reduced to 10% to 30% during peritoneal insufflation whether the patient placed in the head-down or head-up position. Cardiac output, which

decrease shortly after the beginning of the peritoneal insufflation, subsequently increase, probably because of surgical stress. Hemodynamic perturbations occur mainly at the beginning of peritoneal insufflation.

The increase in systemic vascular resistance mediated by mechanical and neurohumoral factors. The return of hemodynamic parameters to baseline values is gradual, taking several minutes, suggesting the involvement of neurohumoral factors like catecholamines, renin-angiotensin system and vasopressin released during pneumoperitoneum contribute to increasing the afterload ultimately leads to increased cardiac work load. Consequently, myocardial ischemia may result.

Initially, owing to autotransfusion of pooled blood from the splanchnic circulation, there is an increase in the circulating blood volume, resulting in an increase in venous return and cardiac output. However, further increases in the intra-abdominal pressure result in the compression of the inferior vena cava, reduction in venous return and subsequent decrease in cardiac output.

Further increase in intra-abdominal pressure decrease cardiac output with a subsequent fall in blood pressure, an effect more pronounced in patients who are hypovolemic or have cardiovascular disease.

Physiological effects of pneumoperitoneum

Cardiovascular	
IAP < 10 mm Hg	↑ VR ⟶ ↑ CO
IAP 10–20 mm Hg	↑ IAP ⟶ ↓ VR ⟶ ↓ CO
	↑ IAP ⟶ ↑ SVR
	BP = ↓ CO × ↑ ↑ SVR
	↔ ↑ BP
IAP > 20 mm Hg	↓ ↓ VR ⟶ ↓ ↓ ↓ CO
	↓ BP
Respiratory	
Lung volumes esp FRC	↓
Airway resistance	↑
Pulmonary compliance	↓
Airway pressure	↑
Risk of barotrauma	↑
V/Q mismatch	↑
Renal	
Renal function	↓
Gastrointestinal	
Risk of regurgitation	↑
Neurological	
ICP	↔ ↑
CPP	↔ ↓

IAP, intra-abdominal pressure; VR, venous return; CO, cardiac output; SVR, systemic vascular resistance; BP, blood pressure; FRC, functional resistance capacity; ICP, intracranial pressure; CPP, cerebral perfusion pressure.

Cardiac Arrhythmias during Laparoscopy

Reflex increases of vagal tone may result from sudden stretching of the peritoneum and during electrocoagulation. Bradycardia, cardiac arrhythmias, and asystole can develop. Vagal stimulation accentuated if the level of anesthesia is too superficial or if the patient is taking β-blocking drugs. These events are easily and quickly reversible. Treatment consists of interruption

of insufflation, atropine administration, and deepening of anesthesia after recovery of the heart rate.

Ventilatory and Respiratory Changes during Laparoscopy

Intraperitoneal insufflation of carbon dioxide, the currently routine technique to create pneumoperitoneum for laparoscopy, results in ventilatory and respiratory changes and cause four principal respiratory complications: CO_2 subcutaneous emphysema, pneumothorax, endobronchial intubation, and gas embolism.

Ventilatory Changes

Pneumoperitoneum decreases thoracopulmonary compliance by 30% to 50% in healthy and obese patients. Reduction in functional residual capacity and development of atelectasis due to elevation of the diaphragm and changes in the distribution of pulmonary ventilation and perfusion from increased airway pressure is expected.

However, increasing intra-abdominal pressure to 14 mm Hg with the patient in a 10 to 20 degree head-up or head-down position does not significantly modify either physiologic dead space or shunt in patients without cardiovascular problems.

Increase in the Partial Pressure of Arterial Carbon Dioxide

During uneventful CO_2 pneumoperitoneum, the $PaCO_2$ progressively increases to reach a plateau, after 15 to 30 minutes of the beginning of CO_2 insufflation, patients under controlled mechanical ventilation during surgeries in the Trendelenburg position or in the head-up position.

Any significant increase in $PaCO_2$ after this period requires a search for a cause independent or related to CO_2 insufflation, such as CO_2 subcutaneous emphysema. The increase in $PaCO_2$ depends on the intra-abdominal pressure.

CO_2 Subcutaneous Emphysema.

CO_2 subcutaneous emphysema can develop as a complication of accidental extra peritoneal insufflation, but also considered as an unavoidable side effect of certain laparoscopic surgical procedures that require intentional extra peritoneal insufflation, such as inguinal hernia repair, renal surgery, and pelvic lymphadenectomy.

During laparoscopic fundoplication for hiatal hernia repair, the opening of the peritoneum overlying the diaphragmatic hiatus allows passage of CO_2 under pressure through the mediastinum to the cervicocephalic region. In this case, interrupt the laparoscopy to allow CO_2 elimination and can be resumed after correction of hypercapnia using a lower insufflation pressure.

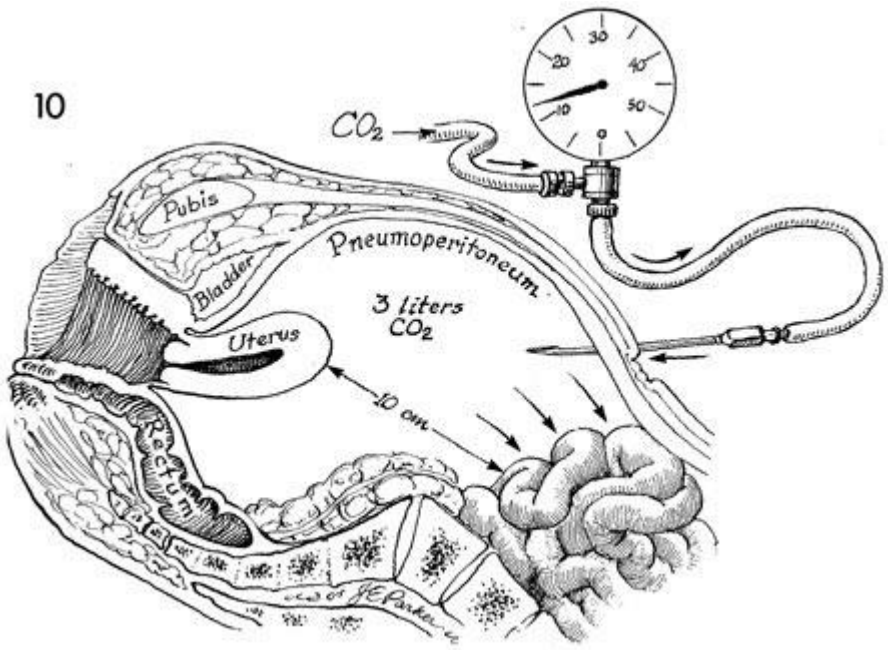
Pneumothorax, Pneumoperitoneum, Penuemopericardium

Movement of gas during the creation of a pneumoperitoneum produce pneumomediastinum, unilateral and bilateral pneumothoraces, and Pneumopericardium. Defects in the diaphragm or weak points in the aortic and esophageal hiatus may allow gas passage into the thorax. Pneumothoraces may also develop secondary to pleural tears during laparoscopic surgical procedures at the level of the gastroesophageal junction (e.g., fundoplication for hiatal hernia). Although opening of peritoneopleural ducts is associated with mainly right-sided pneumothoraces, the pneumothorax associated with fundoplication is more frequently in the left side of the chest.

When capnothorax develops during laparoscopy, treatment with positive end-expiratory pressure (PEEP) is an alternative to chest tube placement. In contrast, if the pneumothorax is secondary to rupture of preexisting bullae, PEEP must not applied and thoracocentesis is mandatory.

Endobronchial intubation

Cephalad displacement of the diaphragm during pneumoperitoneum results in cephalad movement of the carina, potentially leading to an endobronchial intubation. This complication results in a decrease in the


10
CO_2
30
20
40
10
50
0
Pubis
Bladder
Pneumoperitoneum
3 liters
CO_2
Uterus
10 cm
Rectum

oxygen saturation as measured by pulse oximetry (Spo2) associated with an increase in plateau airway pressure.

Gas (CO_2) Embolism

It is the rare, most feared and dangerous complication of laparoscopy. Intravascular injection of gas may follow direct needle or trocar placement into a vessel, or it may occur because of gas insufflation into an abdominal organ. This complication develops principally during the induction of pneumoperitoneum, particularly in patients with previous abdominal surgery. Gas embolism may also occur later during surgery.

Treatment: Immediate cessation of insufflation, stop nitrous oxide, release of the pneumoperitoneum, steep head-down, left lateral decubitus position, Hyperventilation, central venous or pulmonary artery catheter, Cardiopulmonary resuscitation, Cardiopulmonary bypass and Hyperbaric oxygen treatment.

Renal

Pneumoperitoneum at pressure above 10 mmHg during laparoscopic surgery produces transient oliguria, reduced glomerular filtration rate and reduced renal blood flow. Factors that may affect renal function during pneumoperitoneum include direct compression of the renal parenchyma and renal vein, increased resistance in the renal vasculature, and release of

vasoconstrictors, such as vasopressin, angiotensin II, catecholamines, and endothelin (ET)-1.

Risk of Aspiration of Gastric Contents

Patients undergoing laparoscopy are considered to be at risk for acid aspiration syndrome. The increased intra-abdominal pressure results in changes of the lower esophageal sphincter that allow maintenance of the pressure gradient across the gastroesophageal junction and that may therefore reduce the risk of regurgitation. Furthermore, the head-down position prevents any aspiration.

Neurological

Pneumoperitoneum during laparoscopic surgery also has the potential to increase cerebral blood flow (CBF), intracranial pressure, and intraocular pressure due to the increased $PaCO_2$ caused by absorption of CO_2 from the peritoneal cavity. The creation of pneumoperitoneum during laparoscopic surgery elevates intra cranial pressure because increased the abdominal pressure obstructs venous return from the lumbar venous plexus. Pneumoperitoneum also increases cerebral blood flow due to an increase in $PaCO_2$ and an increase in catecholamine release independent of $PaCO_2$.

Metabolic Response

Metabolic acidosis from CO_2 absorption is the primary change with laparoscopy. Systemic CO_2 absorption and its metabolic consequences differ depending on the patient's respiratory status, since the lung eliminates absorbed CO_2 buffered by the blood.

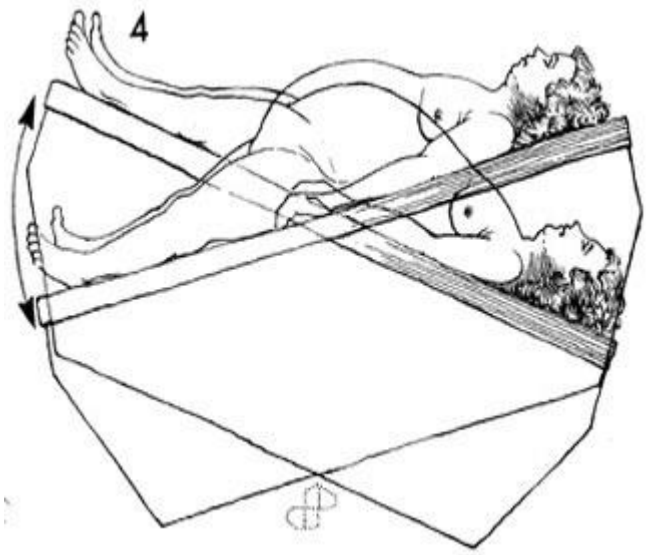
Physiological effects of Positioning

During laparoscopy, the patient is placed in a variety of positions in order to maximize the surgical visual field and facilitate instrumentation. The head-down (Trendelenburg) position is commonly used in appendicectomy, gynecological operations, prostatectomy, and colorectal procedures. The steep head-down tilt is frequently used for laparoscopic gynecologic and urologic procedures. The head-up position (reverse Trendelenburg) used for cholecystectomy, invasive urological surgery and gastric bypass surgery. The tilting of a patient during laparoscopy results in important physiologic responses and potential serious complications.

In normotensive subjects, the head-down position results in an increase in central venous pressure and cardiac output. The baroreceptor reflex response to increased hydrostatic pressure consists of systemic vasodilation and bradycardia.

However, central blood volume and pressure changes are greater in patients with coronary artery disease, particularly in those with poor ventricular function, leading to potentially deleterious increased myocardial oxygen demand.

The Trendelenburg position may also affect the cerebral circulation, particularly in case of low intracranial compliance and result in elevation of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the intraocular venous pressure. Although the intravascular pressure increases in the upper torso, the head-down position decreases transmural pressures in the pelvic viscera, reducing blood loss but increasing the risk of gas embolism.

With the head-up position, a decrease in cardiac output and mean arterial pressure results from the reduction in venous return. This decrease in cardiac output compounds the hemodynamic changes induced by pneumoperitoneum. The steeper the tilt, the greater the fall in cardiac output.

Venous stasis in the legs occur during the head-up position and it is aggravated by the lithotomy position. As pneumoperitoneum further increases blood pooling in the legs, any additional factor contributing to circulatory dysfunction should be avoided. The legs must be freely supported and not tightly strapped, and there should be no pressure on the popliteal space.

Physiological effects of positioning

	Trendelenburg	*Reverse Trendelenburg*
Cardiovascular		
VR	↑	↓
CO	↑	↓
BP	↔	↓
Respiratory		
Lung volumes	↓	↔
V/Q mismatch	↑	↔
Atelectasis	↑	↔

Physiological effects of gas absorption

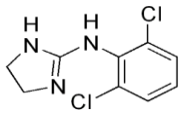
Carbon dioxide is the most frequently used gas for insufflation of the abdomen, as it is colourless, highly soluble, non-toxic, non-flammable and has the greatest margin of safety. It is absorbed readily from the peritoneum, causing an increase in PaCO2. This has direct, as well as indirect (by raising catecholamine levels), effects on the cardiovascular system. Increased cardiac contractility, tachycardia, and reduction in diastolic filling causes decreased myocardial oxygen supply to demand ratio and greater risk of myocardial ischemia.

PHARMACOLOGY OF CLONIDINE

Clonidine, an Imidazoline derivative, synthesized in the early 1960s and produces vasoconstriction, mediated by α_{2-} receptors.

CHEMISTRY

$C_9H_9N_3Cl_2.HCl$



N-(2, 6-Dichlorophenyl)-4,5-dihydro-1H-imidazol-2-amine

PHARMACOLOGY

Mechanism of action

Clonidine is a partial agonist at α-adrenoceptors both within the central nervous system and in the periphery. It is more specific for α_2-adrenoceptors than for α_1-adrenoceptors with a ratio of affinities at these sites of approximately 220:1. Within the central nervous system, α_2-adrenoceptors are located both presynaptically on terminals of neurons and postsynaptically on nor-adrenergic neurons. It is likely that clonidine acts at all central α_2-receptors, stimulation of which is associated with decreased neuronal excitability and inhibition of membrane – bound adenylate cyclase.

High concentrations of clonidine may stimulate central α_1-adrenoceptors enhancing neuronal excitability. Stimulation of peripheral

presynaptic α_2-adrenoceptors on postganglionic noradrenergic or cholinergic neurons by clonidine contributes to reduced saliva flow, reduced intestinal motor activity and gastric acid secretion, and bradycardia.

Endocrine and metabolic effects are apparently mediated by α_2-adrenoceptor. Clonidine inhibits insulin secretion from the pancreatic β cell possibly via a α_{2A} receptor. The pressor effect of high doses of clonidine is due to peripheral vasoconstriction mediated by stimulation of postsynaptic α1 and α_2-adrenoceptors on vascular smooth muscle.

The Imidazoline receptor

Imidazoline receptors include three subtypes (I_1, I_2 and I_3), and are widely distributed in the body, including the central nervous system. Clonidine, as an imidazoline binds to these imidazoline receptors, in addition to its well-described binding to α_2-receptors. Data suggest that imidazoline receptors make only a minor contribution to the ability of clonidine to inhibit norepinephrine release, while the main contribution to the action of clonidine is via α2-receptors.

PHARMACOKINETICS

Clonidine is well absorbed after oral administration, and its bioavailability is nearly 100%, with peak concentrations in plasma and the maximal hypotensive effect observed 1 to 3 hours after an oral dose.

A transdermal delivery patch, an alternative to oral therapy permits continuous administration of clonidine. The drug released at an approximately constant rate for a week, requiring 3 or 4 days to reach steady-state concentrations in plasma.

When the patch is removed, plasma concentration remain stable for about 8 hours and then decline gradually over a period of several days, this decrease in concentration is associated with a rise in blood pressure. Clonidine crosses the placenta and distributes into breast milk.

Distribution t ½	: 11 ± 9 minutes
Elimination t ½	: 9 ± 2 hours
Volume of distribution	: 2.1 ± 0.4 L/kg
Plasma protein binding	: 20-40 % in vitro
Excretion	: 70% of the dose, mainly in the form of unchanged parent drug (40-60%) in urine.

PHARMACOLOGICAL ACTIONS

Cardiovascular Actions

The major pharmacological effects of clonidine involve changes in blood pressure and heart rate, although the drug has a variety of other

important actions. Intravenous infusions of clonidine cause an acute rise in blood pressure, apparently because of the activation of postsynaptic α2-receptors in vascular smooth muscle. Acute oral or intravenous administration of clonidine causes a dose-dependent fall in blood pressure and heart rate in both the supine and erect positions, with the orthostatic response being more prominent.

Respiration

α_2 agonists have minimal depressant effect on ventilation and do not potentiate ventilatory depressant effects of opioids.

ADVERSE EFFECTS

1. Drowsiness, dryness of mouth, dryness of nasal mucosa and eyes. Weakness, fatigue, headache, and withdrawal syndrome.
2. **Cardiovascular:** Bradycardia, hypotension, syncope, congestive heart failure, sinus node arrest, junctional bradycardia, high degree atrio ventricular block, and arrhythmias.
3. **Central Nervous system:** Nervousness, agitation, mental depression, insomnia, vivid dreams or nightmares, anxiety, visual and auditory hallucinations.
4. **Skin rash:** Angioneurotic edema, pruritus, urticaria, and alopecia.
5. **Gastro intestinal tract:** Nausea and vomiting, anorexia.

6. **Genitourinary:** Decreased sexual activity, impotence, and loss of libido.
7. **Hematological :** Thrombocytopenia
8. **Metabolic :** Weight gain and gynacomastia

PRECAUTIONS

1. Clonidine to be used with caution in patients with cerebrovascular disease, ischemic heart disease including myocardial infarction, renal impairment, occlusive peripheral vascular disorders such as Raynaud's disease, or those with a history of depression.
2. Possible transient pressor effect especially in patients already receiving other antihypertensive.
3. Rebound hypertension, beta blockers may exacerbate the rebound hypertension
4. Symptoms of increased catecholamine release such as agitation, sweating, tachycardia, headache, and nausea may occur.
5. Clonidine hydrochloride has been associated with acute attacks of porphyria and considered unsafe in porphyric patients.

Contraindications

Sino-atrial node disease (Sick sinus syndrome)

Atrioventricular node disease.

DRUG INTERACTIONS

Potentially Hazardous Interactions

1. Central nervous depressants:

   Hypnosedatives, antihistamines and alcohol may cause excessive drowsiness in patients treated with clonidine.

2. β-Adrenoceptor antagonists:

   In patients receiving non-cardioselective β-blockers, the rebound rise of blood pressure following clonidine-withdrawal may be more marked due to unopposed α-adrenoceptor mediated vasoconstriction.

3. Antipsychotics:

   Acute severe hypotension observed following concomitant administration of clonidine and chlorpromazine or haloperidol.

4. Tricyclic and other antidepressants:

   Attenuate of the hypotensive effect of clonidine by desipramine. Other studies have failed to show any significant interaction between clonidine and amitriptyline, imipramine, or mianserin.

5. α-Adrenergic antagonists:

   The effects of clonidine may be antagonized by centrally acting α-blockers such as phentolamine, tolazoline and phenoxybenzamine.

Potentially Useful Interactions

1. Diuretics and/or vasodilators used in combination with clonidine to enhance its hypotensive effects. Diuretics will counteract any tendency to fluid retention.
2. Clonidine may substitute for β-blockers in opposing the reflex cardiac stimulation following administration of vasodilators such as hydralazine or nifedipine.

ANAESTHETIC USES

1. **Premedication:** Acts on locus ceruleus produces sedation. In addition, got an anaesthesia sparing effect.
2. **Control of hemodynamics:** It attenuates the haemodynamic response during laryngoscopy, intubation, and laparoscopic surgeries
3. **Epidural:** It acts as a sole agent or in combination with opioids or local anaesthetics to provide excellent analgesia
4. **In Labour analgesia**
5. **Spinal:** With local anaesthetics clonidine improve the quality and duration of the block, minimize the tourniquet pain during lower limb surgery, and prevents shivering.
6. **Caudal:** With local anaesthetics increases the duration of anaesthesia and analgesia 2 or 3 times without hemodynamic side effects.

7. **Peripheral nerve blocks:** Prolongs the duration of anaesthesia and analgesia with local anaesthetics in a dose of 75-150µg.
8. **Bier's Block**
9. **Intra articular analgesia**

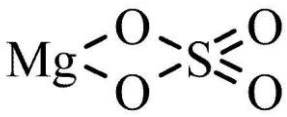
CLONIDINE DOSAGE FORMS

Oral Tablets	Clonidine tablet	0.1, 0.2 and 0.3 mg
Transdermal patches	Clonidine – TTS	0.1, 0.2 and 0.3 G, 3mg/24 Hrs.
Combination Tablets	Clonidine and chlorthalidone	0.1 mg clonidine/15 mg chlorthalidone 0.2 mg clonidine/15 mg chlorthalidone 0.3 Mg clonidine /15 mg chlorthalidone
Injection	Cloneon, duration	500 mcg/ml, 100 mcg/ml as ml 10 ml vials

Overdosage and Treatment

There is no specific antidote for clonidine over dosage. Supportive measures like atropine, ephedrine and intravenous fluids is enough. For hypertensive crisis intravenous furosemide, diazoxide, phentolamine used. Yohimbine partially reverses the analgesia and sedation but not the BP and heart rate changes produced by the epidural clonidine.

Pharmacology of Magnesium



Magnesium (Mg++) is an important cofactor for enzymatic reactions and plays an important role in neurochemical transmission and muscular excitability.

As a nutritional adjunct in hyperalimentation, the precise mechanism of action for magnesium is uncertain. Early symptoms of hypomagnesemia (less than 1.5 mEq/L) may develop within 3 to 4 days or weeks. Predominant effects are neurological, e.g., muscle irritability, clonic twitching and tremors. Hypocalcemia and hypokalemia often follow low serum levels of magnesium. Large stores of magnesium present are intracellularly and in the bones of adults, these stores often mobilized sufficiently to maintain plasma levels.

Mechanism of Action

1. A competitive antagonism on hippocampal presynaptic calcium channels that regulate neurotransmitter release in the central nervous system.
2. Attenuation of catecholamine release from the adrenal medulla and calcium antagonistic effects on vascular smooth muscle cells may contribute to the anaesthetic effects of magnesium.

3. Neuromuscular blockade: the inhibition of calcium-mediated release of acetylcholine from the presynaptic nerve terminal at the neuromuscular junction plays an important role.
4. **Anticonvulsive**: Blocks neuromuscular transmission and decreases the amount of acetylcholine liberated at the end plate by the motor nerve impulse.
5. **Antinociceptive effects:** By Inhibition of calcium influx and antagonism of NMDA receptors.
6. **Central sensitization:** Attenuate or even prevent central sensitization after peripheral tissue injury or inflammation because of inhibition of dorsal horn NMDA receptors.
7. **Central nervous system**: Depressant effect

Pharmacokinetics

Normal plasma magnesium levels range from 1.5 to 2.5 or 3.0 mEq/L. As plasma magnesium rises above 4 mEq/L, the deep tendon reflexes are first decreased and then disappear as the plasma level approaches 10 mEq/L. At this level, respiratory paralysis may occur. Heart block also may occur at this or lower plasma levels of magnesium.

With intravenous administration, the onset of anticonvulsant action is immediate and lasts about 30 minutes. Following intramuscular

administration, the onset of action occurs in about 1 hour and persists for 3 to 4 hours. Effective anticonvulsant serum levels range from 2.5 or 3.0 to 7.5 mEq/L. Magnesium excreted solely by the kidney at a rate proportional to the plasma concentration and glomerular filtration.

Pharmacodynamics

Indications and Clinical Uses:

1. **Deficiency**: For replacement therapy in magnesium deficiency, especially in acute hypomagnesemia.
2. **Total parenteral nutrition:** magnesium sulfate may be added to the nutrient admixture to correct and prevent hypomagnesemia.
3. **Anticonvulsant:** Magnesium sulfate injection is given as a parenteral anticonvulsant for the prevention and control of seizures in pregnancy.
4. **Antihypertensive:** Magnesium sulfate injection used to control hypertension, encephalopathy, and convulsions associated with acute nephritis in children.
5. **Laparoscopic surgeries:** Attenuates the stress response by blocking the catecholamine release

Contra-Indications:

Intravenous magnesium given to mothers with toxemia of pregnancy during the 2 hours preceding delivery.

Adverse Reactions:

1. **Magnesium intoxication**: flushing, sweating, hypotension, depressed reflexes, flaccid paralysis, hypothermia, circulatory collapse, cardiac and central nervous system depression proceeding to respiratory paralysis.
2. **Hypocalcemia:** with signs of tetany secondary to magnesium sulfate therapy.
3. **Central nervous system:** Drowsiness and loss of muscle tone

Precautions:

Because magnesium excreted from the body exclusively by the kidneys, the drug should be used with caution in patients with renal impairment.

Monitoring serum magnesium levels and the patient's clinical status is essential to avoid the consequences of over dosage in toxemia.

Clinical indications of a safe dosage regimen include the presence of the patellar reflex (knee jerk), absence of respiratory depression (approximately 16 breaths or more/minute) and urine output at the level of 100 mL every 4 hours.

Serum magnesium levels usually sufficient to control convulsions range from 3 to 6 mg/100 mL (2.5 to 5.0 mEq/L).

Drug Interactions:

CNS Depressants:

When barbiturates, opiates, general anesthetics, or other CNS depressants administered concomitantly with magnesium sulfate, dosage of these agents carefully adjusted because of the additive central depressant effects.

Neuromuscular Blocking Agents:

Excessive neuromuscular blockade has occurred in patients receiving parenteral magnesium sulfate and a neuromuscular blocking agent.

Cardiac Glycosides:

Magnesium salts administered with extreme caution in digitalized patients.

Symptoms and Treatment of Overdose:

Disappearance of the patellar reflex is a useful clinical sign to detect the onset of magnesium intoxication.

In adults, intravenous administration of 5 to 10 mEq of 10% calcium gluconate will usually reverse respiratory depression or heart block due to magnesium intoxication. In extreme cases, peritoneal dialysis or hemodialysis may be required.

Hypermagnesemia in the newborn may require resuscitation and assisted ventilation via endotracheal intubation or intermittent positive pressure ventilation, as well as intravenous calcium.

Table 1: Dosage and Administration

Dosing Magnesium Sulfate, Adults	
Preeclampsia or eclampsia	4–6 g IV loading dose over 15–20 min (5 min in severe cases), followed by 1–2 g IV continuous infusion or 4–5 g IM in each buttock every 4 h
Torsades de Pointes arrhythmia	Pulseless: 1–2 g IV over 5–20 min With pulse: 1–2 g IV over 5–60 min
Asthma	Life-threatening or severe exacerbation (unlabeled use): 2 g IV over 30–60 min
Severe deficiency	1–2 g/h IV for 3–6 h, followed by 0.5–1 g/h IV as needed
Slow administration of IV magnesium sulfate is preferable in stable patients. Renal impairment requires close monitoring for signs of hypermagnesemia. **IM = intramuscular; IV = intravenous.**	

Clinical Uses:

Attenuation of Laparoscopic stress response

Antihypertise

Eclampsia:

In severe pre-eclampsia or eclampsia, the total initial dose is 10 to 14grams of magnesium sulfate. Intravenous dose of 4 to 5 g in 250 mL of 5% Dextrose Injection or 0.9% Sodium Chloride Injection may be infused.

Nephritic Seizures:

In children with nephritic seizures, the 50% concentration diluted to a 20% solution for intramuscular injection. The dose for children is 20 to 40 mg (0.1 to 0.2 mL of a 20% solution)/kg of body weight, administered intramuscular as needed, to control seizures.

REVIEW OF LITERATURE

1. R.Uma et al[30] did a randomized placebo controlled study to assess the effect of intravenous clonidine on intraoperative hemodynamics in 40 patients who underwent elective laparoscopic cholecystectomy. Patients were randomized into 2 groups. Group C received intravenous clonidine at a dose of 3 µg/kg over 15 minutes prior to induction and Group P received NS (Normal Saline). Pulse rate and mean arterial pressure recorded prior to induction, 2 minutes after intubation, before pneumoperitoneum, 10 and 20 minutes after pneumoperitoneum and 10 minutes after extubation. They concluded that patients in Group C maintained greater intraoperative hemodynamic stability and there was significant decrease in pulse rate and mean arterial pressure in the clonidine group during pemoperitoneum and after extubation.

   (J.Pharm Biomed Sci.2013, Februalry; 27(27): 451-455)

2. Mohua Sengupta et al[32] designed a randomized double blind prospective trail to to evaluate the efficacy of clonidine in achieving haemodynamic stability in patients undergoing laparoscopic cholecystectomy. Sixty patients, of both sex (31-60 yrs of age) undergoing elective laparoscopic cholecystectomy were randomly allocated equally in one of the two parallel groups: C and P. Group C

received clonidine 1.5 μg /kg intravenously over a period of 15 minutes before induction followed by 1 μg/kg /hr by continuous intravenous infusion. Group P received isotonic saline (0.9%) in the same volume. Mean arterial pressure and heart rate in Group C was significantly less after intubation and throughout the period of pneumoperitonium. No significant difference in the parameters of recovery observed between the two groups. They concluded that clonidine improves intra and post- operative haemodynamic stability during laparoscopic surgery without prolonging recovery.

(International Journal of Pharmaceutical, Chemical and Biological Sciences 2013, 3(3), 610-614)

3. Sudheer Rao et al[31] have conducted a prospective, comparative, 2-Arm (Group), double-blind controlled study in 60 ASA grades I and II adult patients of either sex aged 20-60 years, scheduled to undergo laparoscopic cholecystectomy. The subjects were assigned to one of the two groups by closed envelope method, namely Group C (clonidine 3 μg/kg in 20 ml), and Group P (placebo - 20 ml normal saline). Loading dose of test drug diluted in 20 ml of normal saline or placebo, 20 ml of normal saline were administered intravenously. Thirty minutes after the end of the infusion of the test drug, anaesthesia was induced and intubated. Demographic profile of 60 patients were

compared between the two groups of patients, and no significant difference found. Mean heart rate varied from 71.91 ± 4.95 to 99.88 ± 2.83 beats per minute in Group P. In Group C, it varied from 63.78 ± 1.07 to 86.38 ± 6.28 beats per minute. Similarly, rise in mean arterial pressure (106.85 ± 8.36 vs. 86.00 ± 0.57 mm Hg) was more in Group P 15 min following pneumoperitoneum and after intubation (109.26 ± 10.93 vs. 76.84 ± 4.32). Incidence of intraoperative hypertension was 34.3% in Group P (11 patients) that required treatment with intravenous infusion of 0.5 μg/kg/min injection nitroglycerine. They concluded that Clonidine at a dose of 3 μg/kg administered intravenously before peritoneal insufflation with carbon dioxide attenuated the haemodynamic changes by reducing hormonal stress response and plasma cortisol concentration.

(Indian Journal of Anaesthesia January-February 2015)

4. Jee D et al[35] investigated whether intravenous magnesium sulphate attenuates the haemodynamic stress responses to pneumoperitoneum by changing neurohumoral responses during laparoscopic cholecystectomy. Thirty-two patients undergoing laparoscopic cholecystectomy randomly assigned to two groups; the control group was given saline, and a magnesium group received magnesium sulphate 50 mg/kg immediately before pneumoperitoneum. Arterial

pressure, heart rate, serum magnesium, plasma renin activity (PRA), and catecholamine, cortisol, and vasopressin levels measured. Systolic and diastolic blood pressures were greater in the control group (P,0.05) than in the magnesium group at 10, 20, and 30 min post-pneumoperitoneum. Norepinephrine or epinephrine levels were higher in the control group than in the magnesium group. In the control group, vasopressin levels were higher compared with the magnesium group. There were no significant differences between the groups in plasma renin activity and cortisol levels. They concluded that intravenous magnesium sulphate before pneumoperitoneum attenuates arterial pressure increases during laparoscopic cholecystectomy

(British Journal of Anaesthesia 2009; 103)

5. Telci L et al[38] conducted a randomized, placebo-controlled, double-blind study to assess the effect of peroperatively administered intravenous magnesium sulphate on anaesthetic and analgesic requirements during total intravenous anaesthesia. Eighty-one patients (36 women, 45 men) undergoing elective spinal surgery were included in one of two parallel groups. The magnesium group received magnesium sulphate 30 mg/kg as a bolus before induction of anaesthesia and 10 mg/kg/hr by continuous intravenous infusion during the operation period. The same volume of isotonic saline was

administered to the control group. Anaesthesia was maintained with propofol (administered according to the bispectral index) and remifentanil (adjusted according to heart rate and arterial blood pressure) infusions. A significant reduction in hourly propofol consumption observed with magnesium administration. The magnesium group required significantly less remifentanil (P<0.001) and vecuronium (P<0.001). No side effects observed with magnesium administration. They concluded that the administration of magnesium led to a significant reduction in the requirements for anaesthetic drugs during total intravenous anaesthesia with propofol, remifentanil and vecuronium.

(British Journal of Anaesthesia 2002 October)

6. Nand Kishore Kalra et al[29] conducted a randomized, double blinded, placebo controlled study to compare the effect of clonidine and magnesium sulfate in 120 patients undergoing elective laparoscopic cholecystectomy. They were randomized into 4 groups of 30 each. Group K patients received 50 ml normal saline over a period of 15 min after induction and before pneumoperitoneum, group M patients received 50 mg/kg of magnesium sulfate in normal saline (total volume 50 ml) over same time duration. Group C1 patients received 1 µg/kg clonidine and group C2 1.5µg/kg clonidine respectively in normal

saline (total volume 50 ml). Systolic blood pressure, Diastolic blood pressure and heart rate were recorded before induction (baseline value), at the end of infusions and every 5 min after pneumoperitoneum. They concluded that the administration of magnesium sulfate 50mg/kg produces hemodynamic stability comparable to clonidine 1 µg/kg and clonidine in dose of 1.5 µg/kg blunts the hemodynamic response to pneumoperitoneum effectively.

(Journal of Anaesthesiology Clinical Pharmacology;July-September 2011;27; 3)

7. Manjaree Mishra et al[33] conducted a study with Sixty patients aged 20-65 years of ASA grade I and II undergoing laparoscopic cholecystectomy were randomized into 3 groups and given an infusion of clonidine (group I), nitroglycerin (group II), or normal saline solution (group III) after induction and before creation of pneumoperitoneum. Heart rate, mean arterial blood pressure, end-tidal carbon dioxide, and intraocular pressure were monitored. The mean and standard deviation of the parameters studied during the observation period were calculated for the 3 treatment groups and compared. They concluded that the statistically significant differences in heart rate were observed among the various groups, whereas comparisons of mean arterial pressure, intraocular pressure, and end-tidal carbon dioxide

showed statistically significant differences only between clonidine and placebo and between nitroglycerine and placebo.

(Journal of the Society of Laparoendoscopic Surgeons. 2014 Jul-Sep)

8. Ray M et al[34] were conducted a randomised, placebo-controlled, double-blind study designed to assess the effect of intravenous clonidine and magnesium sulphate on intraoperative haemodynamics, anaesthetic consumption and postoperative recovery. Seventy-five patients undergoing elective upper limb orthopaedic surgery were randomised into three groups. Group C received clonidine 3 μg/kg as a bolus before induction and 1μg/kg/hour by infusion intraopertively. Group M received magnesium sulphate 30 mg/kg as a bolus before induction and 10 mg/kg/hour by infusion. Group P received same volume of isotonic saline. Induction time, recovery time, and consumption of propofol as well as fentanyl citrate recorded. Induction of anaesthesia was rapid with both clonidine and magnesium sulphate. Requirements of propofol and fentanyl were significantly less in Group C and Group M ($P < 0.001$). Postoperative recovery was slower in Group M compared with other two groups ($P < 0.001$). They concluded that perioperative use of both clonidine and magnesium

sulphate significantly reduced the consumption of propofol and fentanyl citrate. Magnesium sulphate caused a delayed recovery.

(Indian J Anaesth 2010 March- April)

9. Altan A, et al[36] have conducted a placebo-controlled, double-blind study to assess the effects of magnesium sulphate and clonidine on peroperative haemodynamics, propofol consumption and postoperative recovery. Sixty ASA I-II patients undergoing spinal surgery randomized into three groups. Group M received magnesium sulphate 30 mg/kg as a bolus before induction and 10 mg/kg/h by infusion. Group CL received clonidine 3 µg/kg as a bolus before induction and 2 µg/kg/h by infusion during the operation period. The control group received isotonic solution (group CT). They observed that There was no statistical difference in heart rate and arterial blood pressure between the groups. The time for BIS to reach 60 was significantly shorter in group M and group CL ($P<0.0001$) but postoperative recovery was slower with magnesium sulphate compared with the clonidine and control groups ($P<0.0001$). There was no statistical difference in heart rate and arterial blood pressure between the groups. Propofol requirements for induction and maintenance of anaesthesia were significantly lower with magnesium and clonidine ($P<0.0001$).

They concluded that Clonidine caused bradycardia and hypotension and magnesium sulphate caused delayed recovery, but used as adjuvant with careful management.

(British Journal of Anesthesia 2005 April)

10. Deepshikha C Tripathi et al[39] conducted a prospective, randomized, double-blind controlled to compare the effect of two different doses of intravenous clonidine premedication on hemodynamic stress response during laparoscopic cholecystectomy. Patients were randomized to one of the three groups (n= 30). Group I received 100 ml of normal saline, while groups II and III received 1 μg/ kg and 2 μg/ kg of clonidine respectively, intravenously, in 100 ml of normal saline. Hemodynamic variables (heart rate, systolic, diastolic, mean arterial pressure), SpO2, and sedation score were recorded at specific timings. Mean arterial pressure above 20% from baseline was considered significant and treated with nitroglycerine. In group I, there was a significant increase in hemodynamic variables during intubation, pneumoperitoneum and extubation ($P<0.001$). Clonidine given 1 μg/kg intravenous attenuated hemodynamic stress response to pneumoperitoneum ($P<0.05$). They concluded that the Clonidine, 2 μg/ kg intravenously, 30 min before induction is safe and effective in preventing the hemodynamic stress response during laparoscopic cholecystectomy.

(Journal of Anaesth Clin Pharmacol 2011;27:475-80)

11. Sunil Chiruvella et al[40] conducted a study to compared the effect of Clonidine versus Dexmedetomidine for Hemodynamic Stability during Laparoscopic Cholecystectomy. Group-C (clonidine group) received clonidine 1 μg/kg in normal saline and Group D (dexmedetomidine group) received dexmedetomidine 1 μg/kg in normal saline intravenously. Total volume of the study drug was adjusted to 50 ml and administered over a period of 15 min before induction. Mean heart rate was low for Group D. Four out of 29 patients (15%) in Group D required intravenous atropine due to bradycardia. Systolic arterial pressure was significantly lower in Group D, especially after intubation, at 30 minutes after pneumoperitoneum and after extubation. No significant episode of hypotension was found in any of the groups post pneumoperitoneum. None of the patient showed any evidence of ischemia or arrthymia intraoperatively. They concluded that Dexmedetomidine was more effective in attenuating hemodynamic response to pneumoperitoneum when compared with clonidine. However, with dexmedetomidine there are greater chances of developing hypotension and bradycardia.

(Int J Sci Stud 2014;2(7):186-190.)

12. Gupta Kumkum et al[41] conducted a prospective randomized double blind study to compare the effect of Premedication with clonidine versus fentanyl for intraoperative hemodynamic stability and recovery outcome during laparoscopic cholecystectomy under general anesthesia. Group C patients have received intravenous clonidine 1µg/kg and Group F patients have received intravenous fentanyl 2µg/kg 5 min before induction. Anesthetic and surgical techniques were standardized. All patients were assessed for intraoperative hemodynamic changes at specific time and postoperative recovery outcome. Premedication with clonidine or fentanyl has attenuated the hemodynamic responses of laryngoscopy and laparoscopy. Clonidine was superior to fentanyl for intraoperative hemodynamic stability. No significant differences in the postoperative recovery outcome were observed between the groups. Nausea, vomiting, shivering and respiratory depression were comparable between groups. They concluded that the Premedication with clonidine or fentanyl has effectively attenuated the intraoperative hemodynamic responses of laparoscopic cholecystectomy.

(Anesth Essays Res 2013;7:29-33.)

13. Paul S et al[37] investigated the efficacy of magnesium sulfate to prevent adverse hemodynamic response associated with pneumoperitoneum in patients undergoing laparoscopic cholecystectomy. Sixty patients, of either sex (18-65 years of age), undergoing elective laparoscopic cholecystectomy were randomly allocated in one of the two groups containing 30 patients each. Group M received magnesium sulfate 30 mg/kg intravenously as a bolus before pneumoperitoenum. Group C received same volume of 0.9% saline. Mean arterial pressure and heart rate were significantly less throughout the period of pneumoperitoneum in patients of group M. Intravenous labetalol was required in 40% (12 out of 30) of the patients in group C to control intraoperative hypertension and it as clinically significant in comparison to group M. They concluded that Magnesium sulfate administered before pneumoperitoneum attenuates adverse hemodynamic response and provides hemodynamic stability during pneumoperitoneum created for laparoscopic surgery.

(Anesthesia: Essays and Researches 2013 May-Aug)

MATERIALS AND METHODS

This is a double blinded prospective randomized study was conducted in the Thanjavur medical college, Thanjavur during the period 2014-2015. After obtaining institutional ethical committee approval and informed consent, 60 ASA physical status I and II subjects in the age group of 20-60 years planned for elective laparoscopic surgeries with CO2 pneumoperitoneum were enrolled in this study. They were randomly allocated to one of the two study groups, Group C (Clonidine group) and Group M (Magnesium group).

Statistical test of significance

Comparison of parameters was done using One-Way ANOVA and categorical data was compared using Chi-square test. P Value <0.05 considered as statistically significant.

Inclusion criteria

1. ASA I and II
2. Age group of 20-60 years
3. Patients of both sex
4. Patients posted for elective laparoscopic surgery

Exclusion criteria

1. Patients who refuse to give informed written consent.
2. Patients with systemic disorders like hypertension, diabetes mellitus, left ventricular failure, any degree of heart block, ischemic heart disease, aortic stenosis.
3. Patients on calcium channel blockers, beta blockers, methyldopa, Tricyclic antidepressants, benzodiazepines, monamine oxidase inhibitors.
4. Hypermagnesaemia

Preanaesthetic evaluation

All patients were kept on 6 hours starvation. Patients were premedicated with intravenous ranitidine 0.25 mg/kg, metoclopramide 0.15 mg/kg and glycopyrrolate 0.02 mg/kg intra muscularly in preoperative room 60 minutes before surgery.

In the Operating room

On arrival in the operation theater, monitors were connected (heart rate, NIBP, oxygen saturation, ECG) and baseline vital parameters like heart rate, systolic and diastolic blood pressure, and oxygen saturation were recorded. Fentanyl 2 µg/kg intravenous was given for analgesia. After pre-oxygenation with 100% oxygen for 3 minutes. Induction agent propofol 2- 2.5 mg/ kg and

succinyl choline chloride 1- 2mg/kg given intravenously and intubated with appropriate size endotracheal tube. ETCO2 monitor were connected.

Procedure

Prefilled syringes with the test drugs was given to the anaesthesiologist with the instructions to give the test drug immediately after intubation.

Group C Patients were given a solution containing clonidine 1.5 µg/kg (group C) in 50 ml of normal saline over a period of 15 min.

Group M Patients were given a solution containing magnesium sulfate 50 mg/kg in 50 ml of normal saline over a period of 15 min.

Anesthesia was maintained with oxygen-nitrous oxide mixture (50:50) and intermittent positive pressure ventilation, Inj. vecuronium bromide 0.08mg/ kg as loading dose and thereafter vecuronium bromide 0.02mg/kg as the intermittent boluses for maintenance was given. The tidal volume and respiratory rate adjusted to maintain end tidal carbon dioxide between 35 and 45 mm Hg. During surgery, Ringer's lactate was infused in accordance with maintenance volume requirements and blood loss. CO2 pneumoperitoneum was created and intraabdominal pressure maintained at 14 mm Hg. Trendelenburg position was used for the laparoscopic appendicectomy and Reverse trendelenburg position was used for the laparoscopic cholecystectomy.

Assessment of parameters

The parameters like Systolic blood pressure, Diastolic blood pressure, mean arterial Blood pressure, heart rate and SPO2 were recorded at the following point of time

1. Prior to induction (baseline value)
2. At the end of infusion (P0)
3. 5 min after pneumoperitoneum (P5)
4. 10 min after pneumoperitoneum (P10)
5. 20 min after pneumoperitoneum (P20)
6. 30 min after pneumoperitoneum (P30)
7. 40 min after pneumoperitoneum (P40)

Patients were monitored for any adverse effects like bradycardia, and hypotension during intraoperative period.

Neuromuscular block was reversed with intravenous neostigmine 0.05 mg/kg and glycopyrrolate 0.02 mg/ kg and after adequate recovery, patient extubated.

Adverse effects

Immediately after the extubation the patients were monitored for nausea, vomiting, shivering and level of sedation assessed by Modified Ramsay sedation score.

Modified Ramsay sedation score

Score	**Level of activity**
0	Paralyzed, unable to evaluate
1	Awake
2	Lightly sedated
3	Moderately sedated, follows simple commands
4	Deeply sedated, responds to non-painful stumuli
5	Deeply sedated, responds only to painful stimuli
6	Deeply sedated, unresponsive to painful stimuli

OBSERVATIONS AND RESULTS

This prospective double blinded randomized controlled study was done in 60 ASA I and II patients of either sex aged between 20-60 years, posted for elective laparoscopic surgeries under general anaesthesia. The study was undertaken to compare the efficacy of intravenously administered clonidine and magnesium sulfate to attenuate the hemodynamic response during laparoscopic surgeries and the adverse effects.

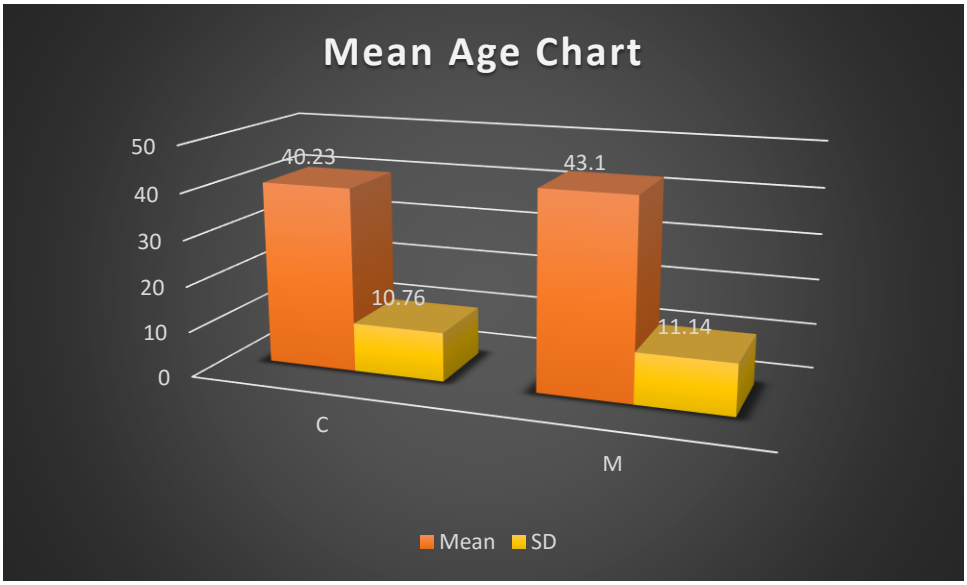
DEMOGRAPHIC CHARACTERISTICS OF STUDY POPULATION

AGE

Age wise distribution of study groups

Study Group	**N**	**Range (years)**	**Mean ± Standard deviation**	**P Value**	Significance
C	30	20 – 60	40.23 ± 10.76	0.919	Not Significant
M	30	20 – 60	43.10 ± 11.51		
Total	60	20 – 60	41.65 ± 11.14		

The age distribution was in the range of 20-60 years in Group C and Group M. The P Value for mean age was not statistically significant.


Mean Age Chart
50
40
30
20
10
0
40.23
10.76
43.1
11.14
C
M
Mean
SD

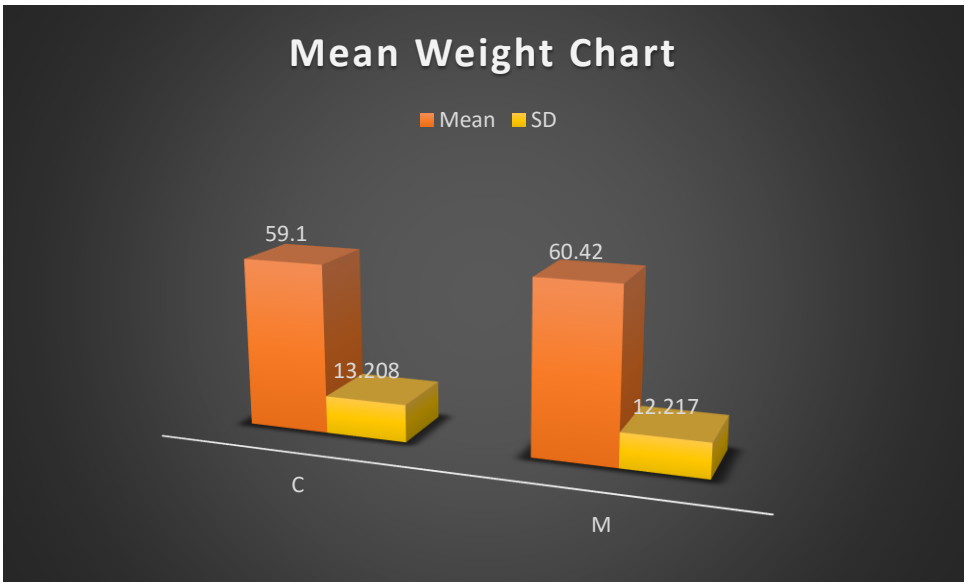
WEIGHT

Comparison of groups on basis of Mean body weight

Study Group	N	Range (Kgs)	Mean ± **Standard deviation**	P Value	Sinigicance
C	30	40– 78	59.10 ± 13.21	0.998	Not significance
M	30	42 – 78	60.42 ± 12.22		
Total	60	40 – 78	59.78 ± 12.61		

The weight distribution was in the range of 40-78 kgs in Group C and 42-78 kgs Group M.

The P Value for mean weight was not statistically significant.

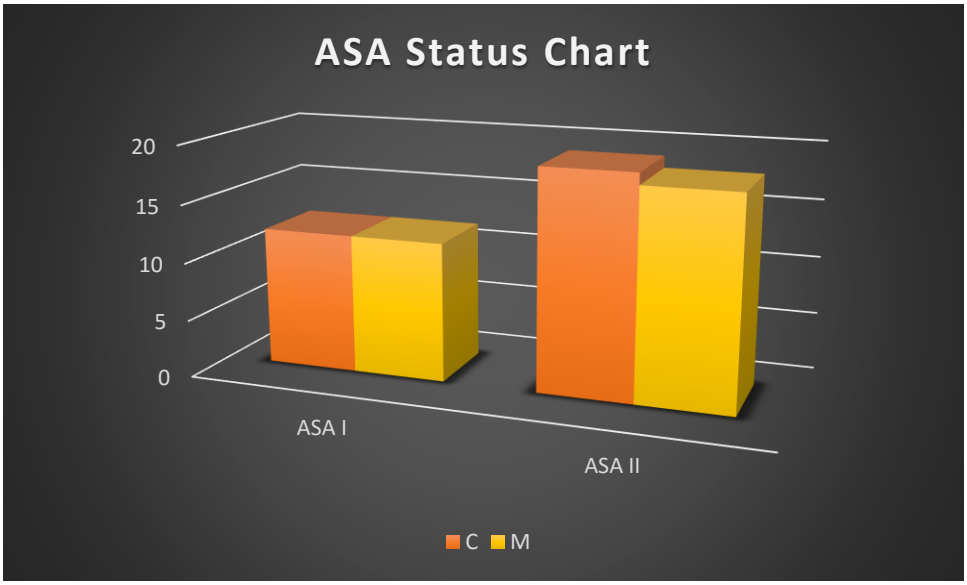

Mean Weight Chart
Mean
SD
59.1
13.208
60.42
12.217
C
M

ASA STATUS

Comparison of groups on basis of ASA Status

Study Group	ASA 1	ASA 2	Total	P Value	Significance
C	12 (40)	18 (60%)	30	0.071	Not significant
M	12 (40)	18 (60%)	30		
Total	24 (16%)	36 (84%)	60		

No statistically significant difference observed in the ASA status among the groups.

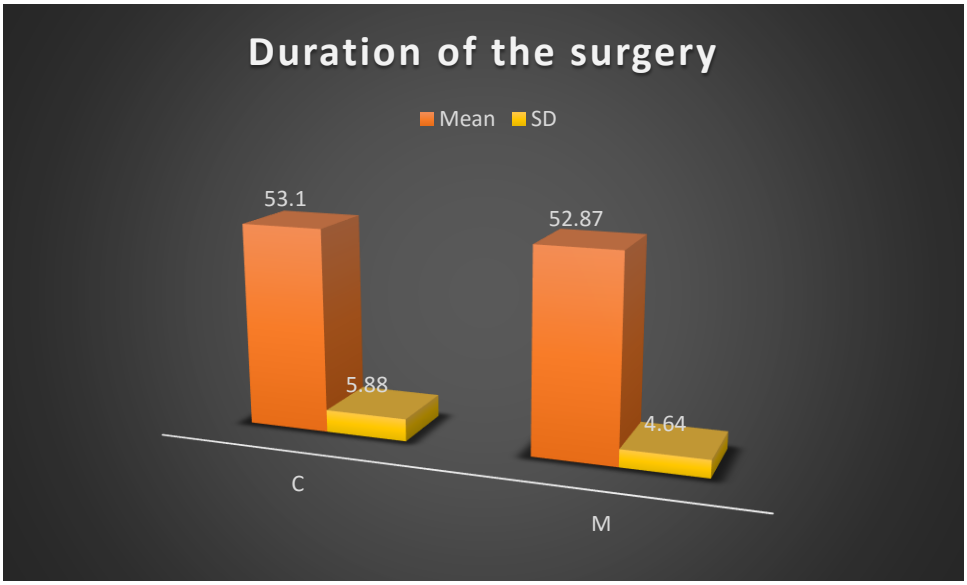

ASA Status Chart
20
15
10
5
0
ASA I
ASA II
C
M

Duration of the surgery

Comparison of groups on basis of Duration of the surgery

Study Group	Mean ± Standard Deviation	P Value	Significance
C	53.10 ± 5.88	0.865	Not significant
M	52.87 ± 4.64		
Total	52.98 ± 5.25		

The mean duration of the surgery in the group C was 53.1 and group M was 52.87. The p value is 0.865 and statistically insignificant.


Duration of the surgery
Mean
SD
53.1
5.88
52.87
4.64
C
M

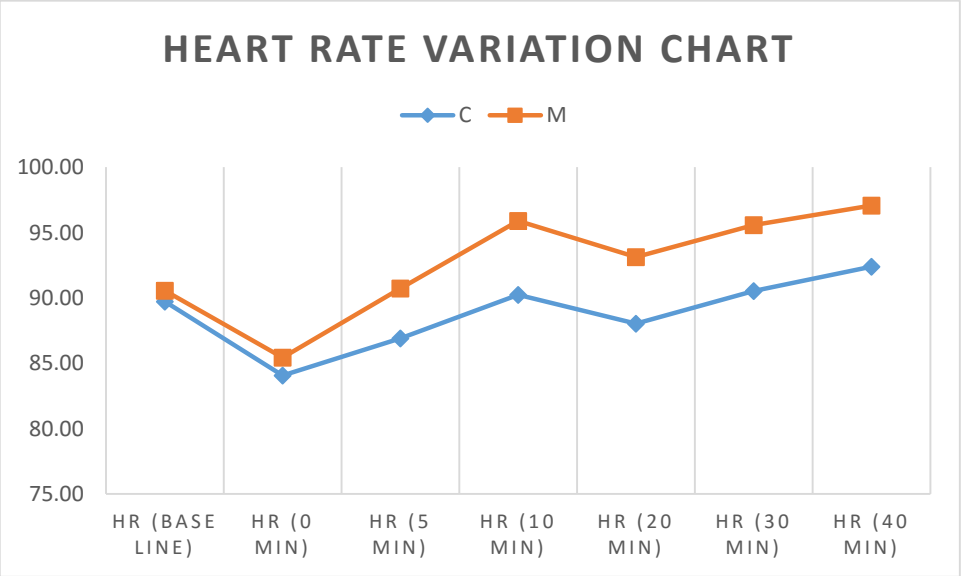
HEMODYNAMIC PROFILE

HEART RATE

Comparison of groups on basis of Heart rate

Heart rate (beats per minute)	Group C n=30 (Mean ± Standard deviation)	Group M n=30 (Mean ± Standard deviation)	P Value	Significance
Base line	89.73 ± 10.77	90.57 ± 11.96	0.778	Not significant
0 min	84.07 ± 10.87	85.43 ± 12.63	0.668	Not significant
5 min	86.90 ± 10.78	90.73 ± 12.55	0.234	Not significant
10 min	90.23 ± 10.77	95.90 ± 12.60	0.066	Not significant
20 min	88.03 ± 10.65	93.13 ± 12.54	0.095	Not significant
30 min	90.53 ± 10.94	95.57 ± 12.26	0.099	Not significant
40 min	92.40 ± 11.05	97.07 ± 12.33	0.128	Not significant

There was no statistically significant difference in the Heart rate status among the groups at any point of time during the study.

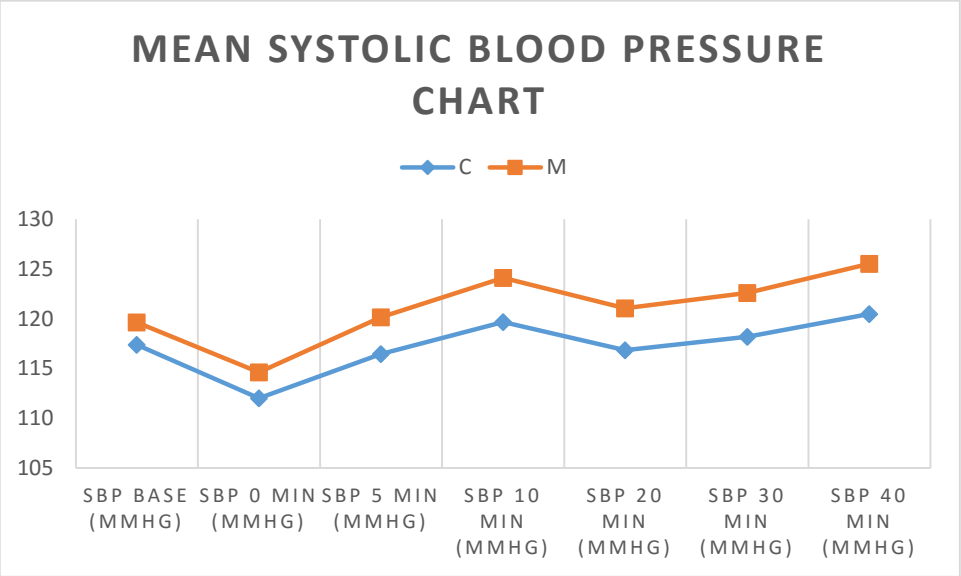

HEART RATE VARIATION CHART
C
M
100.00
95.00
90.00
85.00
80.00
75.00
HR (BASE LINE)
HR (0 MIN)
HR (5 MIN)
HR (10 MIN)
HR (20 MIN)
HR (30 MIN)
HR (40 MIN)

SYSTOLIC BLOOD PRESSURE

Comparison of groups on basis of Mean systolic blood pressure

SBP (mm Hg)	Group C n=30 (Mean ± Standard deviation)	Group M n=30 (Mean ± Standard deviation)	P Value	Significance
Base line	117.40 ± 7.31	119.63 ± 8.24	0.271	Not significant
0 min	112.00 ± 8.46	114.63 ± 8.20	0.226	Not Significant
5 min	116.47 ± 9.10	120.17 ± 8.26	0.104	Not significant
10 min	119.67 ± 9.56	124.13 ± 8.42	0.600	Not Significant
20 min	116.83 ± 9.78	121.07 ± 8.69	0.820	Not Significant
30 min	118.20 ± 9.66	122.60 ± 8.67	0.068	Not significant
40 min	121.17 ± 10.19	125.53 ± 8.78	0.081	Not Significant

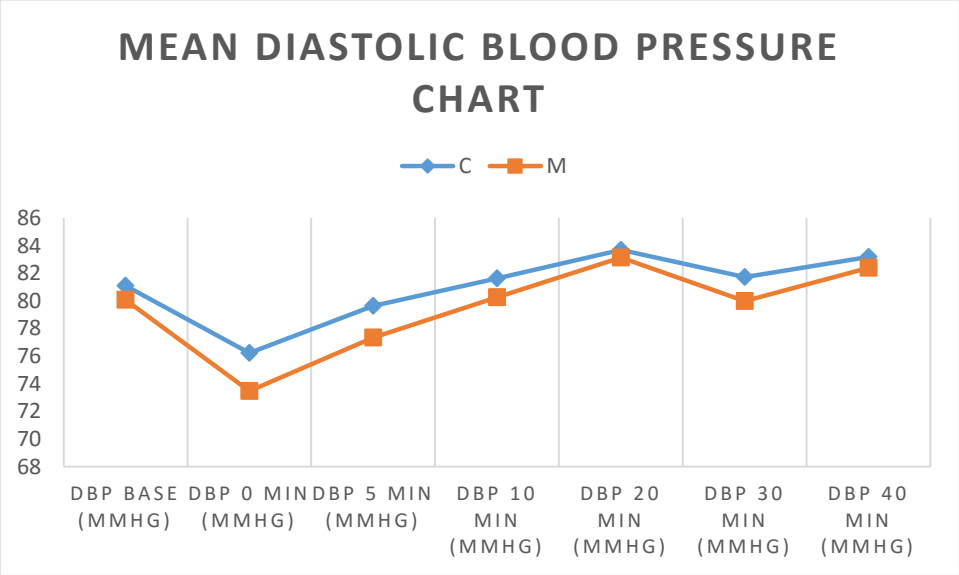
There was no statistically significant fall in systolic blood pressure is noted between the groups.


MEAN SYSTOLIC BLOOD PRESSURE CHART
C
M
130
125
120
115
110
105
SBP BASE (MMHG)
SBP 0 MIN (MMHG)
SBP 5 MIN (MMHG)
SBP 10 MIN (MMHG)
SBP 20 MIN (MMHG)
SBP 30 MIN (MMHG)
SBP 40 MIN (MMHG)

DIASTOLIC BP

DBP	Group C n=30 (Mean ± Standard deviation)	Group M n=30 (Mean ± Standard deviation)	P Value	Significance
Base line	81.10 ± 5.96	80.07 ± 6.71	0.531	Not significant
0 min	76.23 ± 5.63	73.47 ± 6.70	0.089	Not significant
5 min	79.63 ± 5.64	77.33 ± 6.65	0.154	Not significant
10 min	81.63 ± 5.85	80.27 ± 6.49	0.395	Not significant
20 min	83.70 ± 6.05	83.13 ± 6.45	0.727	Not Significant
30 min	81.73 ± 6.11	79.97 ± 6.62	0.287	Not Significant
40 min	83.17 ± 6.10	82.40 ± 6.65	0.644	Not significant

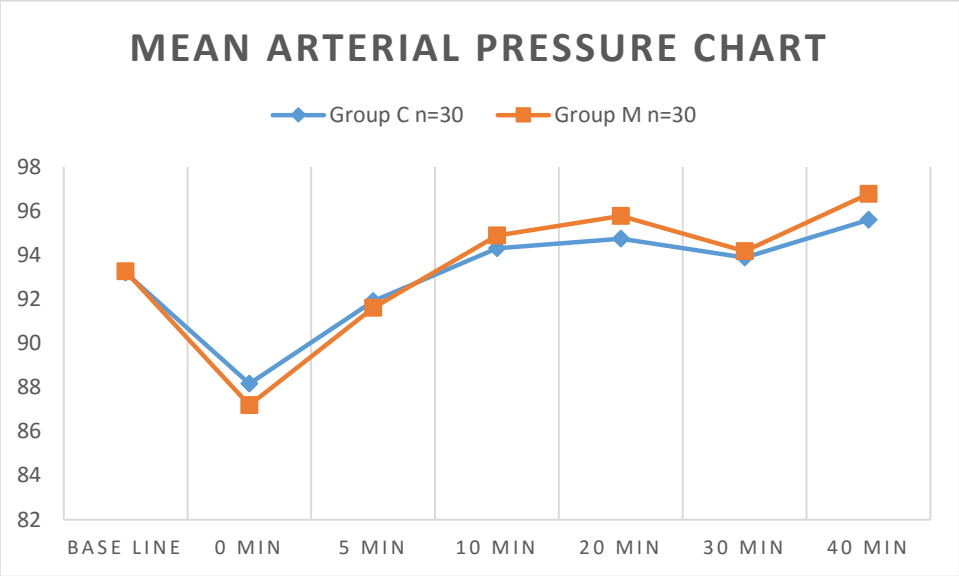
No Statistically significant difference in diastolic blood pressure was noted between the two groups.


MEAN DIASTOLIC BLOOD PRESSURE CHART
C
M
86
84
82
80
78
76
74
72
70
68
DBP BASE (MMHG)
DBP 0 MIN (MMHG)
DBP 5 MIN (MMHG)
DBP 10 MIN (MMHG)
DBP 20 MIN (MMHG)
DBP 30 MIN (MMHG)
DBP 40 MIN (MMHG)

MEAN ARTERIAL PRESSURE

MAP	Group C n=30 (Mean ± Standard deviation)	Group M n=30 (Mean ± Standard deviation)	P Value	Significance
Base line	93.20 ± 4.64	93.26 ± 5.81	0.968	Not Significant
0 min	88.16 ± 5.00	87.19 ± 5.12	0.462	Not Significant
5 min	91.91 ± 5.16	91.61 ± 4.86	0.817	Not Significant
10 min	94.31 ± 5.51	94.89 ± 4.86	0.668	Not Significant
20 min	94.74 ± 5.63	95.78 ± 4.71	0.444	Not Significant
30 min	93.89 ± 5.68	94.18 ± 4.82	0.833	Not Significant
40 min	95.60 ± 5.73	96.78 ± 4.96	0.398	Not Significant

No Statistically significant difference in diastolic blood pressure was noted between the two groups.

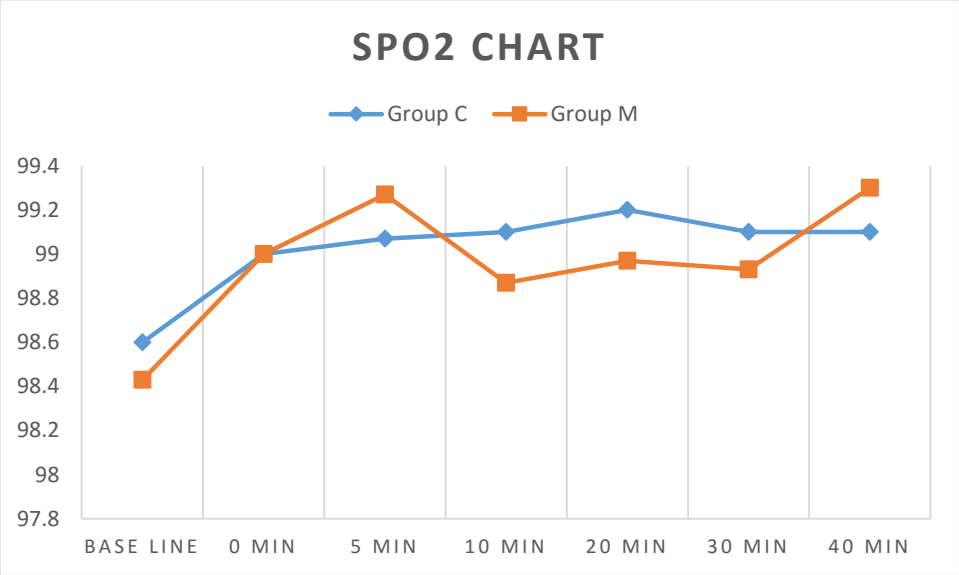

MEAN ARTERIAL PRESSURE CHART
Group C n=30
Group M n=30
98
96
94
92
90
88
86
84
82
BASE LINE
0 MIN
5 MIN
10 MIN
20 MIN
30 MIN
40 MIN

OXYGEN SATURATION

SPO2	Group C n=30	Group M n=30	P Value
Base line	98.6 ± 1.192	98.43 ± 1.104	0.576
0 min	99 ± 0	99 ± 0	-
5 min	99.07 ± 0.785	99.27 ± 0.74	0.314
10 min	99.1 ± 0.885	98.87 ± 0.73	0.270
20 min	99.2 ± 0.805	98.97 ± 0.85	0.280
30 min	99.1 ± 0.845	98.93 ± 0.868	0.454
40 min	99.1 ± 0.803	99.3 ± 0.702	0.309

P value <0.05 (Significant)

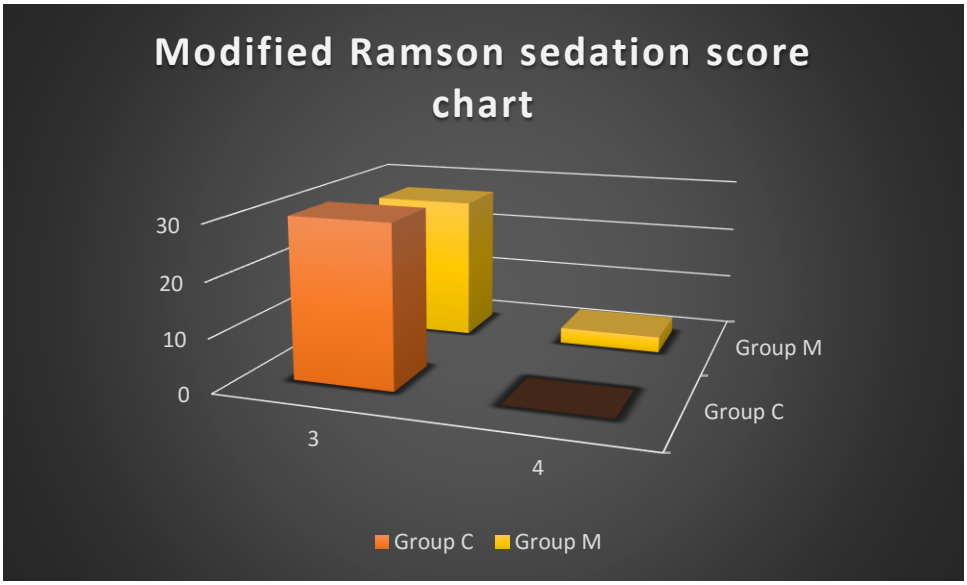
There was no statistically significant difference in the oxygen saturation status between two groups during the study.


SPO2 CHART
Group C
Group M
99.4
99.2
99
98.8
98.6
98.4
98.2
98
97.8
BASE LINE
0 MIN
5 MIN
10 MIN
20 MIN
30 MIN
40 MIN

Modified Ramsay Sedation score

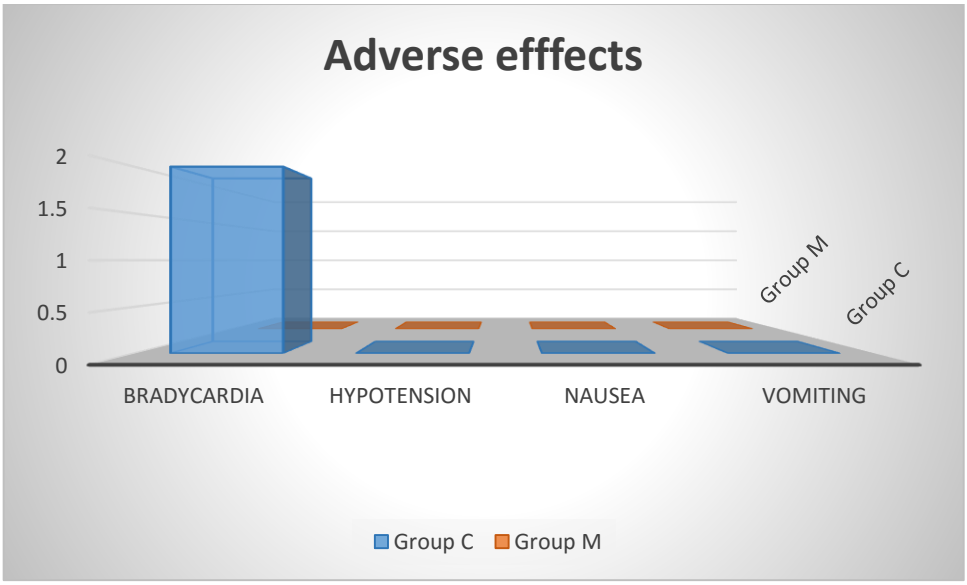
Study Group	N	Score Range	Mean ± Standard Deviation	P Value	Significance
C	30	3-4	3.10 ± 0.31	0.003	Significant
M	30	3-4	3.43 ± 0.50		

Statistically significant difference observed in the Modified Ramsay sedation scale between the two groups. Clonidine found to have significantly lesser sedation than magnesium at the time of extubation.


Modified Ramson sedation score chart
30
20
10
0
3
4
Group M
Group C
Group C
Group M

Adverse effects

Adverse effects	Group C		Group M	
	No	**%**	**No**	**%**
Bradycardia	2	7	0	0
Hypotension	0	0	0	0
Nausea	0	0	0	0
Vomiting	0	0	0	0
Total	30	100	30	100


Adverse efffects
2
1.5
1
0.5
0
Group M
Group C
BRADYCARDIA
HYPOTENSION
NAUSEA
VOMITING
Group C
Group M

DISCUSSION

Laparoscopic surgeries are being performed more and more frequently now a days for various elective procedures. Though Open procedures are being done, laparoscopy is preferred by both the patients and surgeon for its advantages. So there is a need for the better control of hemodynamics intraoperatively in these type of surgeries.

Various pharmacological agents have been studied in the recent past for attenuating the hemodynamic responses to the laparoscopy. Most of the studies have compared the effect of intravenous clonidine or magnesium with that of the control. Very few studies are available that compare intravenous clonidine with magnesium for attenuation of the hemodynamic responses to laparoscopy.

So, we have planned for a prospective, randomized, double blinded study in Thanjavur Medical College, Thanjavur to compare the effect of intravenous clonidine and magnesium on hemodynamic response in patients undergoing laparoscopic surgeries.

Patient Characteristics across the group

The demographic characteristics like age, weight, ASA status of the study population and duration of the surgery were similar in both the two groups, with no statistically significant difference. The mean age in Clonidine group was 40.23 ± 10.76 years and in Magnesium group was

43.10 ± 11.51 years. The mean weight in Clonidine group was 59.10 ± 13.21 kg and in Magnesium group was 60.42 ± 12.22 kg. The patients belonged to either ASA 1 or ASA 2, and were comparable in both groups. The mean duration of the surgery in clonidine group was 53.10 ± 5.88 minutes and in Magnesium group was 52.87 ± 4.64 minutes.

Dosage of the drug

In Group C we have used clonidine 1.5µg/kg in 50ml normal saline and in Group M magnesium sulfate 50mg/kg in 50ml of normal saline was used. The test drug solution were infused over a period of 15 minutes before pneumoperitoneum.

In the study by Nand Kishore Kalra et al[29] compared the attenuation of hemodynamic response during laparoscopic cholecystectomy due to pneumoperitonem was infused with intravenous clonidine 1 µg/kg, clonidine 1.5 µg/kg, magnesium 50mg/kg and placebo and found that both clonidine doses and magnesium had significant attenuation on hemodynmic stress response when compared with placebo. The test drugs solution were infused after intubation for 15 minutes. Clonidine 1.5µg/kg showed statistically significant difference with magnesium 50mg/kg with no incidence of adverse events like bradycardia and hypotension.

Similarly Altan and Turgut et al[4] used clonidine 3 µg/kg intravenously over a period of 15 minutes before induction and then 2

μg/kg/min by continuous infusion intraoperatively. They observed significant incidences of bradycardia and hypotension in their study. Ray et al [34]. used 3 μg/kg of clonidine intravenously over a period of 15 min before induction and then 1 μg/kg/min by continuous infusion during surgery and observed significant incidences of bradycardia and hypotension in their study. Therefore, we reduced the dose of clonidine, given before pneumoperitoneum, to 1.5μg/kg. Even though we reduced the dose of clonidine and avoided the intraoperative infusion, we observed 7% incidence of bradycardia in clonidine group patients.

Jee et al[35] administered magnesium sulfate 50 mg/kg over 2-3 minutes, before pneumoperitoneum in patients undergoing laparoscopic cholecystectomy and observed that it effectively attenuated the hemodynamic stress response due to pneumoperitoneum without any episode of severe hypotension or bradycardia. We used same dose of magnesium sulfate in our study to compare it with clonidine. The magnesium dose selected by us resulted in a steady and smooth reduction of mean arterial pressure and heart rate, with no episodes of hypotension and bradycardia.

Similarly, Paul S et al[37] studied the effects of magnesium in hemodynamic response to laparoscopic surgery and concluded that the mean arterial pressure and heart rate were significantly less throughout the period of pneumoperitoneum in patients who received magnesium 30mg/kg

when compared with placebo. Telci L et al[38] also concluded that the administration of magnesium led to a significant reduction in the requirements of anaesthetic drugs during total intravenous anaesthesia with propofol, remifentanil and vecuronium with better control of hemodynamics. Elsharnouby and Elsharnouby et al used MgSO4 40 mg/ kg intravenously over a period of 15 minutes before induction and then 15 mg/kg/hour by continuous infusion intraoperatively. They noticed episodes of severe hypotension while using this dose of MgSO4.

In our study, we avoided infusion of magnesium sulfate and we did not observe any incidence of hypotension. Rather, we used slightly higher dose of magnesium (50 mg/kg) than Elsharnouby and Elsharnouby et al.

Hemodynamic stability

Various studies have demonstrated the hemodynamic stability with the use of intravenous clonidine and magnesium for laparoscopic surgeries.

The variation in hemodynamic parameters like heart rate, systolic blood pressure, diastolic blood pressure and mean arterial blood pressure was observed in the following intervals; baseline, after infusion of test drug(P0), 5 minutes after pneumoperitoneum(P5), 10 minutes after pneumoperitoneum(P10), 20 minutes after pneumoperitoneum(P20), 30

minutes after pneumoperitoneum(P30) and 40 minutes after pneumoperitoneum(P40).

Heart rate

Nand Kishore Kalra et al[29] observed that statistically significant decrease in heart rate in patients who received clonidine 1.5µg/kg at the following intervals; 30 minutes after pneumoperitoneum (P <0.05) and 40 minutes after pneumoperitoneum (P <0.05) than magnesium 50mg/kg group. There was no statistically significant difference in heart rate between the clonidine 1.5µg/kg and magnesium 50mg/kg. This is in contrast with our study.

A Altan et al[4] observed that there was no statistically significant difference in heart rate was observed between the patients who received clonidine 3µg/kg bolus followed by 2µg/kg/hr infusion, and magnesium sulphate 30mg/kg as a bolus followed by 10mg/kg/hr infusion. This is similar to our study.

Ray et al[34] used clonidine 3µg/kg and then 1µg/kg continuous infusion during intraoperative period and observed significant incidences of bradycardia and hypotension. Based on these observations we reduced the dose of clonidine and did not give infusion to avoid bradycardia and hypotension. We observed no significant variations in the heart rate between the groups.

Sushil Kumar Nayek infused clonidine 1.5µg/kg inravenously

over a period of 15 minutes before induction followed by 1 µg/kg/hr continuous infusion. They observed that statistically significant decrease in heart rate, after induction (P <0.05), 1 minute after intubation (P <0.01), zero minutes (P <0.01), 15 minutes (P <0.05), 30 minutes (P <0.05), 45 minutes (P <0.05) and 60 minutes after pneumoperitoneum (P <0.05). This is in contrast to our study.

R.Uma et al[30] infused clonidine 3µg/kg 15 minutes prior to intubation and observed that statistically significant decrease in heart rate in clonidine group prior to induction (P-0.005) and 10 minutes after pneumoperitoneum (P- 0.015) than the placebo group. This is in contrast with our study.

Similarly Manjaree Mishra et al[7] and Sudheer Rao et al [31] observed significantly decreased heart rate in clonidine group. A Altan et al[4] observed significant decreased in heart rate in clonidine group.

In our study, there was no statistically significant variations in heart rate observed between the two groups at any intervals.

Systolic blood pressure

Nand Kishore Kalra et al[29] observed that statistically significant reduction in systolic blood pressure in patients who received clonidine 1.5µg/kg at 10 minutes (P <0.05) and 30 minutes after pneumoperitoneum (P <0.01) than magnesium 50mg/kg group. This is in contrast with our

study.

A Altan et al [4] observed that there was no statistically significant difference in systolic blood pressure observed between the patients who received clonidine 3µg/kg bolus followed by 2µg/kg/hr infusion and magnesium sulphate 30mg/kg as a bolus followed by 10mg/kg/hr infusion. This study is similar to our study result.

Deepshikha C Tripathi et al [39] observed that the patients received clonidine 2µg/kg showed statistically significant reduction in systolic blood pressure changes at 20 minutes after pneumoperitoneum ($P < 0.05$) than the placebo group. This is in contrast with our study.

Jee et al [35] conducted a study in which patients received magnesium sulphate 50mg/kg, infused immediately before pneumoperitoneum, showed statistically significant decrease in diastolic blood pressure at 10 minutes ($P < 0.05$), 20 minutes ($P < 0.05$) and 30 minutes after pneumoperitoneum ($P < 0.05$) than the placebo group. This is in contrary to our study.

In our study, there was no statistically significant variations in systolic blood pressure observed between the two groups at any intervals.

Diastolic blood pressure

Nand Kishore Kalra et al[29] observed that statistically significant reduction in diastolic blood pressure in patients who received clonidine

1.5µg/kg at 30 minutes (P <0.05) and 40 minutes after pneumoperitoneum (P <0.01) than magnesium 50mg/kg group. This is in contrast to our study.

A Altan et al[4] observed that there is no statistically significant difference in diastolic blood pressure observed between the patients who received clonidine 3µg/kg bolus followed by 2µg/kg/hr infusion, and magnesium sulphate 30mg/kg as a bolus followed by 10mg/kg/hr infusion. This is similar to our study.

Deepshikha C Tripathi [39] et observed that the patients who received 2µg/kg showed statistically significant diastolic blood pressure at 20 minutes after pneumoperitoneum (P <0.05) than the placebo group. This result is in contrast with our study.

Jee et al [35] conducted a study in which patients received magnesium sulphate 50mg/kg, infused immediately before pneumoperitoneum, showed statistically significant decrease in diastolic blood pressure at 10 minutes (P <0.05), 20 minutes (P <0.05) and 30 minutes after pneumoperitoneum (P <0.05) than the placebo group. This is contrary to our study.

In our study, there was no statistically significant variations in diastolic blood pressure observed between the two groups at any intervals.

Mean arterial blood pressure

R.Uma et al [30] infused clonidine 3µg/kg 15 minutes prior to

intubation and observed that statistically significant decrease in mean arterial blood pressure in clonidine group at the following intervals; prior to induction (P-0.005), before pneumoperitoneum (P- 0.025), 10 minutes after pneumoperitoneum (P- 0.000) and 20 minutes after pneumoperitoneum (P-0.000) than the placebo group. This is in contrast with our study.

A Altan et al[4] observed that there was no statistically significant difference in mean arterial blood pressure observed between the patients who received clonidine 3µg/kg bolus followed by 2µg/kg/hr infusion, and magnesium sulphate 30mg/kg as a bolus followed by 10mg/kg/hr infusion. This is similar to our study.

Manjeree Mishra et al observed that the patient who received clonidine 1.5µg/kg showed a statistically significant difference in mean arterial pressure at the following intervals; 5 minutes after pneumoperitoneum (P- 0.037) , 10 minutes after pneumoperitoneum (P <0.001), 15 minutes after pneumoperitoneum (P- 0.006) and 20 minutes, 25 minutes, 30 minutes, 35 minutes and 40 minutes pneumoperitoneum (P <0.01). This is contrary to our study.

Suhrita paul et al [37] compared magnesium sulphate 30mg/kg and placebo. There is a statistically significant decrease in mean arterial blood pressure observed in the magnesium group in the following intervals; 15 minutes after pneumoperitoneum (P <0.05), 30 minutes after pneumoperitoneum (P <0.05) and 30 minutes after pneumoperitoneum (P

<0.05). This is in contrast to our study.

Similarly, Hayashi et al. and Sung et al. have also concluded that clonidine provided better perioperative hemodynamic stability during laparoscopic cholecystectomy. Laisalmi, et al. has also reported that clonidine premedication blunts the stress response of surgery and reduces the requirement of narcotics and anesthetic agent. These are in contrast to our study.

All the studies done to compare the effect of clonidine and magnesium to blunt the stress response to pneumoperitoneum were done in laparoscopic cholecystectomy. But in our study both laparoscopic appendicectomy and laparoscopic cholecystectomy were included. In laparoscopic cholecystectomy the positioning is the head up tilt, where as in laparoscopic appendicectomy trendelenburg position was used, which is in contrast each other.

The effect of positioning on the hemodynamics during laparoscopy and its influence on the result of studies is not addressed in various studies.

In our study, there was no statistically significant variations in mean arterial blood pressure observed between the two groups at any intervals.

Level of sedation

Both clonidine and magnesium produces sedation. In our study, we compared the sedative effect of clonidine and magnesium by using the modified ramsay sedation scale at the time of extubation. We observed that 27 patients out of 30 in the clonidine group had a score of 3 (90%) and 3 patients had a score of 4 (10%). But in the magnesium group out of 30 patients, 18 patients had a score of 3 (60%) and rest of the 12 patients had the score of 4 (40%). This difference in sedative effect could be explained by the prolonged sedative effect of magnesium than clonidine. The p value is <0.003 and found to be statistically significant.

Nand K et at[29] also concluded that patients receiving magnesium for attenuation of hemodynamic stress response showed that time to respond to verbal command like eye opening was not statistically significant between the clonidine group and magnesium group. This is in contrast with our study.

Javaherfroosh F et al[43] conducted a study to observe the effects of clonidine to reduce the post-operative nausea and vomiting in laparoscopic gynecological surgery. They found that the Ramsay sedation score is <3 (P<0.05) in 31/43 (72%) patients and >3 (P<0.05) in 12/43 (28%) patients and found to be statistically significant. This is similar to our study result.

Eduardo Tocchetto Lemes et al[44] conducted a study to observe effects of preoperative intravenous clonidine in the surgical treatment of cataract. They observed that the patients who received clonidine showed small increase

in the degree of sedation at 30 minutes after the surgery when compared with placebo group. This is similar to our study result.

Abass Sedighinejad et al [45] conducted a study to compare magnesium Sulfate and sufentanil for Patient-Controlled Analgesia in Orthopedic Surgery. They concluded that the magnesium group showed no significant difference in sedation score with sufentanil. However, in our study there is significant difference between the clonidine and magnesium sulfate.

Adverse effects

In our study we observed for the adverse effects like bradycardia, hypotension, post-operative nausea, vomiting and shivering, due to laparoscopy. In clonidine group we observed episodes of bradycardia in 2 out of 30 patients (7%). None other patients had any adverse effects. In the magnesium group no patients had any adverse effects.

Nand K et al[29] used clonidine 3 µg/kg and magnesium 50mg.kg intravenously over a period of 15 minutes. They observed no incidences of bradycardia and hypotension in their study. This is in contrast with our study.

Altan and Turgut et al [4] used clonidine 3 µg/kg intravenously over a period of 15 min before induction and then 2 µg/kg/min by continuous infusion intraoperatively. They observed significant incidences of bradycardia and hypotension in their study. This is similar to our study.

Ray et al[34] used 3 μg/kg of clonidine intravenously over a period of 15 min before induction and then 1 μg/kg/min by continuous infusion during surgery and observed significant incidences of bradycardia and hypotension in their study. This is similar to our study.

Suhrita Paul et al [37] conducted a study to observe the effects of magnesium sulphate on hemodynamic response to carbon dioxide pneumoperitoneum in patients undergoing laparoscopic cholecystectomy. They observed the hypotension in magnesium group. But in our study we did not observe any hypotension in any of the group.

Javaherfroosh F et al[43] conducted a study to observe the effects of clonidine to reduce the post-operative nausea and vomiting in laparoscopic gynecological surgery. They concluded that the clonidine group patients had reduced incidence of nausea and vomiting than placebo group. This is in contrast to our study.

Eduardo Tocchetto Lemes et al[44] conducted a study to observe effects of preoperative intravenous clonidine in the surgical treatment of cataract. They found that the clonidine group patients had hypotension and bradycardia. This is in contrast to our study.

Nand Kishore Kalra et al [29] compared the effect of clonidine versus magnesium in attenuating the stress response to laparoscopy showed that clonidine is superior to magnesium in blunting the hemodynamic response to pneumoperitoneum. Nand Kishore kalra et al study has been

done on laparoscopic cholecystectomies, where the head up position is used. In our study majority of cases were laparoscopic appendicectomy in both clonidine and magnesium group.

A greater fall in the systolic blood pressure, diastolic blood pressure and mean arterial pressure in clonidine group over magnesium group was observed in laparoscopic cholecystectomy only, where as in our study majority of cases were laparoscopic appendicectomy cases, in which trendelenburg position was used. The enhanced effect of clonidine over magnesium in attenuation the systolic blood pressure, diastolic blood pressure and mean arterial pressure to pneumoperitoneum is probably offset by the head down tilt or trendelenburg position used in laparoscopic appendicectomy. So, our study shows that clonidine and magnesium are equally effective in attenuating the stress response to pneumoperitoneum.

SUMMARY

We conducted a prospective double blinded randomized control study in 60 patients belonging to ASA I and II undergoing elective laparoscopic surgeries in Thanjavur medical college. Patients of both sexes ranging between 20 to 60 years of age were included. Our aim was to evaluate and compare the effect of intravenously administered clonidine 1.5µg/kg and magnesium sulfate 50mg/kg for attenuating the hemodynamic responses during laparoscopic surgeries.

Patients were divided randomly using closed cover technique into two groups of 30 each. Group C received clonidine 1.5µg/kg in 50 ml of normal saline. Group M received magnesium 50mg/kg in 50 ml of normal saline.

The test drug solution was given after intubation and before pneumoperitoneum. The heat rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, oxygen saturation, adverse effects and level of sedation assessed by Modified Ramsay sedation score were noted in both groups.

The categorical data collected were analyzed by Chi Square test and nominal data are analyzed by One-Way ANOVA. The results were obtained in the form of range, mean and standard deviation. The probability value 'P' of less than 0.05 was considered statistically significant.

In both magnesium and clonidine groups, there was no statistically significant differences observed in heat rate, systolic blood pressure, diastolic

blood pressure, mean arterial pressure and oxygen saturation in our study. However, the level of sedation in clonidine group is less than that of magnesium and found to be statistically significant.

The patients were observed for adverse effects like bradycardia, hypotension, postoperative nausea, vomiting, and shivering. In clonidine group, we observed bradycardia in 7% of patients only.

From our study, we concluded that clonidine 1.5 µg/kg was equally effective as magnesium 50mg/kg in blunting the hemodynamic stress response during laparoscopic surgeries and clonidine had lesser sedation than magnesium at extubation.

CONCLUSION

Intravenous administration of clonidine 1.5µg/kg before pneumoperitoneum is as effective as intravenous magnesium sulfate 50mg/kg before pneumoperitoneum in blunting the haemodynamic stress responses during laparoscopic surgeries and clonidine has lesser sedation than magnesium at extubation.

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PROFORMA

COMPARATIVE STUDY OF INTRAVENOUSLY ADMINISTERED CLONIDINE AND MAGNESIUM SULFATE ON HEMODYNAMIC RESPONSES DURING LAPAROSCOPIC SURGERIES

Name	:	IP No	:
Age	: Yrs	Sex : Male/Female	Weight : Kgs
ASA	: I/II/III/IV		MPG : I/II/III/IV
Diagnosis	:	Procedure :	
Duration	:	Group: C / M	

Pre-Operative examination

Pulse rate	: /min	BP : mmHg	SpO_2: %
CVS	:	RS :	

Intra Operative period

Parameter	Baseline	0 mins	5 mins	10 mins	20 mins	30 mins	40 mins
HR							
MAP							
SpO_2							

Level of sedation at the time of extubation (Modified Ramsay sedation score)

Score	Level of activity
0	Paralyzed, unable to evaluate
1	Awake
2	Lightly sedated
3	Moderately sedated, follows simple commands
4	Deeply sedated, responds to non-painful stumuli
5	Deeply sedated, responds only to painful stimuli
6	Deeply sedated, unresponsive to painful stimuli

Post Operative Period

Nausea

Vomiting

Shivering

KEY TO MASTER CHART

ASA	American Society of Anaesthesiologist
F (Sex)	Female
C(Study group)	Clonidine
M(Study group)	Magnesium
HR	Heart rate
MAP	Mean arterial blood pressure
SPO2	Oxygen Saturation
ETCO2	End tidal carbondioxide

S.No	Name	Age (Yrs)	Sex	Weight (Kgs)	Diagnosis	ASA	Group	Duration of the surgery	Base line					After infusion(P0)					5 mins(P5)					10 mins(P10)					20 mins(P20)					30 mins(P30)					40 mins (P40)					Sedation score	Adverse effects
									HR (per min)	SBP (mmHg)	DBP (mmHg)	MAP(mmHg)	SPO2 (%)	HR (per min)	SBP (mmHg)	DBP (mmHg)	MAP(mmHg)	SPO2 (%)	HR (per min)	SBP (mmHg)	DBP (mmHg)	MAP(mmHg)	SPO2 (%)	HR (per min)	SBP (mmHg)	DBP (mmHg)	MAP(mmHg)	SPO2 (%)	HR (per min)	SBP (mmHg)	DBP (mmHg)	MAP(mmHg)	SPO2 (%)	HR (per min)	SBP (mmHg)	DBP (mmHg)	MAP(mmHg)	SPO2 (%)	HR (per min)	SBP (mmHg)	DBP (mmHg)	MAP(mmHg)	SPO2 (%)		
1	Harikrishnan	43	M	55	Appendectomy	1	(C) Clonidine	50	89	117	74	88	98	58	108	65	79	99	85	112	67	82	99	87	117	69	85	99	85	113	70	84	99	86	115	69	84	98	89	134	71	92	100	3	Bradycardia
2	Golistan	38	M	53	Appendectomy	1	(C) Clonidine	60	101	127	88	101	100	98	120	80	93	99	101	123	82	96	100	103	126	83	97	98	100	124	86	99	98	104	125	85	98	98	107	127	87	100	100	4	Nil
3	Mary	39	F	51	Cholecystectomy	2	(C) Clonidine	44	94	108	76	87	98	92	104	71	82	99	93	105	74	84	99	94	108	75	86	100	91	107	76	86	100	92	108	73	85	100	94	113	75	88	100	3	Nil
4	Seetha	41	F	74	Appendectomy	2	(C) Clonidine	58	96	111	89	96	99	95	108	83	91	99	99	112	88	96	99	102	116	89	98	98	99	111	91	98	99	100	113	89	97	100	101	113	90	98	98	3	Nil
5	Kavitha	24	F	40	Appendectomy	2	(C) Clonidine	54	93	117	89	98	100	86	113	88	96	99	90	122	90	101	100	92	128	93	105	100	91	126	95	105	99	93	128	92	104	100	94	131	94	106	98	4	Nil
6	Sumathi	25	F	68	Appendectomy	1	(C) Clonidine	59	91	130	81	97	100	84	126	80	95	99	88	132	82	99	98	90	136	85	102	99	89	134	87	103	100	92	136	85	102	100	93	138	87	104	100	3	Nil
7	Lakshmi	57	F	76	Appendectomy	2	(C) Clonidine	56	89	122	82	95	99	88	121	76	91	99	89	123	81	95	99	92	127	82	97	98	90	122	83	96	99	94	123	82	96	99	96	111	83	92	99	3	Nil
8	Rajeswari	27	F	68	Appendectomy	2	(C) Clonidine	45	76	112	87	95	100	71	105	78	87	99	74	115	81	92	98	76	117	82	94	98	74	116	85	95	100	75	117	83	94	100	77	118	85	96	98	3	Nil
9	Arivendran	59	M	54	Cholecystectomy	1	(C) Clonidine	58	98	122	77	92	100	94	113	68	83	99	95	115	72	86	100	98	119	73	88	100	97	114	74	87	98	100	115	71	86	98	103	126	73	91	99	3	Nil
10	Chitra	41	F	72	Appendectomy	2	(C) Clonidine	52	78	111	86	94	100	76	102	79	87	99	81	111	84	93	98	83	117	87	97	99	81	115	89	98	98	85	116	87	97	100	86	122	88	99	99	3	Nil
11	Kalaivani	53	F	41	Cholecystectomy	2	(C) Clonidine	56	80	128	74	92	98	73	119	72	88	99	77	127	75	92	100	78	130	78	95	100	75	129	80	96	99	76	130	79	96	98	78	114	81	92	98	3	Nil
12	Nageswaran	60	M	48	Cholecystectomy	2	(C) Clonidine	49	73	109	82	91	98	65	102	77	85	99	70	105	78	87	98	72	109	79	89	100	69	105	82	90	100	70	106	81	89	98	73	119	82	94	99	3	Nil
13	Krishnaveni	37	F	71	Appendectomy	2	(C) Clonidine	53	97	121	82	95	97	93	120	81	94	99	96	123	82	96	99	97	125	84	98	99	94	121	87	98	100	97	122	86	98	98	99	125	88	100	99	4	Nil
14	Nandhini	37	F	49	Appendectomy	2	(C) Clonidine	60	80	107	85	92	100	75	98	82	87	99	76	99	85	90	100	78	100	86	91	98	77	97	87	90	100	81	99	84	89	100	82	101	85	90	100	3	Nil
15	Moovendar	45	M	77	Appendectomy	1	(C) Clonidine	43	102	122	86	98	99	94	115	77	90	99	56	116	80	92	100	100	122	83	96	100	97	120	85	97	98	100	121	82	95	98	102	123	83	96	99	3	Bradycardia
16	Kamalam	44	F	44	Appendectomy	2	(C) Clonidine	59	90	129	71	90	98	86	122	69	87	99	90	127	73	91	98	92	128	75	93	98	90	127	76	93	99	91	128	73	91	100	93	129	74	92	100	3	Nil
17	Hansika	36	F	78	Cholecystectomy	2	(C) Clonidine	48	93	116	77	90	97	90	109	75	86	99	94	111	80	90	99	96	114	83	93	100	94	110	84	93	99	97	112	82	92	99	99	100	83	89	98	4	Nil
18	Sudha	55	F	76	Cholecystectomy	2	(C) Clonidine	60	84	109	89	96	100	83	108	82	91	99	87	109	87	94	100	88	111	89	96	100	87	108	92	97	98	90	109	91	97	100	91	131	92	105	99	3	Nil
19	Vijaya	49	F	41	Appendectomy	2	(C) Clonidine	53	100	112	78	89	97	95	105	74	84	99	98	113	79	90	100	100	114	82	93	100	97	112	85	94	100	100	113	82	92	99	103	138	84	102	100	3	Nil
20	Saravanan	34	M	64	Appendectomy	1	(C) Clonidine	54	107	121	85	97	98	99	116	83	94	99	103	119	86	97	98	106	123	88	100	99	103	119	90	100	100	107	120	87	98	99	108	111	88	96	100	3	Nil

21	Arokiyasamy	50	M	41	Cholecystectomy	1	(C) Clonidine	58	90	126	84	98	97	82	125	78	94	99	87	134	82	99	100	90	139	85	103	100	87	134	87	103	99	88	135	86	102	100	89	118	87	97	99	3	Nil
22	Rajalingam	20	M	51	Cholecystectomy	2	(C) Clonidine	49	108	126	89	101	97	100	124	82	96	99	104	130	83	99	99	105	133	85	101	100	102	132	88	103	100	106	133	87	102	98	107	126	89	101	98	3	Nil
23	Silambarasan	35	M	65	Appendectomy	1	(C) Clonidine	60	85	115	73	87	98	78	109	68	82	99	81	112	71	85	99	82	113	73	86	100	81	112	76	88	99	83	114	73	87	99	85	126	74	91	98	3	Nil
24	Dhanalakshmi	45	F	65	Appendectomy	2	(C) Clonidine	44	72	112	82	92	100	71	111	80	90	99	74	118	84	95	99	75	120	87	98	99	72	118	88	98	98	75	119	86	97	98	77	122	87	99	99	3	Nil
25	Mayakrishnan	37	M	75	Cholecystectomy	1	(C) Clonidine	48	74	114	71	85	97	70	109	70	83	99	73	110	75	87	100	74	113	76	88	100	72	110	79	89	98	73	112	77	89	100	75	114	78	90	98	4	Nil
26	Valli	34	F	52	Appendectomy	2	(C) Clonidine	58	88	125	85	98	100	81	121	79	93	99	83	122	82	95	99	86	125	85	98	99	85	124	86	99	100	88	126	84	98	99	90	119	85	96	100	3	Nil
27	Kalaiselvi	44	F	47	Appendectomy	1	(C) Clonidine	57	84	108	72	84	99	78	103	68	80	99	81	106	70	82	99	82	109	72	84	98	79	105	74	84	100	83	107	73	84	100	84	134	74	94	100	3	Nil
28	Kala	43	F	45	Appendectomy	2	(C) Clonidine	45	110	110	75	87	98	109	100	73	82	99	113	107	76	86	98	114	110	78	89	98	112	106	80	89	99	113	108	78	88	99	116	109	80	90	99	3	Nil
29	Mathini	20	F	73	Appendectomy	2	(C) Clonidine	59	96	124	78	93	99	89	123	72	89	99	94	129	77	94	99	95	133	78	96	98	93	129	80	96	100	96	130	78	95	99	99	133	79	97	99	4	Nil
30	Maheswari	34	F	52	Appendectomy	1	(C) Clonidine	44	74	111	86	94	97	69	101	77	85	99	75	107	83	91	98	80	108	85	93	98	78	105	89	94	100	81	106	87	93	99	82	110	89	96	100	3	Nil
31	Thilagavadahi	41	F	40	Appendectomy	1	(M) MgSO4	51	106	108	71	83	98	100	104	67	79	99	103	108	73	85	99	108	112	77	89	99	105	109	81	90	98	109	110	77	88	99	111	114	79	91	99	3	Nil
32	Rajendran	60	M	46	Appendectomy	1	(M) MgSO4	58	101	115	75	88	97	94	114	68	83	99	98	122	72	89	100	104	123	75	91	99	102	120	77	91	100	103	122	74	90	99	105	124	77	93	100	3	Nil
33	Farhana	48	F	43	Cholecystectomy	1	(M) MgSO4	52	82	129	70	90	97	75	127	64	85	99	82	133	68	90	100	86	134	72	93	98	82	132	75	94	98	84	133	73	93	100	85	135	76	96	99	3	Nil
34	Anandavalli	38	F	42	Cholecystectomy	2	(M) MgSO4	50	106	117	75	89	98	104	115	68	84	99	108	123	71	88	100	112	125	73	90	99	110	122	76	91	99	111	123	74	90	98	112	124	77	93	99	4	Nil
35	Rajalakshmk	45	F	71	Appendectomy	2	(M) MgSO4	47	93	109	84	92	99	85	105	79	88	99	90	114	83	93	98	96	118	85	96	100	94	115	87	96	99	97	116	83	94	100	98	117	85	96	100	3	Nil
36	Vimal	22	M	60	Appendectomy	1	(M) MgSO4	45	93	126	89	101	97	86	117	79	92	99	92	124	81	95	98	96	128	84	99	99	93	124	86	99	98	97	125	82	96	98	98	127	85	99	100	4	Nil
37	Annaduari	35	M	78	Cholecystectomy	1	(M) MgSO4	53	74	130	79	96	98	71	122	75	91	99	77	123	77	92	100	81	128	81	97	98	79	127	83	98	99	80	128	80	96	100	81	130	83	99	100	3	Nil
38	Maheswari	34	F	52	Appendectomy	1	(M) MgSO4	60	87	130	86	101	99	80	126	76	93	99	84	127	80	96	100	90	133	83	100	99	86	129	87	101	99	90	130	85	100	100	92	134	88	103	99	3	Nil
39	Nandagopal	59	M	63	Appendectomy	1	(M) MgSO4	53	97	116	75	89	98	96	114	65	81	99	102	120	68	85	100	108	126	71	89	100	105	123	74	90	100	108	124	70	88	98	110	127	72	90	100	3	Nil
40	Roselin thenmozhi	58	F	58	Appendectomy	2	(M) MgSO4	50	98	118	78	91	99	92	108	72	84	99	96	109	77	88	99	102	110	80	90	98	99	109	82	91	100	100	110	79	89	100	101	113	81	92	99	4	Nil
41	Lalitha	20	F	57	Appendectomy	2	(M) MgSO4	55	77	112	76	88	97	69	102	73	83	99	75	105	75	85	100	80	111	77	88	99	77	107	80	89	99	79	109	78	88	99	81	113	80	91	99	3	Nil
42	Shanmugavalli	54	F	48	Cholecystectomy	2	(M) MgSO4	58	74	123	89	100	99	67	115	84	94	99	73	121	88	99	99	78	126	91	103	100	76	123	93	103	100	80	125	91	102	99	81	129	94	106	99	4	Nil
43	Chinnathambi	45	M	78	Cholecystectomy	2	(M) MgSO4	46	108	129	88	102	97	107	119	80	93	99	114	125	82	96	99	119	129	84	99	99	117	128	88	101	98	121	130	84	99	98	123	134	86	102	99	3	Nil
44	Pavithra	45	F	63	Appendectomy	1	(M) MgSO4	46	92	115	90	98	98	89	108	86	93	99	95	109	92	98	99	99	112	94	100	99	96	107	97	100	100	100	109	95	100	99	102	111	97	102	99	3	Nil
45	Arulmarrry	36	F	50	Appendectomy	2	(M) MgSO4	49	103	104	72	83	97	95	99	69	79	99	100	108	75	86	99	105	113	78	90	98	101	108	82	91	99	102	110	78	89	98	103	113	80	91	98	3	Nil
46	Pitchaiammal	22	F	74	Cholecystectomy	2	(M) MgSO4	56	78	127	79	95	99	70	118	72	87	99	74	123	77	92	100	80	125	81	96	99	77	120	85	97	98	81	122	82	95	100	82	126	84	98	100	3	Nil

47	Veerammal	40	F	71	Appendectomy	1	(M) MgSO4	59	94	121	80	94	100	90	115	75	88	99	97	116	78	91	99	103	122	80	94	99	100	119	83	95	99	102	121	79	93	100	104	122	82	95	100	4	Nil
48	Ayisha	34	F	65	Appendectomy	2	(M) MgSO4	55	77	118	89	99	97	71	109	86	94	99	74	114	88	97	99	79	115	90	98	100	77	110	92	98	100	80	111	89	96	98	82	114	92	99	100	3	Nil
49	Selvanathan	48	M	75	Appendectomy	1	(M) MgSO4	52	98	105	71	82	100	90	104	68	80	99	96	109	73	85	99	102	114	76	89	98	100	113	79	90	100	101	115	75	88	98	103	119	78	92	99	3	Nil
50	Vinoth kumar	50	M	77	Appendectomy	1	(M) MgSO4	48	108	130	78	95	99	101	129	67	88	99	108	132	71	91	100	113	135	74	94	98	109	130	78	95	99	110	131	74	93	98	111	134	76	95	98	4	Nil
51	Parameshwari	54	F	44	Cholecystectomy	2	(M) MgSO4	57	92	107	76	86	99	89	104	68	80	99	93	110	71	84	99	97	116	74	88	98	95	113	78	90	98	99	115	76	89	99	100	118	78	91	100	3	Nil
52	Vijayakumari	60	F	52	Cholecystectomy	2	(M) MgSO4	58	74	118	89	99	100	72	117	81	93	99	79	127	87	100	100	85	132	90	104	100	83	130	92	105	100	86	132	89	103	100	88	136	91	106	100	3	Nil
53	Rajendran	40	M	55	Appendectomy	2	(M) MgSO4	51	105	127	77	94	100	100	124	73	90	99	105	125	75	92	98	110	127	77	94	98	108	124	80	95	98	109	125	76	92	98	110	129	78	95	98	3	Nil
54	Ilangovan	33	M	78	Appendectomy	2	(M) MgSO4	45	83	116	77	90	98	79	113	68	83	99	84	123	74	90	100	90	126	78	94	98	88	124	80	95	98	90	125	76	92	99	91	128	78	95	100	3	Nil
55	Nagammal	29	F	77	Cholecystectomy	2	(M) MgSO4	55	92	111	90	97	98	86	107	79	88	99	93	117	82	94	100	99	119	85	96	99	95	116	89	98	100	97	118	86	97	98	98	122	89	100	99	3	Nil
56	Sanjeevi	48	M	46	Appendectomy	2	(M) MgSO4	57	107	121	71	88	99	106	115	64	81	99	110	123	67	86	99	116	128	70	89	100	112	126	72	90	98	113	128	68	88	99	115	129	70	90	99	4	Nil
57	Balasubramanian	59	M	66	Appendectomy	2	(M) MgSO4	54	81	129	74	92	99	74	125	64	84	99	78	135	69	91	98	83	141	72	95	98	80	139	74	96	98	84	141	72	95	100	86	145	75	98	99	3	Nil
58	Jothimani	50	F	66	Cholecystectomy	2	(M) MgSO4	60	73	124	81	95	100	69	118	77	91	99	75	124	82	96	100	79	129	84	99	99	77	125	86	99	99	80	127	83	98	100	82	131	86	101	98	3	Nil
59	Nagavenni	37	F	62	Appendectomy	2	(M) MgSO4	49	89	125	87	100	97	88	122	76	91	99	93	130	79	96	99	97	136	83	101	99	95	134	85	101	98	97	136	81	99	98	99	139	83	102	100	3	Nil
60	Vinothini	49	F	64	Appendectomy	1	(M) MgSO4	57	75	129	86	100	100	68	124	81	95	99	74	126	85	99	98	80	131	89	103	99	76	126	93	104	100	77	127	90	102	98	78	129	92	104	100	4	Nil