"COMPARISON OF POSTOPERATIVE ANALGESIA WITH INTRAVENOUS INFUSION OF MAGNESIUM SULPHATE AND KETAMINE AFTER INDUCTION OF GENERAL ANAESTHESIA IN PATIENTS UNDERGOING LAPAROSCOPIC CHOLECYSTECTOMY"

Submitted by

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Dissertation submitted to the

BLDE(DEEMED TO BE UNIVERSITY), VIJAYAPUR, Karnataka

In partial fulfilment of the requirements for the award of the Degree of

DOCTOR OF MEDICINE

IN

ANESTHESIOLOGY

Under the guidance of

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LIST OF ABBREVIATIONS USED

ASA	American society of anaesthesiologists
BP	Blood pressure
CNS	Central nervous system
CO_2	Carbon dioxide
COX	Cyclooxygenase
DBP	Diastolic blood pressure
EtCO2	End-tidal carbon dioxide
FRC	Functional residual capacity
HR	Heart rate
H/h	Hours
IAP	Intra abdominal pressure
IV	Intravenous
IVPCA	Intravenous patient controlled analgesia
IVRA	Intravenous regional anaesthesia
MAP	Mean arterial pressure
Na	Sodium
NMDA	N-methyl-d-aspartic acid
NO	Nitric oxide
N_2O	Nitrous oxide
No.	Number
NSAID's	Non steroidal anti inflammatory drugs
NS	Normal Saline
PABA	P-amino- benzoic acid

PaCO2	Partial pressure of arterial carbon dioxide
PACO2	Partial pressure of alveolar carbon dioxide
PACU	Post anesthesia care unit
PCEA	Patient controlled epidural analgesia
PONV	Post operative nausea & vomiting
PR	Pulse rate
RR	Respiratory rate
SB	Systolic blood pressure
SPET	Single positron emission tomography
SPSS	Statistical presenting system software
TENS	Transcutaneous electrical nerve stimulation
VAS	Visual analogue scale
VRS	Verbal rating scale
WDR	Wide dynamic range neurons

ABSTRACT

INTRODUCTION:

Laparoscopic procedures have reduced post-operative pain compared to open procedures but still post-operative pain control is considered by many to be inadequate even in this age of minimal invasive surgery and this needs to be addressed as the need for post-operative analgesic may delay discharge and increase hospital stay. This study was designed to compare the efficacy of intra operative infusions of injection Magnesium sulphate and Ketamine for post-operative analgesia.

Aim:

To compare the analgesic effect of Magnesium sulphate and Ketamine infusions

Objectives:

a. The time lapse between the operation and the first demand of analgesia by the patient
b. Total requirement of analgesic doses for a period of 24 hrs

SUBJECTS

This randomised study was conducted on 80 adult patients undergoing laparoscopic cholecystectomy under general anesthesia randomised into 2 groups of 40 each.

METHODS:

It is a randomized controlled study of patients undergoing laparoscopic cholecystectomy, where the patients were randomly allocated into two study groups- Group M and Group K. Group- M will receive bolus of 50mg/kg followed by infusion of 10 mg/kg/h Magnesium Sulphate and Group K will receive bolus of 0.2mg/kg followed by infusion of 0.05 mg/kg/h Ketamine. The primary end points of the study

were the time lapse between the operation and the first demand of analgesia by the patient, the intensity of postoperative pain on visual analogue scale (VAS) at the time of first demand of analgesia. The secondary endpoints included the analgesia request rate in the initial 24 hours postoperatively.The statistical analysis done using Student t- test and Chi square test.

RESULTS:

The timing of first shot of rescue analgesic was significantly shorter in group M compared to group K. Significantly lower visual analogue scores were observed in group K verses group M during the initial 24 hours

CONCLUSION

Intraoperative Ketamine infusion reduced the total number of rescue analgesia than Magnesium sulphate.

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INTRODUCTION

INTRODUCTION

Laparoscopic procedures are associated with speedy post-operative recovery, early discharge and lower rates of post-operative complication and these have made it become the most admired and accepted technique in the recent past.[1, 2] Laparoscopy is not pain free procedure altogether but previous studies have shown that it is associated with lesser post-operative pain than open laparotomy.[2-10] One of the recent randomized controlled trial has publicized that there may be more intense pain and greater analgesic requirement in the immediate post-operative period after laparoscopic surgery than open laparotomy.[2]

Laparoscopic cholecystectomy is now considered the gold standard treatment and has become a benchmark technique for gall bladder surgery for symptomatic cholelithiasis. This procedure has reduced post-operative pain compared to open cholecystectomy but still there is significant post-operative pain in considerable number of patients in the first 24 hours and this needs to be addressed as the necessitate for post-operative analgesic may postpone discharge and increase hospital stay .

Surgery suppresses the immune system and that this suppression is proportionate to the invasiveness of the surgery. Good analgesia can reduce this deleterious effect. Afferent neural blockade with local anaesthetics, high-dose opioids, epidural opioids and clonidine, patient controlled opioids therapy, and nonsteroidal anti-inflammatory agents are options.[2]

Good postoperative analgesic management probably carries benefits other than increased patient comfort. The magnitude of the neuro-endocrine stress response, postoperative pulmonary complications and the incidence of myocardial ischemia can

be decreased. Early mobilisation can be achieved and the patient can be discharged from hospital sooner. [2]

Pain following laparoscopic surgery is multidimensional in nature with pain arising from the site of dissection, the pneumoperitoneum, the irritative effects of residual carbon dioxide in the abdominal cavity and prolonged elevation of diaphragm by pneumoperitoneum and that from the incision sites. Pain after laparoscopic surgery can be divided into visceral, parietal and referred pain to the shoulder. The different methods to diminish the pain include low pressure pneumoperitoneum, local wound infiltration, saline washout, a gasless technique for creating working space and instillation of the subdiaphramatic region with local anaesthetic. Shoulder tip pain appearing after laparoscopic surgery, a major aspect of total abdominal pain, is considered to be the result of stretching of diaphragm by the pneumoperitoneum, leading to neuropraxia of the phrenic nerve and local inflammatory stimuli such as ischemia, compression and chemical irritation stimulate the subdiaphramatic fibres.

On the day of surgery, pain is typically a diffuse right upper quadrant pain that may or may not be associated with right shoulder tip pain. The cause of this pain is thought to be related to abdominal muscle distension during laparoscopic procedure, irritative effects of residual carbon dioxide in the abdominal cavity and prolonged elevation of diaphragm by pneumoperitoneum.

Use of opioids for perioperative analgesia is associated with sedation, respiratory depression and postoperative nausea and vomiting. [3]

Magnesium is predominantly an intracellular ion. Its blocking effects on NMDA receptors are responsible for the analgesic and sedative characteristics of this ion. A reduction in the minimum alveolar concentration (MAC) of inhalational agents

in animals and the use of opioids in humans under anaesthesia has been demonstrated.[5,8,9,10,13]

The analgesic properties of Ketamine are related to its actions as a non-competitive N-methyl-D-aspartate receptors antagonist; these receptors present an excitatory function on pain transmission and this binding seems to prevent or reverse the central sensitisation of every kind of pain, including postoperative pain.[6,7,10,11,12] Among the adverse effects, some (for example nausea) were related to the administration of both analgesics and to the kind of surgery, others (hallucination, nystagmus, photophobia, psychomotor excitation, psychotic symptoms) were due to Ketamine, and others (respiratory depression and hypotension) could be related to opioid analgesics. [6]

AIMS AND

OBJECTIVES

AIMS AND OBJECTIVES

AIM OF THE STUDY:

To compare the analgesic effect of Magnesium sulphate and Ketamine infusion

OBJECTIVES OF THE STUDY:

PRIMARY OBJECTIVES

To evaluate,

- The time lapse between the operation and the first demand of analgesia by the patient. (The need for rescue analgesia).
- The intensity of postoperative pain on visual analogue scale (VAS) at the time of first demand of analgesia.

SECONDARY OBJECTIVES

- The analgesia request rate in the initial 24 hours postoperatively.

BRIEF HISTORY OF LAPAROSCOPIC SURGERIES

The process of inspecting the abdominal cavity through an endoscope is called laparoscopy. Initially, gynaecologists used these instruments to diagnose pelvic pain, holding the rigid telescope in one hand and looking through it with the naked eye, it was possible to manipulate a second instrument in the abdominal cavity to move abdominal structures, aspirate cysts, and apply clips to fallopian tubes for sterilization. The development of small video cameras in 1980s made it feasible for the surgeon to use both hands to position surgical instruments, furthermore one or more assistants could contribute to the procedure by sharing the same view as the surgeon[14].

Laparoscopy is becoming one of the most common surgical procedures performed on outpatient basis. Technical advantages in the field of laparoscopic surgery such as the miniaturization of instruments, the use of gasless laparoscopy, and the use of more efficient lighting techniques, will help to reduce surgical trauma and discomfort and thereby widen the scope of laparoscopy[15].

Laparoscopic surgery, one of the most obvious forms of minimally invasive surgery no doubt significantly reduced skin and muscle wounds and thereby reduces pain and immobility in the postoperative period leading to sooner recovery and shorter hospital stays. There are disadvantages to laparoscopic surgeries as well. Surgical times may be longer, especially during the learning phase. The anaesthetic management in laparoscopic surgery is challenging and as these surgeries introduce new and serious complications that do not exist or are rare with the traditional approach[15]

Laparoscopy was introduced in 20th century. In 1901, George Kelling of Germany, performed the first laparoscopic procedure in dogs and in 1910, Hans Christian Jacobaeus of Sweden performed the first laparoscopic operation in humans

and coined the term "laparoscopy" The first laparoscopic procedure done was salpingectomy in the year 1975.

In the early 1970's and 80's laparoscopy was first introduced for gynecological procedures. The first laparoscopic appendicectomy was done in the year 1981. The first Cholecystectomy was performed by Langenbuch on July 15, 1882 in Berlin[16].One hundred and four year later in 1985, Muhe performed the first laparoscopic cholecystectomy and the following year he presented to the German Surgical Congress but was greeted with outright hostility. The first laparoscopic cholecystectomy recorded in the medical literature was performed in March 1987 by Mouret, in Lyon, France[17]. Subsequently the technique was perfected by Dubois, Perrisat and Reddick and in a very short period it became the gold standard operation for conditions of the gall bladder.Various series have demonstrated that the laparoscopic approach leads to a reduction in postoperative pain and diminished postoperative hospitalization and disability. The success of any laparoscopic procedure depends on the proper selection of the case and the technical skill and experience of the laparoscopist.

The indications for laparoscopic cholecystectomy are the same as for the open method, that being "Symptomatic cholelithiasis".

A. Indications:

1. Symptomatic gallstones
2. Resolved biliary pancreatitis
3. Acalculus cholecystitis
4. Biliary colic
5. Gall bladder polyp
6. Chronic cholecystits

B. Absolute contraindication:

1. Uncorrectable coagulopathy
2. Frozen abdomen from adhesion
3. Severe cardiac dysfunction
4. Concomitant disease requiring laparotomy

C. Relative contraindication:

1. Morbid obesity
2. Prior upper abdominal surgery
3. Pregnancy
4. Chronic obstructive airway disease

PAIN PHYSIOLOGY AND MECHANISM OF PAIN

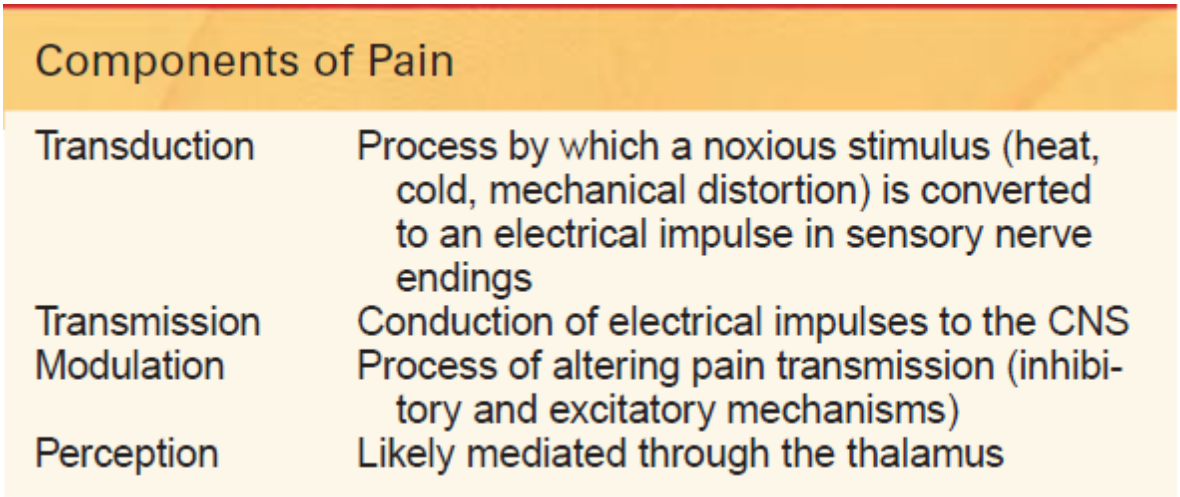
Pain is not just a sensory modality but an experience .The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage." This definition recognizes the interplay between the objective, physiologic sensory aspects of pain and its subjective, emotional and psychological components[18].

Pain is clinically divided into, acute pain which is primarily due to nociception and chronic pain, which may also be due to nociception, but in which psychological and behavioural factors often play a major role. One of the types of acute pain is the postoperative pain and can be further differentiated based on the origin into somatic and visceral pain. Somatic pain is due to nociceptive input arising from skin, subcutaneous tissues, and mucous membranes. It is characterized by being well-localized and described as sharp, pricking, throbbing or burning sensation. Visceral pain on the other hand is due to nociceptive input arising from internal organ or one of its covering. It is usually dull diffuse pain which is frequently associated with abnormal sympathetic or parasympathetic activity causing nausea, vomiting, sweating and /or changes in blood pressure or heart rate[18].

NEURO-PHYSIOLOGY OF PAIN

Pain sensation involves a series of complex neurophysiologic processes, collectively termed *nociception*.

FIGURE 1:



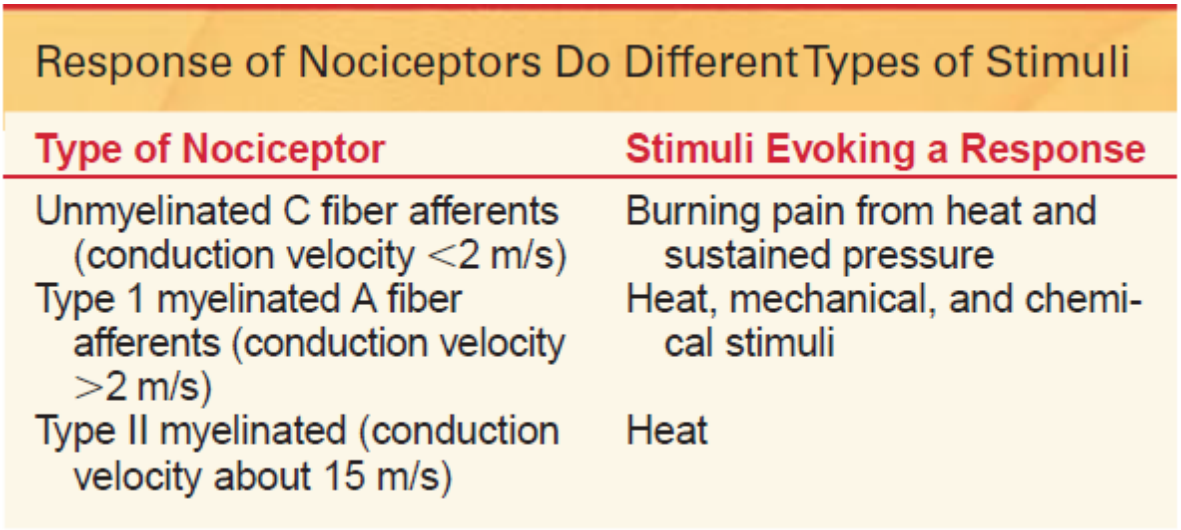
PERIPHERAL NERVE PHYSIOLOGY OF PAIN

A. **NOCICEPTORS**

Sensation is often described as either protopathic (noxious) or epicritic (non-noxious). Epicritic sensation (light touch, pressure, proprioception, and temperature discrimination) is characterized by low-threshold receptors (specialized endorgans on the afferent neurons) and conducted by large myelinated nerve fibres while; protopathic sensation (pain) is sub served by high-threshold receptors (free nerve endings)[20].

Noxious sensations can often be broken down into two components: a fast, sharp, and well-localized sensation "first pain" which is conducted by Aδ fibres; and a duller, slower onset, and poorly localized sensation "second pain" which is conducted by C fibres. This protopathic pain is transmitted mainly by free nerve endings that sense mechanical or chemical tissue damage.

FIGURE 2:



Response of Nociceptors Do Different Types of Stimuli

Type of Nociceptor	Stimuli Evoking a Response
Unmyelinated C fiber afferents (conduction velocity <2 m/s)	Burning pain from heat and sustained pressure
Type 1 myelinated A fiber afferents (conduction velocity >2 m/s)	Heat, mechanical, and chemical stimuli
Type II myelinated (conduction velocity about 15 m/s)	Heat

SEVERAL TYPES OF THIS PAIN IS RECOGNIZED

Mechano-nociceptors, which respond to pinprick, silent nociceptors, which respond only on the presence of inflammation, polygonal mechano-heat receptors which is more prevalent and respond to excessive pressure, extreme of temperature, and pain producing substances.

Nociceptors are either somatic that include those in skin and deep tissues (muscle, tendons, joints), or visceral nociceptors that include those in internal organs[19.]

B. **Sensitization of nociceptors** refers to the increased responsiveness of peripheral neurons to heat, cold, mechanical, or chemical stimulation.

1. The conditions associated with inflammation that do not resolve, resulting in sensitization of peripheral and central pain signalling pathway and increased pain sensations to normally painful stimuli (*hyperalgesia*) and the perception of pain sensations in response to normally nonpainful stimuli (*allodynia*) lead to chronic pain..

2. Nociceptors are directly activated by endogenous chemicals, neurotransmitters and peptides (such as substance P), whereas serotonin, histamine may activate the inflammatory cells which, in turn, release cytokines (FIGURE. 3).

FIGURE 3:

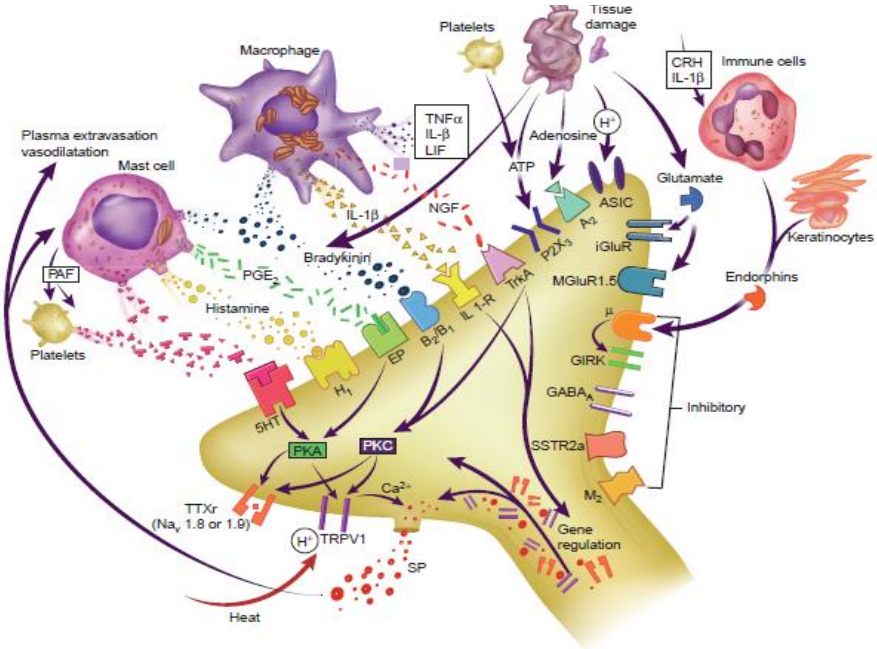


FIGURE 6-1 Cellular mechanism underlying nociceptor sensitization induced by peripheral inflammation. Activated immune cells (macrophages, mast cells, and other immune cells) and injured cells release numerous chemicals, which may directly or indirectly sensitize the peripheral nerve terminals. A_2, adenosine A_2 receptor; ASIC, acid-sensing ion channel; B_2/B_1, bradykinin receptor B_2/B_1; CRH, corticotropin-releasing hormone; EP, E-prostanoid receptor; GIRK, G protein–coupled inward rectifying potassium channel; H_1, histamine H_1 receptor; iGluR, ionotropic glutamate receptor; IL-1β, interleukin-1β; mGluR, metabotropic glutamate receptor; NGF, nerve growth factor; $P2X_3$, purinergic receptor P2X ligand-gated ion channel 3; PAF, platelet-activating factor; PGE_2, prostaglandin E_2; PKA, protein kinase A; PKC, protein kinase C; SP, substance P; SSTR2A, somatostatin receptor 2A; TNF-α, tumor necrosis factor α; TrkA, tyrosine kinase receptor A; TRPV1, transient receptor potential vanilloid receptor 1; TTXr, tetrodotoxin-resistant sodium channel; μ, mu-opioid receptor; M_2, muscarinic receptor; 5HT, serotonin; LIF, leukemia inhibitory factor.

C. **Primary Hyperalgesia and Secondary Hyperalgesia**

Hyperalgesia at the novel site of injury is termed primary hyperalgesia, and hyperalgesia in the intact skin surrounding the injury is termed secondary hyperalgesia.

CENTRAL NERVOUS SYSTEM PHYSIOLOGY.

Pain transmission is a dynamic process involving several pathways, numerous receptors, neurotransmitters, and secondary messengers (FIGURE. 4).

A. **Dorsal Horn: The Relay Centre for Nociception**

1. Afferent fibres from peripheral nociceptors enter the spinal cord in the dorsal root, ascend or descend several segments in Lissauer's tract, and synapse with the dorsal horn neurons for the primary integration of peripheral nociceptive information.
2. The central terminals of primary afferents occupy highly ordered spatial locations in the dorsal horn. The dorsal horn consists of six laminae (FIGURE. 5.

B. **Gate theory** proposes that painful information is projected to the supraspinal brain regions if the gate is open, whereas painful stimulus is not felt if the gate is closed by the simultaneous inhibitory impulses (FIGURE. 5).

C. **Central Sensitization of Dorsal Horn Neurons**

1. Peripheral inflammation and nerve injury could alter the synaptic efficacy and induce central sensitization in the dorsal horn neurons and is considered a fundamental mechanism underlying the induction and maintenance of chronic pain.
2. One form of central sensitization is windup of dorsal horn neurons, an activity-dependent progressive increase in the response of neurons over the course of a train of inputs.
3. The second form of central sensitization is a heterosynaptic, activity-dependent plasticity that outlasts the initiating stimulus for tens of minutes (FIGURE. 6).

D. **Ascending Pathway for Pain Transmission**

1. The spinothalamic tract and spinohypothalamic tract from the spinal cord to sites in the brainstem and thalamus are important for the perception and integration of nociceptive information.
2. Pain, temperature, and itch sensation are carried by the spinothalamic tract.

E. **Supraspinal Modulation of Nociception**

1. Several brain areas have been identified that are critically involved in the formation of emotional aspects of pain and the central modulation of pain perception.
2. Pain-evoked cerebellar activity may be more important in regulation of afferent nociceptive activity than in the perception of pain.

F. **Descending Pathways for Pain Modulation**.

Originate from supraspinal regions and promote and suppress nociceptive transmission through the dorsal horn (FIGURE. 7).

FIGURE 4:

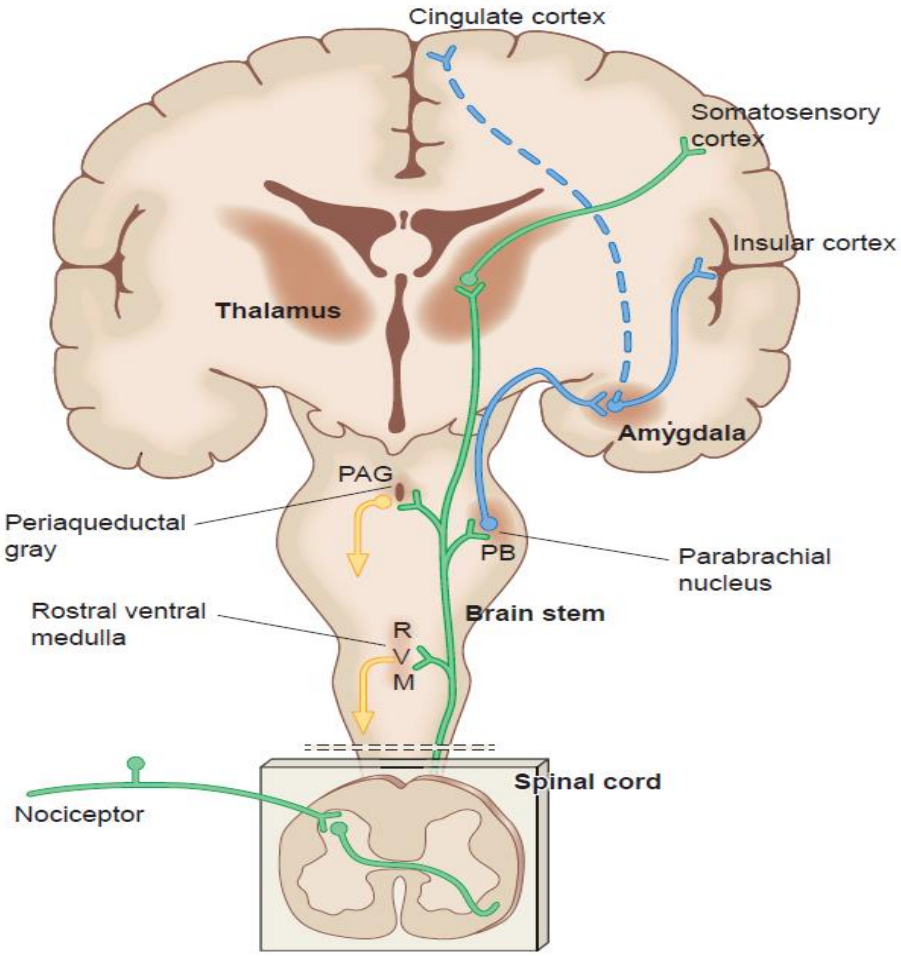


FIGURE 6-2 The projection pathway for the transmission of pain information to the brain. Primary afferent nociceptors convey noxious information to projection neurons within the dorsal horn of the spinal cord. A subset of these projection neurons transmit information to the somatosensory cortex via the thalamus, providing information about the location and intensity of the painful stimulus. Other projection neurons engage the cingulate and insular cortices via connections in the brainstem (parabrachial nucleus) and amygdala, contributing to the affective component of the pain experience. This ascending information also accesses neurons of the rostral ventral medulla and midbrain periaqueductal gray to engage descending feedback systems that modulate the transmission of nociceptive information through the spinal cord.

FIGURE 5:

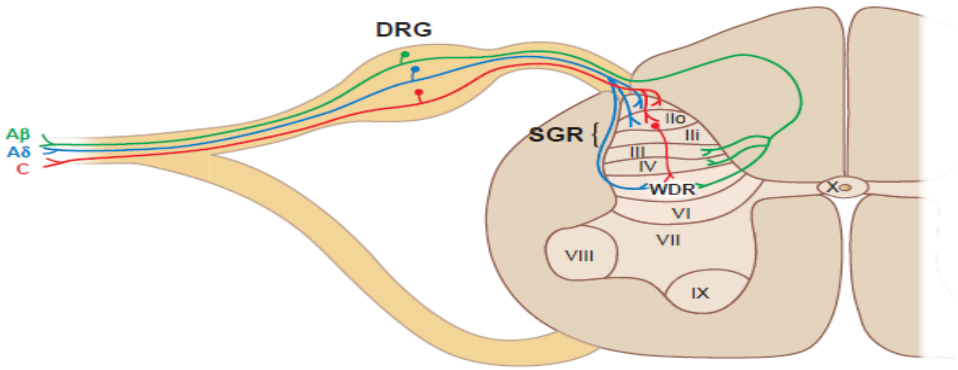


FIGURE 6-3 Schematic representation of the spinal projections of primary afferent fibers. In general, unmyelinated C fibers synapse with the interneurons in laminae I (marginal layer) and II (substantia gelatinosa of Rolando *[SGR]*). Cutaneous A-δ fibers usually project to laminae I, II, V, and A-β fibers primarily terminate in laminae III–V in dorsal horn. Large-diameter myelinated fibers innervating muscles, joint, and viscera may also terminate in laminae I, IV–VII, and the ventral horn. Second-order wide dynamic range *(WDR)* neurons are located in lamina V and receive input from nociceptive and nonnociceptive neurons.

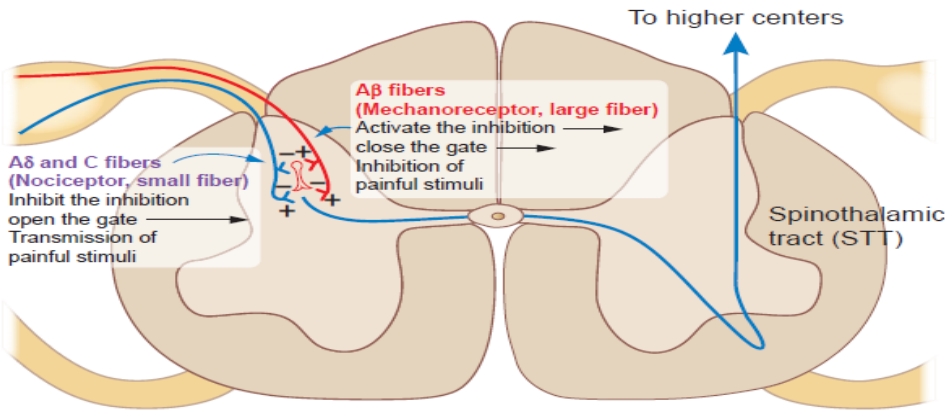


FIGURE 6-4 Illustration of gate theory for pain modulation in spinal dorsal horn. Lightly rubbing the skin of a painful, injured area seems to somehow relieve the pain. Large-diameter myelinated afferents (Aβ) conveying pressure and touch information have "faster" conduction speed than A-δ fibers or C fibers conveying painful information to the dorsal horn. Thus, the application of light peripheral mechanical stimuli resulting in excitation of A-β fibers can activate the inhibitory interneurons in the dorsal horn and thus close the "gate" to the simultaneous incoming pain signals carried by A-δ fibers and C fibers. Although the gate control theory is overly simplistic, it remains a valid conceptual framework for understanding pain and pain-related experiences.

FIGURE 6:

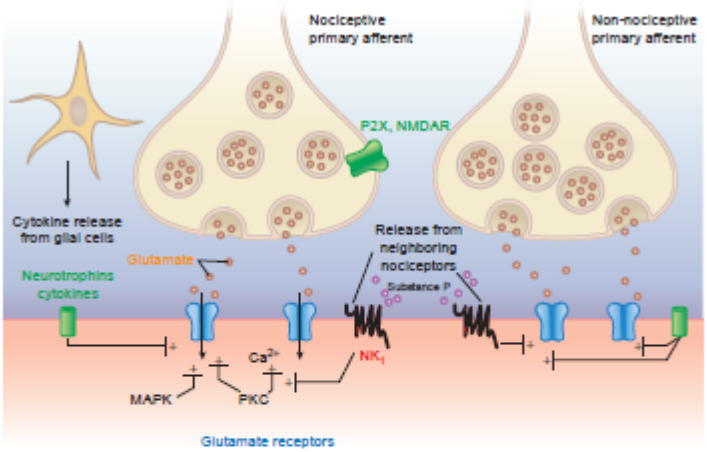


FIGURE 6-5 The synaptic mechanism underlying peripheral, nociceptive, stimuli-induced, and persistent heterosynaptic potentiation of dorsal horn neurons. Transmitters and mediators released from primary afferents and surrounding microglial cells, including substance P, neurotrophins, and cytokines may act at a distance on dorsal horn neurons to produce long-lasting heterosynaptic potentiation of glutamatergic transmission. Note that both inputs from nociceptors and nonnociceptors may be potentiated. *MAPK*, mitogen-activated protein kinase; *P2X*, purinoceptor; *PKC*, protein kinase C; *NK1*, neurokinin 1 (substance P receptor).

FIGURE 7:

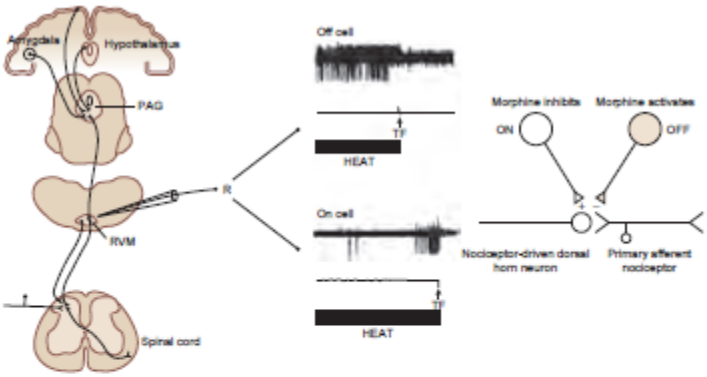


FIGURE 6-6 Properties of proposed medullary pain-modulating neurons. Single-unit extracellular recordings were performed by microelectrodes placed in the rostral ventromedial medulla *(RVM)* while peripheral noxious stimuli (heat) were applied. As shown by the oscilloscope sweeps, the firing of the off-cell pauses just prior to the tail flick reflex (indicating pain sensation) in response to noxious heat, whereas the typical on-cell firing occurs before the tail flick. The right diagram illustrates that both on and off cells project to the spinal cord, where they exert bidirectional control over nociceptive dorsal horn neurons.

V. Transition from Acute Pain to Chronic Pain

A. Following any injury acute pain and the accompanying sensitization do not typically persist after the initial injury has healed. In contrast, chronic pain is persistent pain that persists after all tissue healing appears to be complete and extends beyond the expected period of healing.

B. There is no clear delineation between when acute ends and chronic pain begins. Two common and practical cut off points are often used, 3 months and 6 months after initial injury, because the likelihood that the pain will resolve diminishes with time and the likelihood that chronic pain will persist rises.

C. Neurobiologic basis of the transition from acute pain to chronic pain is the sensitization of peripheral and central nociceptive neurons.

VI. Some Specific Types of Pain

A. **Neuropathic pain** is pain that persists after tissue injury has healed and is characterized by reduced sensory and nociceptive thresholds (allodynia and hyperalgesia).

1. Cancer patients are at increased risk of neuropathic pain caused by radiotherapy or a variety of chemotherapeutic agents.
2. Current treatments (opioids, Gabapentin, Amitriptyline, and medicinal Cannabis) for neuropathic pain are only modestly effective.
3. The pathophysiologic processes that lead to neuropathic pain have the hallmarks of a neuroinflammatory response following innate immune system activation.

B. **Visceral pain** is diff use and poorly localized (somatic pain localized and characterized by distinct sensations), typically referred to somatic sites (muscle and skin), and it is usually associated with stronger emotional and autonomic reactions.

1. Among all tissues in the body, the viscera are unique in that each organ receives innervation from two sets of nerves, either vagal and spinal nerves or pelvic and spinal nerves, and the visceral afferent innervation is sparse relative to somatic innervation.
2. The vagus afferent innervation plays an important role in the prominent autonomic and emotional reactions in visceral diseases associated with pain (FIGURE. 8).

PAIN PATHWAY

Pain is conducted along three neuron pathways; from the periphery to the cerebral cortex.

FIRST ORDER NEURON

Cells of these neurons are located in the dorsal root ganglia (for the body) and specific cranial nerve ganglia (for the head and neck) e.g Gasserian ganglion for trigeminal nerve. The Proximal end of their axons reach spinal cord via the dorsal sensory root of cervical, thoracic, lumbar, and sacral level (for the body) and through the cranial nerves (for head and neck).

SECOND ORDER NEURONS

Pain fibres may ascend or descend three spinal cord segments in the Lissauer‟s tract before synapsing with the second order neuron in the gray matter of the ipsilateral dorsal horn, this synapsing may be through interneurons. Second order neurons are either; nociceptive specific which serves only noxious stimuli and are normally silent or wide dynamic range (WDR) neurons that can receive also non-

noxious afferent input. WDR neurons are more prevalent in the dorsal horn and are responsible for the increased intensity of firing in response to same stimulus "wind-up".

Lamina II of the gray matter of the dorsal horn of the spinal cord, (also called the substantia gelatenosa) contains many interneurons and is believed to play a role in the processing and modulating nociceptive input.

Axons of most of the second order neurons cross the midline to the contra-lateral side of the spinal cord forming the lateral spinothalamic tract that send its fibres to the thalamus, the reticular formation, nucleus raphe and periaquidactal gray[21,22].

THIRD ORDER NEURONS

Those are located in the thalamus and send their fibres to the somato-sensory area I and II in the cerebral cortex[23].

FIGURE 8:

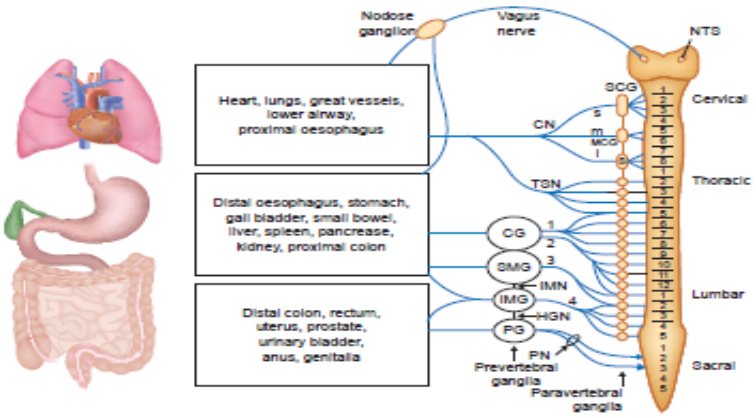


FIGURE 6-7 Visceral innervation. The vagus nerve, with cell bodies in the nodose ganglion and central terminals in the nucleus tractus solitarii *(NTS)*, innervates organs in the thoracic and abdominal cavities. Afferent nerves with terminals in the spinal cord innervate the same thoracic and abdominal organs as well as those in the pelvic floor. Visceral spinal afferents pass through pre- and/or paravertebral ganglia en route to the spinal cord; their cell bodies are located in dorsal root ganglia (not illustrated). Prevertebral ganglia: *CG*, coeliac ganglion; *SMG* and *IMG*, superior and inferior mesenteric ganglia, respectively; and *PG*, pelvic ganglion. Paravertebral ganglia: *SCG* and *MCG*, superior and middle cervical ganglia, respectively; and *S*, stellate ganglion. Nerves: *CN*, cardiac nerves (s, m, and i, superior, middle, and inferior, respectively); *TSN*, thoracic splanchnic nerves; *1, 2, 3* and *4*, greater, lesser, least, and lumbar splanchnic nerves, respectively; *IMN*, intermesenteric nerve; *HGN*, hypogastric nerve; and *PN*, pelvic nerve.

PAIN ASSESSMENT AND MANAGEMENT

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage."[24]

It is well recognized that a considerable variability both across patients and within a patient across time has been displayed in pain intensity. In order to diagnose pain and to determine the effectiveness of treatment interventions it is important that pain measurement and discerning factors that may affect its measurement are to be considered.

Gracely and Dubner(1981) proposed five properties of an ideal pain measurement system that have theoretical and practical advantages[25].Currently, most of the pain measurement instruments used in clinical set up though do not fully satisfy all the properties are unidimensional and focus more on acute pain.

As the pain is subjective, personal experience, logical and true assessment of patient's pain must be the patient's own report. Self report is the gold standard in pain measurement[26.]

MEASUREMENT OF PAIN

Pain measurement is done by two methods

(1) Type I methods:

Those are objective methods, done by the physician as he assigns numbers about the patient condition. It includes the following:

Physiological indices:

Endocrinal (increase in serum cortisol and catecholamine).

Cardiovascular (increase in blood pressure and heart rate)

Respiratory (increase in respiratory rate and decrease in tidal volume)

Neuro-pharmacological:

Correlation with beta endorphin (decreased in acute painful conditions)

Thermography (hypo-emission in chronic pain)

Neurological:

Nerve conduction velocity

Evoked potentials

Single positron emission tomography (SPET).

Behavioural:

Sighing, crying, shouting, trembling.

(2)Type II methods: It includes either:

Single dimension methods:

- Category scale (verbal rating scale)
- Numerical rating scale
- Graphic rating scale

Multi-dimensional methods:

- Mc Gill pain Questionnaire, MPQ
- Dartmouth pain Questionnaire, DPQ
- West Haven-Yale pain Questionnaire, WHYPQ.

Measurement of pain in clinical practice depends largely on verbal dialogue between the patient and the doctor or nurse. A rating scale is mandatory in research projects and ideally when clinical data are being collected.

Although pain is a subjective experience, great attention has been paid to the quantification of this experience. As pain is subjective experience, everyone has different perceptions of that experience. Differences are found in how individuals quantify pain. For example, some individuals would never say that their pain was a 10 on a scale from 0 to 10. On the other hand, other individuals report their pain as a constant 10 despite looking calm and relaxed. Also, all numeric scales used to measure pain have floor and ceiling effects. If the patients describe their pain to be a 10, there is no way to report an increase in pain intensity.

A number of individual differences between patients make comparisons of pain measurements more difficult. For example, the past experiences of the patients influence their present perception of pain. Also, demographic factors such as gender, age, and ethnic background influence the individual's perception of pain. Again, patients who are clinically depressed and anxious tend to report increased pain intensity[27].

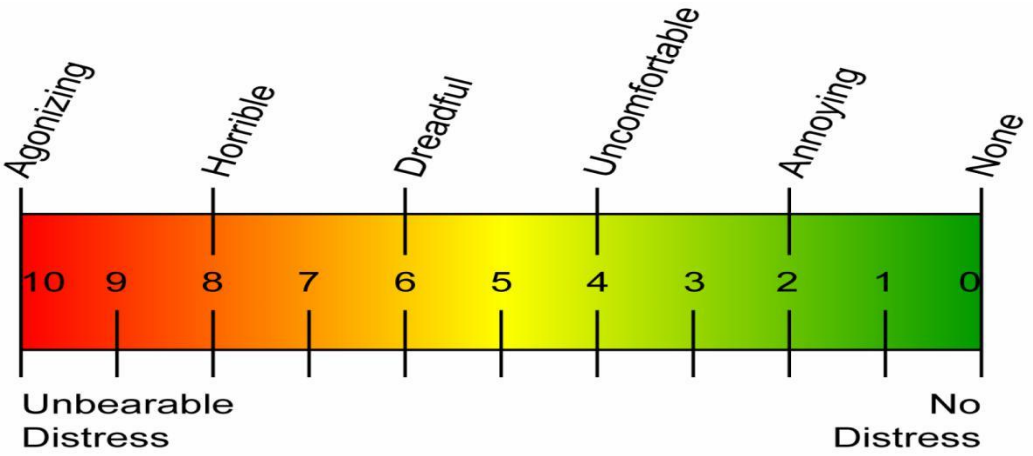
The unidimensional pain scale that can measure pain intensity and are self reported by the patients are Verbal Rating Scale (VRS), Numerical rating scale and Visual analogue scale (VAS) and in our hospital setup they are the most easily

applicable pain scales considering the rural population that forms the majority of patient population here.

The Visual Analogue Scale (VAS):

The visual analogue scale uses a straight line with extremities of pain intensity on either end. The line is typically 10 cm long with one end defined as "no pain" and the other end being "excruciating unbearable pain". The line can be either vertical or horizontal. The patients are asked to place a mark on the line to describe the amount of pain that they are currently experiencing. The distance between the end labelled "no pain" and the mark placed by the patient is measured and rounded to the nearest centimetre. To assist in describing the intensity of pain, words can be placed along the scale (e.g., mild, moderate, or severe). Such descriptors can help to orient the patient for the degree of pain; this particular variation of the VAS has been known as a graphic rating scale. Explanation to the patient is needed by the clinician when using the VAS. Occasionally, the patient may be confused about the line, perceiving it to represent time of degree of relief rather than degree of pain intensity.

FIGURE 9: VISUAL ANALOGUE SCALE



The strength of VAS is that it is simple and is easily reproducible on successful presentations. Several biases affecting psychophysical responses alter the

responses to VAS. Lack of certain amount of visual and motor coordination in postoperative period may modify the results.

The Verbal Rating Scale:

Verbal rating scales are another means of assessing the varieties and intensities of pain. A verbal rating scale uses a list of words from which patients choose descriptors of their pain. There are a number of different verbal rating scales including four-item scales, five-item scales, six-item scales, 12-item scales, from the least intense to the most intense. The Prince-Henry pain scale is the most popular scale; it is a 5- point scale, words are often ranked according to severity and numbered sequentially from the scale which quantifies pain from 0 to 4 as shown below:

0 No pain on coughing

1 Pain on coughing but not on deep breathing

2 Pain on deep breathing but not at rest

3 Mild pain at rest

4 Severe pain at rest

The strength of VRS is the ease with which it can be administered and scored. It assumes equal interval between the adjectives and does not allow for finer grade pain assessments and it lacks sensitivity which are the limitations of this scoring method.

Factors affecting pain measurement

Many studies have showed that various factors affect the perception of pain.

1. Patient's beliefs
2. Doctor's beliefs
3. Age and sex
4. Placebo effects
5. Cultural background

It is well appreciated fact that doctor's negative or positive feedback greatly influences a patient's pain perception and pain reporting.

There appear to be no racial/ethnic differences in the ability to discriminate painful stimuli. The difficulties inherent in the translation of pain descriptors across cultural boundaries make pain tolerance, rather than pain threshold, the more relevant transcultural pain measure.[28]

Experimental evidence suggests that the threshold at which a given stimulus is perceived as painful is relatively constant both for an individual and between individuals. However, higher thresholds at which pain described as severe or at which particular behavioural response occurs are much more variable and appear to depend on cultural factors.[29]

The epidemiological surveys of patients with pain and in clinical studies of response to pain have shown that the apparent gender differences have been identified in pain tolerance and women are reported to have lower pain threshold than men.[30]

The variations in pain experiences are also greatly associated with patient's age.[31]

Therefore, while assessing pain, one should take into account of the factors known to influence pain measurement. The measure is reliable and valid for the chosen age group of patients and practical in the clinical situation and that it is appropriate for the type of pain being assessed.

Clinical correlation to the pain measurement and individualized treatment is a must for good pain management.

Pain after Laparoscopic Cholecystectomy

Laparoscopy is a convincing alternative to open surgery for a range of procedures in various surgical specialities. The smaller incisions, lower morbidity and mortality, reduced length of hospital stay faster recovery and earlier return to normal activities and work are the advantages of Laparoscopy over open surgery.[32-34]

Laparoscopic surgery has the greatest advantage compared with open surgery of reduced postoperative pain. However, after laparoscopy patients frequently describe sub diaphragmatic and shoulder tip pain in addition to the discomfort of port site. [35, 36] Some authors have reported that 80% of patients require opioid analgesia after laparoscopic surgery.

Recent advances in the pathophysiology of pain have shown that the enhanced postoperative pain due to central neural hyper excitability can be reduced or prevented.[37,38]

Experimental studies have demonstrated pain hypersensitivity can result from post injury neuroplasticity and windup or expansion of receptive fields of central nervous system neurons.[39]

Animal studies have demonstrated that behavioural response and neuronal sensitization of posterior horn neurons can be modified by an afferent block with local anaesthetics performed "before nociceptive stimuli are triggered".[40]

As far as studying postoperative pain in humans is concerned, none of these study models can be applied fully or have a concrete clinical application. The most common complaint after laparoscopic cholecystectomy is the early pain and its intensity is subjective.[41]There is still room for surgeons to improve management of post laparoscopy pain. First, patients' satisfaction of less postoperative pain. Second, better pain control would result in early discharge and shorter recovery time.

The pattern of pain after laparoscopic cholecystectomy is complex and does not resemble pain after other (laparoscopic) operations, so all type of laparoscopic procedure is not likely to benefit from identical analgesic treatment.[42]

Pain after laparoscopy multifactorial, may be short-lived or it may persist for at least 2 days. After laparoscopic cholecystectomy, visceral pain was found to predominate in the first 24 hours, whereas shoulder pain, on the first day is less severe, increases and becomes significant on the following day.

Mechanism of pain in laparoscopy:

In addition to the trauma caused to the abdominal wall and the visceral organs by the endoscope and the surgical instruments, there are other mechanisms responsible for pain after laparoscopy. Inflammatory mediators are released following tearing of blood vessels, traumatic traction of the nerves due to rapid distension of the peritoneum. The upper abdominal pain after lower abdominal surgery or after diagnostic laparoscopy may be a result of peritoneal inflammation which persists for at least 3 days. Evidence of peritoneal inflammation and neuronal rupture was found on peritoneal biopsy performed 2-3 days after laparoscopy and there was a linear inverse relationship between severity of postoperative pain and abdominal compliance at the time of laparoscopy.

Therefore, abdominal distension should better be slow with adequate muscle relaxation to ensure suitable abdominal compliance. The prolonged presence of shoulder tip pain suggests excitation of the phrenic nerve that is caused by the persistence of gas in the abdomen (pneumoperitoneum). There is statistically significant association between the pain score and the width of the gas bubble, and the aspiration of the gas under the diaphragm can be reduce this pain.

A) Factors associated with gaseous pneumoperitoneum

1. Neuropraxia of the phrenic nerve: It has been suggested that the postoperative pain results from the phrenic nerve neuropraxia following distension of the diaphragm during gas insufflations, which may include the related C4 dermatome.
2. The type of insufflated gas and intra-abdominal pH: the dissolution of CO_2 creates the acid milieu which damages the phrenic nerves. The intraperitoneal pH was 6.0 when CO_2 gas is insufflated and measured in the immediate postoperative period. The pH rises to 6.4 – 6.7, and to 6.8 – 6.9 on the 1^{st} and 2^{nd} postoperative day respectively. Thereafter it normalizes to above 7.0.[43] Similar values were found when argon gas was substituted.
3. Residual intraabdominal gas: Pain after laparoscopy can also be due to residual intraabdominal gas after the procedure, loss of peritoneal surface tension and support to the abdominal viscera.[44,45] If the gas is not evacuated at the end of the laparoscopic procedure for a longer period there will be dissolution of carbon dioxide resulting in intra-abdominal acidosis, and the consequent peritoneal irritation.
4. Temperature of gas: A prospective randomized study of standard insufflation gas (20 degree C) versus gas at body temperature was carried out to study the effect of gas temperature on postoperative pain after gynaecologic laparoscopic procedures. This study found that diaphragmatic and shoulder tip pain reduction was significantly greater for those patients in whom warmed gas was used, with the lasting effect of 3 days.[46]

5. Humidity of gas: In order to investigate the outcome when humidified gas was insufflated during laparoscopic cholecystectomy instead of standard dry gas, a prospective randomized controlled trail was conducted at the Queen Elizabeth Hospital, Adelaide.[45] The humidified insufflation showed significantly reduced postoperative pain, a trend of less post operation analgesic consumption, along with shorter hospital stay and earlier return to work.

The animal studies have observed that dry gas insufflation is implicated in ultrastructural damage to exposed membranes, an effect that was not seen with the use of humified gas The exact relation between dry gas and postoperative pain is not yet determined.

B:Operational factors:

1. Wound pain: From center to centre and for different procedures, the number, site and size of the incisions used vary. In both open and laparoscopic procedures, local anaesthesia administration to the wound created, is recommended by many authors to reduce significant amount of pain, minimal side effects are anticipated, and the use of local anaesthesia is recommended.[47]

2. Wound drainage: In the lateral aspect of the abdomen, traversing muscle layers wound drains after laparoscopic surgery usually is sited. Due to a greater incidence of pain, infection, and potential incisional herniation at this site if the defect is not formally closed, the umbilical incision is less commonly used. It is recommended to carefully individualize the wound drainage, rather than doing it as a routine consideration.

C. Sociocultural and individual factors:

A study comparing the course after laparoscopic cholecystectomy in French and American patients effectively demonstrated how the sociocultural environment affects hospital stay and recovery time and that this variable encountered on almost a daily basis by most surgeons. In 73 % of the French and in 93% of the Americans post operation discomfort resolved within 2 weeks. A higher percentage of the Americans returned to work in a given period than did the French patients.[48] The individual postoperative pain perception and recovery time has been influenced by previous pain experiences and individual thresholds despite the best practices.

Postoperative pain is localized to the epigastrium and right upper quadrant, in direct relation to the port sites and the area between them. Several studies have described pain according to the presumed mechanism; visceral pain which can be theoretically be blocked by intraperitoneal infiltration and parietal pain, which can be blocked by port site infiltration.

The hypothesis of several trials published in the last decade has shown that in the early postoperative period, clinically relevant postoperative pain relief can be achieved with peripheral use of local anaesthetics after laparoscopic surgery.

There is a substantial interindividual variation in the incidence and intensity of pain after laparoscopic cholecystectomy. The intensity of pain after laparoscopic cholecystectomy peaks within the first few hours, and the pain is more severe compared to patients undergoing laparotomy. But however, by 24 hrs laparoscopy shows less pain than laparotomy. It involves three different components with different intensity, time course and pathophysiological mechanisms. These pain components are incisional pain (parietal pain component); deep intra-abdominal pain (visceral pain component) and shoulder tip pain (presumed referred visceral pain.).[49]

Several surgical factors such as port incisions, the use of intraabdominal gas, and intraabdominal surgical manipulation may influence pain after laparoscopic cholecystectomy and have been investigated in various randomized controlled studies

MANAGEMENT OF POSTOPERATIVE PAIN

PROPHYLACTIC MEASURES

The proper preoperative and postoperative surgical and psychological care reduces the incidence, severity, and duration of pain and suffering during the postoperative period. The role of psychological techniques in the relief of acute pain has been minimized, although the accepted definition of pain emphasizes the cognitive, emotional response to tissue damage. Recovery, postoperative pain and psychological distress after surgery can be improved by psycho educational care.

Through health-care information (information in preparation for surgery, timing of procedures, function and roles of health-care providers, self-care actions, and pain and discomfort information); psychosocial support (identifying and alleviating concerns, reassurance, problems solving, and encouraging questions and skills teaching (coughing, breathing and bed exercises, relaxation, hypnosis) Psycho educational care was classed.

The severity of postoperative pain can be decreased by optimal surgical care, carrying out the operation with dispatch and observance of other surgical principles, skilful and gentle handlings of tissues assist to minimize trauma. The magnitude of postoperative pain can be decreased by proper postoperative care which involves continuing psychological support, early ambulation, proper care of wounds and of course good nursing care.[50]

ACTIVE MEASURES

Postoperative pain can be partially or completely relieved by one of the following methods:

I. Systemic analgesics and adjuvant drugs

II. Local infiltration and field block

III. Regional analgesia with local anaesthetics

IV. Regional analgesia with combined local anaesthetics and opioids

V. Electrical analgesia achieved with transcutaneous electrical stimulation or electroacupuncture[53]

I. SYSTEMIC ANALGESICS AND ADJUVANT

DRUGS: A. NARCOTICS

Exogenously administered opioids produce analgesia by the actions similar to that of endogenous opioid peptides (enkephalins, B-endorphins and dynorphins) at specific receptors within the CNS. Pharmacological studies led to the proposal of five classes of opioid receptors. Each receptor mediates a spectrum of pharmacologic effects.[51]

All opiates in clinical use produce analgesia via the same molecular mechanism, i.e., binding to G-protein coupled opioid receptors with subsequent inhibition of adenylate cyclase, activation of inwardly rectifying K-channels, and inhibition of voltage-gated Ca-channels, all of which decrease neuronal excitability[52].

Whatever the route of administration of analgesics the prime interest is to provide effective sustained pain relief, with minimal side effects. Optimal doses of narcotics given to patients in pain depress the respiratory centre slightly; they decrease the ventilation/perfusion abnormality and thus improve oxygenation of arterial blood, equally important the fact that pain relief permits patients to breath more deeply and to cough somewhat better when they are instructed by nursing and surgical staff.

Although opioid analgesics are effective in treating postoperative pain, concerns regarding their ability of increase nausea and vomiting and to produce respiratory depression have limited their use during laparoscopic procedures.[54]

ROUTES OF ADMINISTRATION:

There is a wide inter-subject and intra-subject variability in the relationships of opioid dose, serum concentration, and analgesic response in the treatment of postoperative pain; e.g., intramuscularly administered narcotics may result in a wider variability in serum drug concentration than other intravenously administered one, on the other hand , intravenous route provide good and rapid analgesia but produce marked respiratory depression and thus the patient must be observed for 15-20 minutes after first injection to assess pain relief and undesirable side effects.[55]

INTRAVENOUS PATIENT CONTROLLED ANALGESIA

A significant improvement in postoperative analgesia was the development of appropriate delivery system that allows the use of intravenous patient–controlled analgesia (IVPCA). Pumps used allow the patient of inject a small bolus of an intravenous opioid drug whenever he or she feels pain, thus maintaining the analgesic book level in the appropriate range, pumps also has got a "lock-out" system which provides an adequate time delay for the patient to achieve analgesia from each injected dose, and also guards against over dosage that can lead to respiratory depression. Recent machines also provide a continuous infusion of analgesic which give the patient uninterrupted sleep but can lead to an increase in the total quantity of analgesic given.[56] Morphine is the least expensive and perhaps the most popular, but the development of side effects (pruritis, nausea, dysphoria) may require switching to an alternative.[57]

The use of oral opioid; immediate and sustained release preparations provides quick and effective analgesia and can be used to bridge the analgesic gap that is often apparent after patient-controlled analgesia has been stopped and the simple analgesics begins.

Transdermal opioids (Fentanyl patches) provide excellent alternative, especially when oral route is not allowed. Transdermal route avoids hepatic first-pass metabolism and provide analgesia for 2-3 days , however its slow onset and the inability to rapidly change dosage in response to changing opioid requirement can limit its use.

PERIPHERAL OPIOID ANALGESIA

The central nervous system actions of opioids are responsible for the majority of opioid-related side effects. Recent work has concentrated upon on peripheral sensory nerves, endogenous opioid agonist production by inflammatory leukocytes, and work on the development of novel selectively peripherally acting opioid agonist. Inflammatory cells migrate to and deliver opioid peptides to the receptors expressed by the sensory nerve terminal at the site of tissue damage and play a major role in peripheral opioid analgesia.[58]

The extravasated inflammatory cells get attracted to injured and inflamed tissues thereby leading to production of opioids which is governed by corticotrophin releasing hormone, interleukin-1B and catecholamines. Interestingly, the recruitment of opioid- producing inflammatory cells to damaged tissues is effectively modulated by central afferent nerve blockade. However studies have demonstrated that only in the presence of inflammation, the analgesic effect of peripherally applied opioids is apparent. Clinical studies have established that significant analgesia with minimal side-effects can be produced with small doses of morphine applied peripherally to the site of tissue damage.[59]

PHARMACOLOGICAL PROPERTIES OF NARCOTICS:

CNS EFFECTS:

Opioids eliminates pain, depresses respiration, suppresses cough, stimulates the third nerve nucleus causing miosis and stimulates the chemoreceptor trigger zone causing nausea and vomiting.[60]

HAEMODYNAMIC EFFECTS:

Opioids cause bradycardia and decrease the sympathetic tone.[61]

SMOOTH MUSCLE EFFECTS:

Opioids stimulate circular smooth muscles causing biliary colic, retention of urine and bronchial constriction which is also partly due to histamine release.

Tolerance: When tolerance develops to a particular opioid, cross-tolerance to other opioids concomitantly develops.[62]

B. NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

Non-steroidal anti-inflamatory drugs (NSAID) block the synthesis of prostaglandins by inhibition of the enzyme cyclo-oxygenase. Cyclo-oxygenase enzyme catalyzes the conversion of arachidonic acid to the cyclic endoperoxide, which are the precursors of prostaglandins. Prostaglandins mediate several components of the inflammatory response including fever, pain and vasodilatation. NSAID differ in potency with respect to their analgesic, anti-inflammatory and antipyretic properties.

NSAIDs have traditionally been used to relieve pain after minor surgery or have been prescribed two or three days after major surgery when the more powerful analgesics have been withdrawn. NSAIDs have been used early in the setting of major surgery in combination with opioids, and the quality of analgesia from these combinations have been shown to be better than that achieved by opioids alone.

Moreover, it has consistently been shown that NSAIDs given soon after major surgery reduce opioid requirements by about one third.

The three major problems associated with NSAID therapy are

- Gastropathy,
- Impaired hemostasis
- Nephrotoxicity.

All are directly related to inhibition of prostaglandin synthesis. NSAIDs can also have idiosyncratic side effects that are not prostaglandin-mediated. Such idiosyncratic reactions are rare but can be serious. These may include exacerbation of bronchospasm, bone marrow toxicity, dermatological reactions, hepatitis and CNS symptoms.

C. INTRAVENOUS PARACETAMOL

Acetaminophen (also known as Paracetamol) when it is administered in analgesic dosages, is the safest and most cost-effective non-opioid analgesic. Although both parenteral and rectal acetaminophen produces analgesic effects in the postoperative period, concurrent use with a NSAID is superior to acetaminophen alone. There is increasing evidence of a central antinociceptive effect, and potential mechanisms for this include inhibition of a central nervous system COX-2, inhibition of a putative central cyclooxygenase "COX-3" that is selectively susceptible to Paracetamol, and modulation of inhibitory descending serotinergic pathways. Paracetamol has also been shown to prevent prostaglandin production at the cellular transcriptional level, independent of cyclooxygenase activity. Paracetamol is therefore an effective postoperative analgesic, with potency slightly less than a standard dose of morphine or the NSAIDs. The introduction of an I.V preparation and reports of the

analgesic and anti-inflammatory properties and safety advantages of a nitric oxide (NO)-releasing form may represent significant advances in the use of this drug.[63]

D. ALPHA-2 ADRENERGIC AGONISTS

Clonidine also improved and prolonged central neuraxial and peripheral nerve blocks when administered as part of multimodal analgesic regimens. For example, epidural infusion of clonidine in combination with Ropivacaine improved analgesia after major abdominal surgery in children. However, when used to treat postoperative pain, clonidine (0.3 mg IV) was apparently ineffective.[64]

Dexmedetomidine is a pure alpa 2-agonist that also reduces postoperative pain and opioid analgesic requirement. However, its use was associated with increased postoperative sedation and bradycardia.[65]

E. MISCELLANEOUS NON-OPIOID COMPOUNDS

Adenosine, Droperidol, Neostigmine and Gabapentin are non-opioid pharmacologic compounds used during the perioperative period that have been alleged to possess analgesic-sparing properties.

Gabapentin (a structural analogue of gamma-aminobutyric acid) is an anticonvulsant that has proven useful in the treatment of chronic neuropathic pain and may also be a useful adjuvant in the management of acute postoperative pain. For example, premedication with Gabapentin (1.2 g PO) reduced postoperative analgesic requirement significantly without increasing side effects.[66]

Neostigmine, a cholinesterase inhibitor, has been reported to possess analgesic properties when doses of 10–200 μg were administered in the subarachnoid or epidural spaces. Although peripherally administered Neostigmine failed to produce postoperative analgesia, epidural administration of Neostigmine (1 μg/kg) produced more than 5 h of pain relief after knee surgery. The primary adverse effects associated

with neuraxial Neostigmine appear to be mild sedation, postoperative nausea and vomiting (15%– 30%).[67]

Inositol triphosphate, a new anti-inflammatory drug reduced postoperative pain and the need for opioid analgesics after cholecystectomy surgery.

II. LOCAL INFILTRATION AND FIELD BLOCK

Infiltration of the wounds with dilute solution of Bupivacaine or use of rectus block for abdominal incision has been found effective in partially relieving postoperative pain after laparoscopy. Nevertheless, supplemental intraoperative analgesia as well as effective analgesia in the early postoperative period after emergence from anaesthesia with preincisional local anaesthetic administration offers an obvious advantage over infiltration at the end of surgery.

REGIONAL ANALGESIA WITH LOCAL ANAESTHETICS

Epidural anaesthesia may be performed at any one of the four segments of the spine (cervical, thoracic, lumbar, and sacral). Sacral epidural anaesthesia is usually referred to as caudal anaesthesia. Thoracic epidural analgesia is technically more difficult and the possibility of injury to the spinal cord is greater.

III) CONTINUOUS SEGMENTAL EPIDURAL BLOCK

The dosing regimen for epidural analgesia can be controlled by the patient. This is the technique of "patient-controlled epidural analgesia (PCEA)". With this technique an adequate sensory block must first be initiated with a bolus injection(s). The block is then maintained either by demand injections alone or by a background infusion plus demand injections signalled by the patient as soon as there is a recurrence of minimal or undesired discomfort. Advantages of this technique include the ability to minimize drug dosage, flexibility and benefits of self-administration, and reduced demand on professional time. The used pump must be able to give a

continuous set infusion rate, to give demand doses with set lockout periods, and to limit a total dose over a set period of time.

B) INTERPLEURAL ANALGESIA

Interpleural regional analgesia consists of the installation of local anaesthetic in the space between the parietal and visceral pleura through a catheter. The injection may be single, intermittent, or a continuous infusion. The technique is becoming increasingly popular in the treatment of postoperative pain after surgery involving thoracic dermatomes, e.g. cholecystectomy, splenectomy, nephrectomy, breast surgery, and chest wall operations.

Analgesia after interpleural administration of local anaesthetics seems to be due to the diffusion of the drug through the parietal pleura into the subpleural and then the paravertebral space, where the intercostals nerves are only covered by the parietal pleura, i.e. the effect is via multiple intercostals nerve blockade.

Bupivacaine has been the most widely used local anaesthetic for interpleural analgesia. A dose of 20 ml of 0.25% in a normal adult provides analgesia lasting for 3-5 hours after cholecystectomy.

Addition of Adrenaline can prolong the duration of analgesia and decrease the absorption of the drug into the systemic circulation which may cause systemic toxicity.

Contraindications to interpleural catheter placement are those conditions that make the risk of lung puncture and/or local anaesthetic toxicity unacceptably high. For example, pleural effusion, pleural fibrosis, pleura inflammation (recent pneumonia), lung malignancy, and anticoagulation and bleeding diathesis.

The chief complications of interpleural analgesia are pneumothorax and local anaesthetic toxicity. Other complications of the technique include haemothorax, Horner's syndrome and, rarely, pleural effusions.

C) INTRAPERITONEAL ANALGESIA

Intraperitoneal instillation of local anaesthetics is another simple, yet effective, technique for providing pain relief during the early postoperative period after laparoscopic procedures. It was found that the response to intraperitoneal local anaesthetics is mediated by local peritoneal effects rather than by systemic absorption. Addition of adrenaline to intraperitoneal local anaesthetic led to a lower peak serum concentration of drug and a delayed time to reach peak serum concentrations when compared to the plain solutions.[68]

Variable analgesic effects of infiltration of local anaesthetics in the periportal areas, infiltration of the periportal parietal peritoneum, intraperitoneal spraying, subdiaphragmatic space, and into the subhepatic space have been reported. Some to them failed to show analgesic effects, when 240 mg of Lignocaine or 100 mg of Bupivacaine are injected intraperitoneally, the time required to reach peak plasma levels are similar to the time required in other forms of regional applications of these drugs. The difference in the time required to reach peak plasma concentration for Lignocaine (30 minutes) Bupivacaine (60 minutes) may be related to the increased protein binding capabilities of Bupivacaine and its sequestration in the peritoneal adipose tissue. With application of Bupivacaine 0.25% the maximum plasma concentrations, ranging from 0.35 to 2.1 mgL^{-1} , were found after 5- 30 minutes. However no clinical signs of neuro- or cardiovascular toxicity were observed.[69]

At the end of laparoscopy, to prevent postoperative pain and dramatically decrease the need for morphine local anaesthetic instillation (Bupivacaine) is performed, thereby improving patient comfort, shortening the hospital stay.

III. REGIONAL ANALGESICS WITH NEURO-AXIAL OPIOIDS

Several mechanisms have been proposed to explain movement of opioids between the epidural space and spinal cord including: diffusion through the spinal meninges, preferential diffusion through the spinal nerve root cuff and uptake by radicular arteries traversing the epidural space with subsequent distribution to the spinal cord.

Following 2-5 mg of Morphine epidural injection, analgesia onsets within 15-30 minutes and lasts for 6-24 hours. Epidural injection of 20-100 mg of Meperidine produces analgesia in 5-10 and lasts 6-8- hours. Fentanyl, like Meperidine, is lipophilic drug that rapidly traverses the dura and penetrates the spinal cord to produce analgesia in 5-10 minutes, but lasts 4-6 hours only. To offset this drawback, the initial bolus can be followed by continuous infusion with an accurately calibrated infusion pump. Sophisticated infusion pumps allow accurate titration of opioids; consequently they are used with greater frequency for epidural and subarachnoid administration of these agents.

The dose of narcotics for subarachnoid injection should be limited to 0.5-1 mg morphine, 10-30 mg Meperidine, or an equi-analgesic dose of other narcotic agents diluted to 1 ml in saline. With morphine analgesia develops in 15-30 minutes and last 8-24 hours while with Meperidine analgesia occurs more rapidly and lasts 15-24 hours.

Clonidine (selective 2-adrenergic agonists) has shown to have longer lasting analgesia when co administered with epidural opioids in a dose of 3-5 μg kg^{-1}.

However, it can cause hypotension by central vasomotor effect. Adrenaline also prolongs the analgesia of epidural opioids, possibly due to reduction of vascular uptake.

IV. REGIONAL ANALGESIA WITH COMBINED LOCAL ANAESTHETICS AND OPIOIDS:

This approach more rapid analgesia, more effective blockade and the advantage of prolonged analgesia due to the combined actions of local anaesthetics and opioids. [70]

V. ELECTRICAL ANALGESIA

Another form of postoperative pain control is the use of transcutaneous electrical nerve stimulation (TENS) near the incision site. TENS is often effective in relieving postoperative pain and reducing narcotic requirement. TENS appears to be most effective relieving pain caused by trauma to muscles, bone, and peripheral nerves. TENS also lessens the intensity of exercise-induced pain and facilitates ambulation after abdominal surgery. Patients with fully localized visceral pain and those who are anxious or depressed are less likely to benefit from TENS[101]. Studies suggest that the efficacy of electro-analgesic therapies depend on the location, timing, intensity and frequency of electrical stimulation. Of interest, simple mechanical intradermal needles significantly reduce the postoperative pain and the opioid analgesic requirement as well as postoperative nausea and vomiting when placed in the paravertebral region before abdominal surgery.[71]

Also transcutaneous acupoint electrical stimulation reduced postoperative nausea, but not vomiting, in outpatients undergoing laparoscopic cholecystectomy.

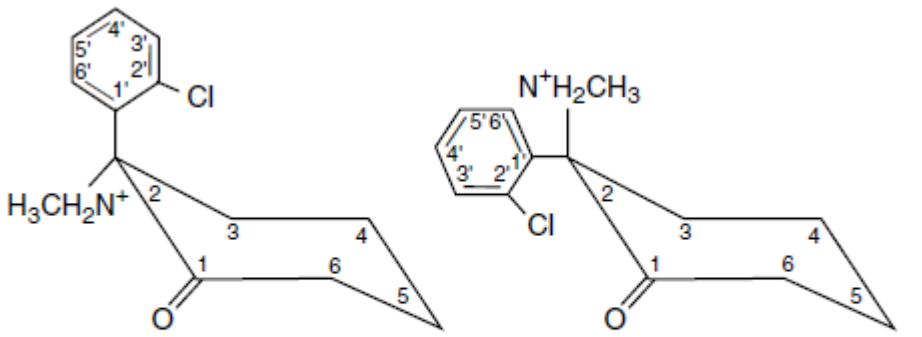
Cryo-analgesia, ultrasound and laser stimulation, as well as hypnotherapy are the other non-pharmacologic approaches that have been used as analgesic adjuvant in the perioperative period.[72]

PHARMACOLOGY OF KETAMINE

INTRODUCTION:

Ketamine was synthesized in 1962 by Stevens and was first used in humans in 1965 by Corssen and Domino. Ketamine was released for clinical use in 1970. Ketamine belongs to phencyclidine derivative which produces "dissociative anesthesia." Dissociative anesthesia is characterized by evidence on the EEG of dissociation between the thalamocortical and limbic systems.[73,74] Dissociative anesthesia resembles a cataleptic state in which the eyes remain open with a slow nystagmic gaze. The patient is non communicative, although wakefulness may appear to be present. Varying degrees of hyper tonus and purposeful skeletal muscle movements often occur independently of surgical stimulation. The patient is amnesic, and analgesia is intense.

Chemical structure



$S_1(+)$ Ketamine hydrochloride $R_1(-)$ Ketamine hydrochloride

Figure 26-14 Stereoisomers of ketamine as it is formulated.

Ketamine structurally resembles phencyclidine. It has two optical isomers due to presence of asymmetric carbon atom.[73] The left- handed optical isomer of ketamine is designated S(+)-ketamine and the right-handed optical isomer is designated R(-)-ketamine. The most frequently used preparation is the racemic form of ketamine,

although S(+)-ketamine is clinically available. The analgesic potency of S(+)-ketamine is approximately twice that of racemic Ketamine and four times greater than R(-)-ketamine.[75,76] Ketamine isomer induces less fatigue and cognitive impairment than equianalgesic small-dose racemic ketamine.[106] Both isomers of Ketamine inhibit uptake of catecholamine back into postganglionic sympathetic nerve endings. The preservative used for Ketamine is benzethonium chloride.

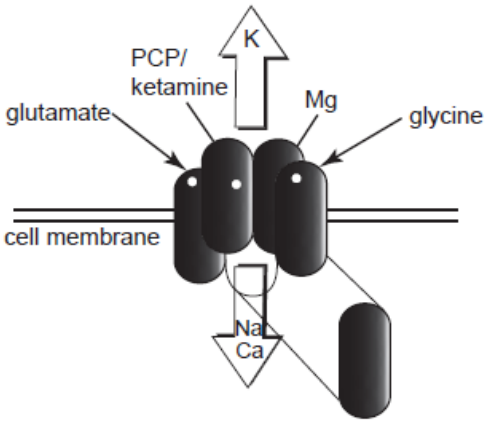


FIGURE 5-24 Schematic diagram of the *N*-methyl-D-aspartate (NMDA) glutamate receptor channel complex. The receptor consists of five subunits surrounding a central ion channel that is permeable to calcium, potassium, and sodium. Binding sites for the agonist glutamate and the obligatory coagonist glycine are indicated. NMDA receptors are ligand-gated ion channels that are activated by the excitatory neurotransmitter glutamate. Glutamate is the most abundant neurotransmitter in the central nervous system. One of the subunits has been removed to show the interior of the ion channel and binding sites for magnesium and ketamine, which produce noncompetitive NMDA receptor blockade. (From Kohrs R, Durieux ME. Ketamine: teaching an old drug new tricks. *Anesth Analg*. 1998;87;1186–1193, with permission.)

Mechanism of Action

Ketamine interacts with multiple CNS receptors. Ketamine binds noncompetitively to the phencyclidine recognition site on *N*-methyl-d-aspartate (NMDA) receptors. In addition, Ketamine exerts effects at other sites including opioid receptors, monoaminergic receptors, muscarinic receptors, and voltage-sensitive sodium and L-type calcium channels and neuronal nicotinic acetylcholine receptors.[77-79] Inflammatory mediators produced locally by compression of nerve roots can activate neutrophils that then adhere to blood vessels and impair blood flow. Ketamine suppresses neutrophil production of inflammatory mediators and improves blood flow.[80] Ketamine inhibits cytokines directly in blood which may contribute to the analgesic effects of this drug.

N-Methyl-d-Aspartate Receptor Antagonism

NMDA receptors are ligand-gated ion channels that are unique in that channel activation requires binding of the excitatory neurotransmitter, glutamate with glycine as an obligatory co-agonist.[225] Ketamine inhibits activation of NMDA receptors by glutamate and decreases pre-synaptic release of glutamate. The interaction with phencyclidine binding sites appears to be stereo selective, with the S(+) isomer of Ketamine having the greatest affinity.

Physicochemical Characteristics

- Molecular weight : 238 kD
- Partially water soluble
- Forms a white crystalline salt with a p*K*a of 7.5.[107]
- It has a lipid solubility 5 to 10 times that of thiopental.[108]

Pharmacokinectics

Metabolism

Ketamine is metabolized by hepatic microsomal enzymes. The major pathway involves *N*-demethylation to form Norketamine (metabolite I), which is then hydroxylated to hydroxynorketamine. These products are conjugated to water-soluble glucuronide derivatives and are excreted in the urine.[107] This active metabolite may contribute to prolonged effects of Ketamine (analgesia), especially with repeated doses or a continuous IV infusion. [109]

Distribution

Ketamine is not significantly bound to plasma proteins and leaves the blood rapidly to be distributed into tissues The high lipid solubility of Ketamine is reflected in its large volume of distribution, nearly 3 L/kg. Distribution half-life is 11 to 16 minutes

Clearance

Clearance is high, 890 to 1227 mL/min, which accounts for the short elimination half-life of 2 to 3 hours. The mean total body clearance (1.4 L/min) is approximately equal to liver blood flow.

Dosage :

Intense analgesia can be achieved with sub anesthetic doses of Ketamine, 0.2 to 0.5 mg/kg IV.[81] Plasma concentrations of Ketamine that produce analgesia are lower after oral than IM administration, presumably reflecting a higher Norketamine concentration due to hepatic first pass metabolism that occurs after oral administration. Analgesia is thought to be greater for somatic than for visceral pain. The analgesic effects of Ketamine are likely due to its activity in the thalamic and

limbic systems, which are responsible for the interpretation of painful signals. Small doses of Ketamine are also useful adjutants to opioid analgesia.[82]

Induction of anesthesia is produced by administration of Ketamine, 1 to 2 mg/kg IV or 4 to 8 mg/kg IM. Injection of Ketamine IV does not produce pain or venous irritation. The need for large IV doses reflects a significant first-pass hepatic effect for Ketamine. Consciousness is lost in 30 to 60 seconds after IV administration and in 2 to 4 minutes after IM injection. Unconsciousness is associated with maintenance of normal or only slightly depressed pharyngeal and laryngeal reflexes. Return of consciousness usually occurs in 10 to 20 minutes after an injected induction dose of Ketamine, but return to full orientation may require an additional 60 to 90 minutes. Emergence times are even longer after repeated IV injections or a continuous infusion of Ketamine. Amnesia persists for about 60 to 90 minutes after recovery of consciousness, but Ketamine does not produce retrograde amnesia.

Effects on the Central Nervous System

The primary site of CNS action of Ketamine seems to be the thalamoneocortical projection system. The drug selectively depresses neuronal function in parts of the cortex) and thalamus, while stimulating parts of the limbic system, including the hippocampus. This process is termed as *functional disorganization* of nonspecific pathways in midbrain and thalamic areas.[83,84] Ketamine also depresses transmission of impulses in the medial medullary reticular formation, which is important for transmission of the affective-emotional components of nociception from the spinal cord to higher brain centers.[85]

Ketamine increases cerebral metabolism, CBF, and ICP. Because of its excitatory CNS effects, which can be detected by generalized EEG development of

theta wave activity and by petit mal seizure–like activity in the hippocampus,[87] Ketamine increases $CMRO_2$.

Effects on the Respiratory System

There can be a transient (1 to 3 minutes) decrease in minute ventilation after the bolus administration of an induction dose of Ketamine (2 mg/ kg intravenously). Unusually large doses can produce apnea,[88] Ketamine is a bronchial smooth muscle relaxant. A potential respiratory problem, especially in children, is the increased salivation that follows Ketamine administration.

Effects on the Cardiovascular System

It stimulates the cardiovascular system and is usually associated with increases in blood pressure, heart rate, and cardiac output. The mechanism by which Ketamine stimulates the circulatory system seems to be central rather than a peripheral mechanism.

Uses

- **Induction and Maintenance of Anesthesia**: In patients with reactive airway disease owing to its bronchodilation effects. Otherwise healthy trauma victims whose blood loss is extensive also are candidates for rapid-sequence anesthesia induction with Ketamine.[114] Patients with septic shock also may benefit from Ketamine.[89]
- **Post operative pain Management**
- **Sedation :**Ketamine is used for sedation or general anesthesia for the following pediatric procedures: cardiac catheterization, radiation therapy, radiologic studies, dressing changes,[90] and dental work.[86] A sub anesthetic dose (≤1.0 mg/kg intravenously) is used for dressing changes In adults and

children, Ketamine can be used as a supplement or an adjunct to regional anesthesia

Routes of Administration

Ketamine has been administered intravenously, intramuscularly, transcutaneously, orally, nasally, and rectally, and as a preservative- free solution epidurally or intrathecally.[91]

Side Effects and Contraindications

Emergence reactions:

The common manifestations of these reactions are vivid dreaming, extracorporeal experiences (sense of floating out of body), and illusions (misinterpretation of a real, external sensory experience).[92]These incidents of dreaming and illusion are often associated with excitement, confusion, euphoria, and fear.[93]They occur in the first hour of emergence and usually abate within 1 to several hours. It has been postulated that the psychic emergence reactions occur secondary to Ketamine-induced depression of auditory and visual relay nuclei, leading to misperception or misinterpretation

Contraindications:

- Patients with increased ICP and with intracranial mass lesions breathing spontaneously should not receive Ketamine because it can increase ICP and has been reported to cause apnea.[94]
- Ketamine may be contraindicated in patients with an open eye injury or other ophthalmologic disorder, in which a Ketamine induced increase in intraocular pressure would be detrimental
- It is contraindicated as the sole anesthetic in patients with ischemic heart disease.[95]

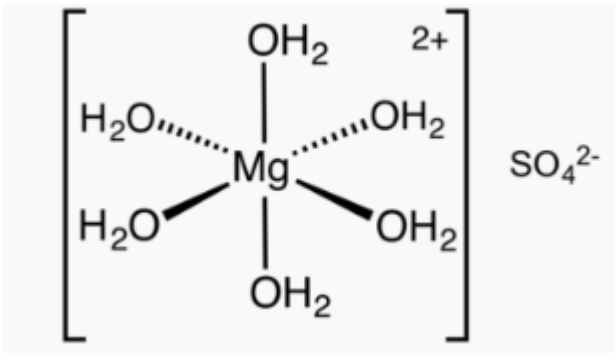
- It is unwise to give Ketamine to patients with vascular aneurysms because of the possible sudden change in arterial pressure
- Psychiatric disease, such as schizophrenia, and a history of adverse reaction to Ketamine or one of its congeners.[96]

PHARMACOLOGY OF MAGNESIUM SULPHATE

INTRODUCTION:

Magnesium sulphate is the fourth most common cation in the body and activates approximately 300 enzyme systems, including many involved in energy metabolism.[103] Only 1–2% of total body magnesium stores is present in the ECF compartment; 67% is contained in bone, and the remaining 31% is intracellular. Magnesium is an essential regulator of calcium access into the cell and of the actions of calcium within the cell. Magnesium plays an essential role in the regulation of most cellular functions and may be regarded as a natural physiologic calcium antagonist.[103] It is essential for the production and functioning of ATP, which is fully functional only when chelated to magnesium. Other processes dependent on magnesium include the production of DNA, RNA, and protein synthesis.[103]

CHEMICAL STRUCTURE OF MAGNESIUM SULPHATE:



MECHANSM OF ACTION

ACTION ON NMDA RECEPTORS

Magnesium can prevent the induction of central sensitization from peripheral nociceptive stimuli at the spinal action site by blocking NMDA receptors in a voltage-dependent manner.[5,8,9,10,13] With the same mechanism, when small doses of magnesium sulphate was added to local anaesthetics for spinal anaesthesia, the duration of anaesthesia was prolonged, postoperative analgesic requirement was

reduced and the side effects of high doses of local anaesthetics and opioids were decreased

Anticonvulsant Activity of Magnesium Sulfate

Seizures consist of an excessive release of excitotoxic neurotransmitters including glutamate. Excessive glutamate can activate the N-methyl-D-aspartate (NMDA) receptor, leading to massive depolarization of neuronal networks and bursts of action potentials. Magnesium may act to increase the seizure threshold by inhibiting NMDA receptors, thereby limiting the effect of glutamate. [105]

Vascular Effects of Magnesium Sulfate

Magnesium is a potent vasodilator of uterine and mesenteric arteries, and aorta, but has minimal effect on cerebral arteries. In vascular smooth muscle, magnesium competes with calcium for binding sites, in this case for voltage-operated calcium channels (VOCC).[103] Decreased calcium channel activity lowers intracellular calcium, causing relaxation and vasodilatation. In endothelium, magnesium has been shown to increase production of prostaglandin I_2 (through unknown mechanisms), which in turn decreases platelet aggregation. Magnesium also increases NO production causing vasodilatation.

Effect of Magnesium Sulfate on Cerebral Edema and the Blood-brain Barrier

The calcium antagonistic effects of magnesium can also affect the cerebral endothelium that forms the blood-brain barrier. Decreased cell calcium inhibits endothelial contraction and opening of tight junctions that are linked to the actin cytoskeleton. Decreased tight junction permeability limits paracellular transport of vascular contents, ions and proteins, which can promote vasogenic edema and seizures. It is also possible that magnesium sulfate diminishes transcellular transport by limiting pinocytosis that is known to occur rapidly during acute hypertension.

Magnesium may also downregulate aquaporin 4 (AQP4), a water channel protein localized to astrocytic end feet, and possibly cerebral endothelium, that is associated with cerebral edema formation (through unknown mechanisms). [103]

Pharmacokinetics:

Magnesium intake averages 20–30 mEq/d (240– 370 mg/d) in adults. Primary route for elimination is through kidneys, averaging 6–12 mEq/d. Twenty-five percent of filtered magnesium is reabsorbed in the proximal tubule, whereas 50–60% is reabsorbed in the thick ascending limb of the loop of Henle. Only 30–40% is absorbed, mainly in the distal small bowel

Effects on different systems of the body

Central nervous system & Peripheral nervous system

Magnesium depresses the central nervous system. In the early 1900s, it was used effectively as a general anesthetic. Magnesium penetrates the blood-brain barrier poorly, however, and its level in the cerebrospinal fluid is well controlled by an active transport mechanism.[103] In the peripheral nervous system, magnesium interferes with the release of neurotransmitters at all synaptic junctions and potentiates the action of local anesthetics.[103] At the neuromuscular junction, magnesium concentrations of 5 mmol/L cause significant presynaptic neuromuscular blockade and enhance the action of the nondepolarizing muscle relaxants.[103] Magnesium prolongs the action of depolarizing neuromuscular blocker drugs (e.g., succinylcholine); administration before the use of succinylcholine prevents the release of potassium provoked by the neuromuscular blocking drug

Cardiovascular system

In the cardiovascular system, magnesium produces vasodilatation by direct action on blood vessels and by interfering with a wide range of vasoconstrictor

substances. It also reduces peripheral vascular tone by sympathetic blockade and inhibition of catecholamine release.[103] In the isolated heart, increased concentrations of extracellular magnesium ion markedly depress contractile force.

Respiratory system

It has no effect on central respiratory drive. The respiratory depressant effect is caused by the neuromuscular blockade which it produces. Acts as a effective bronchodilator on brochial smooth muscles

Kidney

Magnesium is a renal vasodilator and a diuretic.

Role in Obstetrics

Magnesium is a powerful tocolytic and has been used for many years in the management of premature labor. Magnesium also is used in obstetrics to prevent patients with preeclampsia from developing seizures.

HYPOMAGNESEMIA

SIGNS & SYMPTOMS:

Most patients are asymptomatic, others may present with anorexia, weakness, fasciculation, paresthesias, confusion, ataxia, and seizures may be. Cardiac manifestations include electrical irritability, increased incidence of atrial fibrillation, P–R and QT intervals prolongation.

Intra-operative complications while anesthetizing a patient with hypomagnesemia include perioperative arrhythmias, respiratory muscle power is impaired, central nervous system irritability with seizures and hyperreflexia (e.g., Chvostek sign) and skeletal muscle spasm (e.g., Trousseau sign)

CAUSES:

- **Primary nutritional disturbances**: Inadequate intake, total parenteral nutrition, re-feeding syndrome
- **Gastrointestinal disorders:** Specific absorptive defects, malabsorption syndromes, prolonged diarrhea, prolonged nasogastric suction, pancreatitis
- **Endocrine disorders:** Hyperparathyroidism, hypoparathyroidism, hyperthyroidism, primary hyperaldosteronism, Bartter's syndrome, diabetic or alcoholic ketoacidosis, administration of epinephrine, SIADH, hungry bone syndrome after parathyroidectomy
- **Chronic alcoholism, alcoholic withdrawal, increased renal excretion**: Ethanol ingestion; idiopathic; after renal transplantation; drugs (Cisplatin, Aminoglycoside, Amphotericin B, diuretics, Pentamidine, Theophylline); recovery phase of acute tubular necrosis

TREATMENT:

In a 70-kg adult with normal renal function in whom intravenous therapy is warranted includes magnesium sulfate 1 to 2 g (8 to 16 mEq) over 15 minutes followed by 1 g/hr until serial serum magnesium levels indicate the deficiency has been corrected.[104]

HYPERMAGNESEMIA

SIGNS & SYMPTOMS: Symptoms and electrocardiographic changes of hypermagnesemia correspond to serum levels,

5 to 10 mg/dL: Depressed cardiac conduction, widened QRS complexes, prolonged P–R intervals, and Nausea

20 to 34 mg/dL: Sedation, hypoventilation, decreased deep tendon reflexes, and muscle weakness

24 to 48 mg/dL: hypotension, bradycardia, and diffuse vasodilatation

48 to 72 mg/dL: Areflexia, coma, and respiratory paralysis

CAUSES:

Increases in plasma are nearly always due to excessive intake (magnesium-containing antacids or laxatives), renal impairment (GFR < 30 mL/min), or both. Less common causes include adrenal insufficiency, hypothyroidism, rhabdomyolysis, and lithium administration. Magnesium sulfate therapy in preeclampsia and eclampsia can cause hypermagnesemia in the mother as well as in the fetus.

TREATMENT:

In mild hypermagnesemia discontinuing the source is all that is necessary. A loop diuretic in conjunction with intravenous fluid replacement enhances urinary magnesium excretion in patients with adequate renal function. Definitive therapy involves dialysis. Temporary reversal of the effects of magnesium can be managed with calcium therapy. Because hypermagnesemia potentiates the effects of depolarizing and nondepolarizing muscle relaxants, these agents must be carefully titrated in conjunction with appropriate assessment of neuromuscular blockade.[103] In cases of severe magnesium toxicity, ventilatory or circulatory support, or both, may be necessary.

USES:

- Oral Magnesium sulphate is commonly used as a saline laxative or osmotic purgative.
- Replacement therapy for hypomagnesemia[97]
- Magnesium sulphate is a antiarrhythmic agent for torsades de pointes in cardiac arrest under the ECC guidelines and for managing Quinidine-induced arrhythmias.[98]
- As a bronchodilator after beta-agonist and anticholinergic agents have been tried, e.g. in severe exacerbations of asthma,[99] magnesium sulphate can be nebulised to reduce the symptoms of acute asthma.[99] It is commonly administered via the intravenous route for the management of severe asthma attacks.
- Magnesium sulphate is effective in decreasing the risk that pre-eclampsia progresses to eclampsia.[100] I.V Magnesium sulphate is used to prevent and treat seizures of eclampsia. It reduces the systolic blood pressure but doesn't alter the diastolic blood pressure, so the blood perfusion to the foetus isn't compromised. It is also commonly used for eclampsia where compared to diazepam or phenytoin it results in better outcomes.[101,102]

REVIEW OF LITERATURE

REVIEW OF LITERATURE

E. Albrecht, K. R. Kirkham, S. S. Liu and R. Brull (2013) This study was performed to determine the efficacy of intravenous administration of Magnesium sulphate in post operative analgesia. Magnesium was administered as a single dose in six trials, as a bolus followed by infusion in 15 trials and an infusion only in two trial, and a combined with tramadol in patient Analgesia pump in two trials and it was concluded that perioperative administration of Intravenous magnesium sulphate reduced opiod consumption and to a lesser extent, pain scores, in the first 24 h postoperatively, without any reported serious adverse effects.[8]

J.-Y. Hwang, H.-S.Na, Y.-T.Jeon, Y.-J.Ro, C.-S.Kim and S.-H.Do (2010) conducted a randomised, double blind, prospective study where they evaluated the effect of i.v. infusion of magnesium sulphate during spinal anaesthesia on post-operative analgesia and post operative analgesic requirement. Forty patients undergoing total hip replacement arthroplasty under spinal anaesthesia were included. After the induction of spinal anaesthesia, the magnesium group received magnesium sulphate 50mg per kg for 15mins and then 15mg per kg per hr by continuous i.v. infusion until the end of surgery. Post-operative scores were significantly lower in Magnesium group at 4, 24, and 48 h after surgery thus concluding that magnesium sulphate improves post-operative analgesia. No side effects of hypermagnesemia were noted.[9]

Muge Arikan, Bilge Aslan, Osman Arikan, EyupHorasanli, Abdulkadir But (2013) This randomised, double blind, placebo-controlled, clinical study was conducted to compare the effects of magnesium and ketamine on postoperative pain and morphine consumption. One hundred and twenty women scheduled for total abdominal hysterectomy were included in this study. Total morphine consumption for

48 h was significantly lower in group Ketamine than in Group Magnesium. (Sample size n=120)[10]

Sabine Himmelseher, M.D., Marcel E. Durieux, M.D>, Ph.D. (2005) studied effects of Ketamine in post operative pain management in various surgeries. A following dosing schedule was therefore proposed; In painful procedure, a 0.5mg/kg slow bolus of Ketamine followed by 500mcg/kg/h before or after induction of general anaesthesia but before taking an incision. Thus concluded that pain therapy can be improved using intra operative and postoperative Ketamine in variety of surgeries and anaesthetic techniques. [11]

Sarvjeet Kaur, Richa Saroa, and Shobha Aggarwal (2015) studied the effect of intra operative infusion of low-dose Ketamine on postoperative analgesia and its management with opioids. Intra operative infusion of low-dose Ketamine resulted in effective analgesia in first 6 h of the postoperative period, which was evident from reduced pain scores and reduced opioid requirements (P = 0.001). The incidence of side effects and patient satisfaction were similar in both groups.[12]

H. Kara, N. Sahin, V. Ulusan and T. Aydogdu (2006) conducted this study to determine whether perioperative infusion of magnesium would reduce postoperative pain and anxiety. Twenty-four patients, undergoing elective hysterectomy, received a bolus of 30 mg kg−1 Magnesium sulphate or the same volume of isotonic sodium chloride solution intravenously before the start of surgery and 0.5 g h−1 infusion for the next 20 h. Intraoperative and postoperative analgesia were achieved with Fentanyl and morphine respectively. Patients were evaluated pre- and postoperatively for anxiety. Fentanyl consumption and total morphine requirements were significantly decreased in the magnesium group compared to the

control group. Postoperative anxiety scores and sedation were similar between groups.[13]

B. M. Ure, H. Troidl, W. Spangenberger, A. Dietrich, R. Lefering, E. Neugebauer(1994), performed this study on 382 patients undergoing laparoscopic cholecystectomy to assess the intensity of pain and the timing of pain. Pain was measured by visual analogue scale (VAS) of 0-100 and verbal rating scale. 37 VAS points 5 and 16 points was the mean level of pain at 5 hours after surgery and on the third day respectively. Pain was greater than 50 VAS points in 106 patients (27.8%). 73.8% of the patients used analgesics and 29.3% of the patients used opioids. Female patients experienced greater pain than male patients ($P<0.05$), but analgesics consumption was similar in both groups. On the first postoperative day, pain was localized to the abdominal wall wounds by 41.1% of the patients and to the right upper abdomen by 36.1% of the patients. Significant pain was experienced by one-third of our patients only upto first postoperative day.[115]

Joris J, Thiry E, Paris P, Weerts J, Lamy M (1995), investigated the effects of Bupivacaine administered intraperitoneal on pain after laparoscopic cholecystectomy. 40 ASA grade I-II patients were randomly assigned to 2 groups. 80 mL of Bupivacaine 0.125% with Epinephrine 1/200,000 (n = 20) was given to group 1 and the same volume of saline (n = 20) instilled under the right hemidiaphragm to group 2. Intensity of pain was assessed at 1, 2, 4, 6, 8, 24, and 48 h after surgery. This study demonstrates that for most of the pain experienced after laparoscopic cholecystectomy is visceral pain and that it is not significantly benefited by intraperitoneal Bupivacaine.[114]

Bisgaard T, Klarskov B, Trap R, Kehlet H, Rosenberg J(2000), conducted a double-blind controlled study to assess the effect of smaller port incisions on pain following laparoscopic cholecystectomy. Patients were randomly divided into 2 groups whether LC was done with three 2-mm trocars and one 10-mm trocar (micro-LC). Patients received incisional local anaesthetics, NSAID, and Paracetamol. Pain

was recorded preoperatively and postoperatively for the first 3 h and daily for the 1st week.The study included 26 patients because five patients allocated to micro-LC was changed to LC. Out of the rest 21 patients, overall pain assessment was done. Reduced postoperative pain for the first 3 hours with Micro-LC technique. However, because of the unacceptable rate of conversion to LC, micro-LC needs further technical development.[41]

Anurag Yadava, Sunil K Rajput, Sarika Katiyar and Rajnish K Jain(2017), in their study compared the quality and duration of post-operative analgesia using intraperitoneal Tramadol plus Bupivacaine (TB) or Magnesium plus Bupivacaine (MB). 186 patients undergoing laparoscopic cholecystectomy were randomly divided into two groups: group TB received intraperitoneal Tramadol with Bupivacaine and group MB received intraperitoneal Magnesium sulphate ($MgSO_4$) with Bupivacaine. The visual analogue scale (VAS) was used to assess pain, haemodynamic variables and side effects were noted. The primary outcome was to compare the analgesic efficacy and duration of pain relief. The secondary outcomes included comparison of haemodynamic parameters and side effects among the two groups. The results displayed that the mean of VAS pain score after 1, 2, 4, 6 and 24 h of surgery was more in TB group compared to MB group, and the difference was statistically significant ($P < 0.05$). The total rescue analgesia consumption in 24 h after surgery was 2.4 g (mean) of Paracetamol in TB group and 1.4 g (mean) of Paracetamol in MB group which was statistically significant ($p < 0.05$). There were no statistically significant differences in the secondary outcomes. The study concluded that intraperitoneal instillation of Bupivacaine-$MgSO_4$ renders patients relatively pain-free in first 24h after surgery, with longer duration of pain-free period

and less consumption of rescue analgesic as compared to Bupivacaine-Tramadol combination.[116]

MATERIALS AND METHODS

MATERIALS AND METHODS

Source of data

This study was carried out in the Department of Anaesthesiology, B.L.D.E's (Deemed to be university) Shri B M Patil Medical College, Hospital and Research Centre, Vijayapur, from December 2016 to August 2018. The source of data is from inpatients of Shri B M Patil Medical College, Vijayapur, undergoing laparoscopic cholecystectomy under general anaesthesia. 80 patients who are willing to participate during the study period were taken and followed up for a period of 24 hours.

METHOD OF COLLECTION OF DATA:

Study Design: A randomised clinical trial

Randomisation: Done by chit method

Study Period: One and half year from December 2016 to August 2018.

Sample Size: With anticipated Mean difference of Visual analogue scale as 0.3 between Magnesium and Ketamine group, anticipated standard deviation as 0.46 the minimum sample per group is 40 with 80% power and 10% level of significance

The formula used is

$$N = \frac{(Z_\alpha + Z_\beta)^2 * 2 * SD^2}{MD^2}$$

Where Z = Z statistic at level of significance

MD = Anticipated Mean Difference

SD = Anticipated Standard Deviation

Statistical analysis

Data were analyzed using Mean+/-standard deviation Chi square test for association, comparison of means using t test.

Study group: Study was conducted on 80 ASA grade I or II adult patients of either sex, aged between 18-60 years scheduled for elective laparoscopic cholecystectomy.

Inclusion criteria:

- ASA Class I and II.
- Age 18 – 60 years.
- Either sex
- Scheduled for elective laparoscopic cholecystectomy
- Consenting for study procedure.

Exclusion criteria:

- Body mass index >30
- Pregnancy and lactation
- Hepatic or renal insufficiency.
- Conversion of laparoscopic surgery into open surgery.

Investigations Required:

- Hemoglobin% , Complete Blood count , Bleeding Time, Clotting Time.
- Urine routine
- Random Blood Sugar
- Blood Urea and serum Creatinine
- Chest x-ray, ECG.
- HIV, HbsAg
- ECHO(If needed)

Preliminaries:

- Written informed consent.
- Intravenous access with a 20 gauge I.V cannula under aseptic techniques.

Equipments :

a) For the procedure :

- Injection Magnesium sulphate
- Injection Ketamine
- Sterile syringes.
- Intravenous cannula No20 and drip set
- Infusion pump
- Inj. Glycopyrolate 0.01-0.02 mg/kg, Inj. Midazolam 0.1 mg/kg, Inj. Ondansetran 0.15 mg/kg, Inj. Fentanyl 1-2 mcg/kg, Inj. Propofol 2 mg/kg, Inj. Succinylcholine 1-1.5 mg/kg, Inj. Vecuronium 0.1 mg/kg.

b) For emergency resuscitation :

- The anesthesia machine, emergency oxygen source (E type cylinders), pipeline O2 supply, working laryngoscopes, appropriate size endotracheal tubes and connectors.

- Working suction apparatus with suction catheter.
- Oropharyngeal airways.
- Intravenous fluids.
- Drugs: Thiopentone, Diazepam, Succinylcholine, Hydrocortisone, Atropine, Adrenaline, Aminophylline, Mephentermine, Calcium gluconate, Lipiodol and Sodium bicarbonate.

c) Monitors:

- Pulse oximeter.
- Noninvasive blood pressure monitor by sphygmomanometer.
- Echocardiogram.

Monitoring parameters:

- Heart Rate (HR)
- Oxygen saturation (SpO_2)
- Non-invasive blood pressure monitor by sphygmomanometer (SBP, DBP)
- Mean arterial pressure (MAP)
- Spontaneous breathing respiratory rate (RR).

Procedure : A randomized study was undertaken, 80 patients posted for laparoscopic cholecystectomy were assigned randomly into 2 groups, each containing 40 patients. After approval from the institute and ethical clearance from college Ethical Committee, informed consent was taken from the patients.

- ✓ All patients were examined on the day before surgery and thoroughly investigated according to institution protocol and were counseled with regards to general anesthesia
- ✓ Patient meeting above criteria were asked to participate in study after informed consent and overnight fasting.

- ✓ Visual Analogue Scale (VAS) was explained to the patient during preoperative visit.
- ✓ On the day of surgery, patients were taken to operation theatre. Standard monitoring devices including ECG leads, Sphygmomanometer cuff, and pulse oximeter were connected and baseline values will be recorded.
- ✓ IV line is secured with 20 G cannula and IV Ringer's Lactate solution started at 2 ml/kg/hr and premedication with Inj Midazolam 0.08-0.15mg/kg, Inj Glycopyrolate 0.01mg/kg Inj. Ondansetran 0.15mg/kg, and Inj.Fentanyl 0.1mcg/kg given intravenously.
- ✓ For induction of general anesthesia Inj. Propofol 2-3 mg/kg IV, Inj. Succinylcholine 1-1.5 mg/kg IV was given and patients were intubated with endotracheal tube. Inj. Vecuronium 0.1 mg/kg IV (loading dose) was given, all patients were provided mechanical ventilation with Oxygen, Nitrous oxide, Isoflurane and Inj. Vecuronium (maintenance dose) for maintainance . $ETCO_2$ is monitored using capnography to maintain CO_2 level in the expired air within the range of 4% to 4.5%.
- ✓ Group- M received bolus of 50mg/kg followed by infusion of 10 mg/kg/h Magnesium Sulphate
- ✓ Group K received bolus of 0.2mg/kg followed by infusion of 0.05 mg/kg/h Ketamine
- ✓ Postoperative pain scores were obtained by using VAS.
- ✓ The patients were aware that the scale served is to analyze the intensity of pain alone, and is not a representation of generalized postoperative discomfort.

- ✓ All the patients received elective intravenous Inj. Diclofenac (1 mg/kg) analgesia on demand and the time for demand was noted. The requirement of a repeat dose of Inj. Diclofenac, if any is noted and recorded.
- ✓ A detailed statistical analysis was done including sex, age, weight, medical history before operation, duration of surgery, the intensity of post- operative pain assessed by visual analogue scale (VAS) at the time of first demand of analgesia, the time lapse between the operation and the first demand of analgesia by the patient, the frequency of demand for analgesia in the initial 24 hours postoperatively.
- ✓ The patients were allowed to assume erect position, mobilized, and given an oral diet 12 h after surgery.
- ✓ An overnight hospital stay was mandatory for all the patients.

Post-Operative Period:

- ✓ Patients were cared for in the recovery room according to the standard protocol and then they were shifted to the postoperative ward.
- ✓ The time of arrival in the recovery was defined as zero hour postoperatively. Pain intensity was measured at fixed time interval at 4hrs, 8hrs, 12 hrs, 16hrs, 20hrs and 24hrs respectively, using VAS. Patients were given 75 mg of Diclofenac sodium intramuscularly on request and the total number of doses of analgesics used was recorded in a standard pro forma.

FIGURE: 15 KETAMINE INFUSION

FIGURE: 16 MAGNESIUM SULPHATE INFUSION

Statistical analysis

All characteristics were summarized descriptively. For continuous variables, the summary statistics of mean, standard deviation (SD) were used. For categorical data, the number and percentage were used in the data summaries. Chi-square (χ^2)/Freeman-Halton Fisher exact test was employed to determine the significance of differences between groups for categorical data. The difference of the means of analysis variables between two independent groups was tested by unpaired t test. The t test (also called Student's T Test) compares two averages (means) and tells you if they are different from each other. Bivariate correlation analysis using Pearson's correlation coefficient (r) was used to test the strength and direction of relationships between the interval levels of variables. If the p-value was < 0.05, then the results were considered to be statistically significant otherwise it was considered as not statistically significant. Data were analyzed using SPSS software v.23.0. and Microsoft office.

RESULTS

RESULTS

A total of eighty patients participated in the study.

AGE AND SEX DISTRIBUTION

TABLE NO 1: DISTRIBUTION OF CASES ACCORDING TO AGE AMONG THE STUDY GROUPS

Age (Yrs)	GROUP K		GROUP M		p value
	N	%	N	%	
≤20	2	5	2	5	0.438
21-30	8	20	8	20	
31-40	12	30	14	35	
41-50	8	20	7	17.5	
51-60	10	25	9	22.5	
Total	40	100	40	100	

GRAPH 1: DISTRIBUTION OF CASES ACCORDING TO AGE AMONG THE STUDY GROUPS

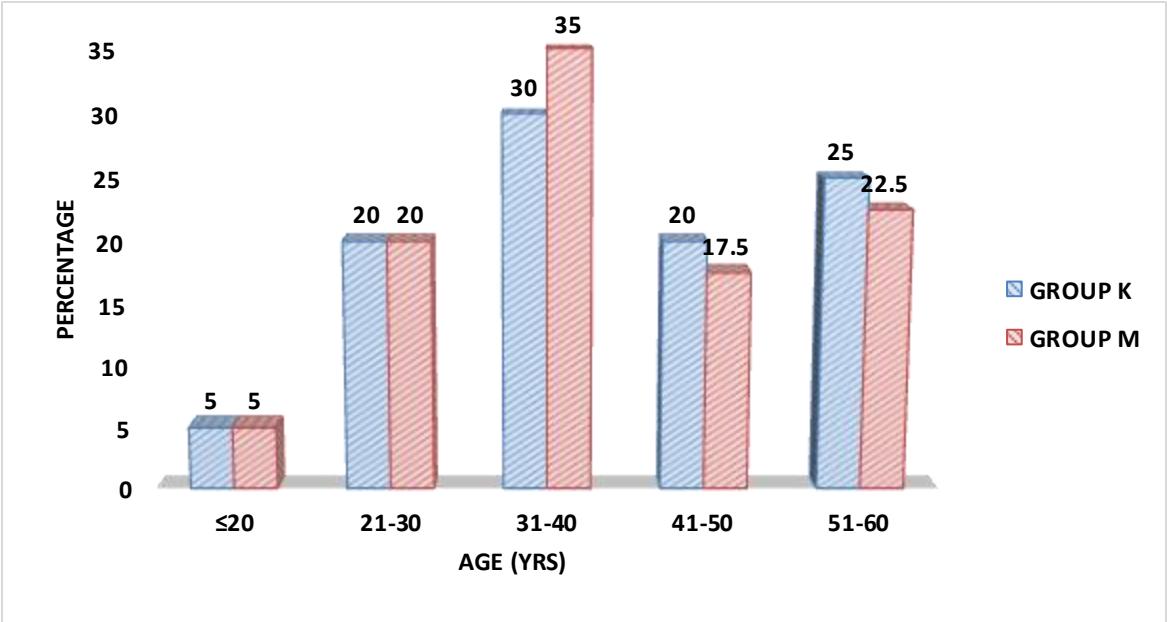
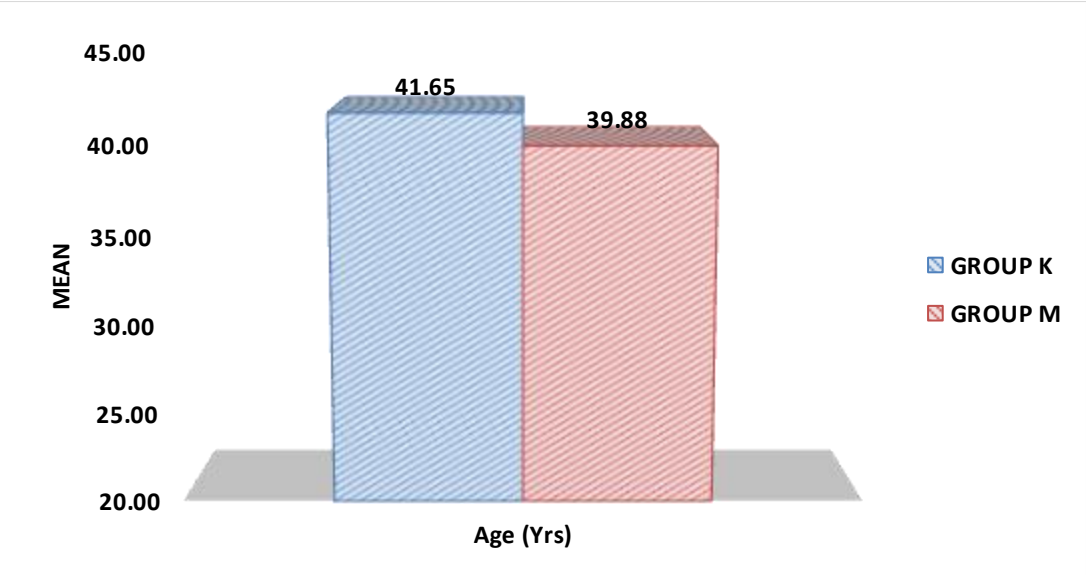


TABLE NO 2: COMPARISON OF MEAN AGE AMONG THE STUDY GROUPS

PARAMETERS	GROUP K		GROUP M		p value
	Mean	SD	Mean	SD	
Age (Yrs)	41.65	13.38	39.88	12.30	0.539

GRAPH 2: COMPARISON OF MEAN AGE AMONG THE STUDY GROUPS

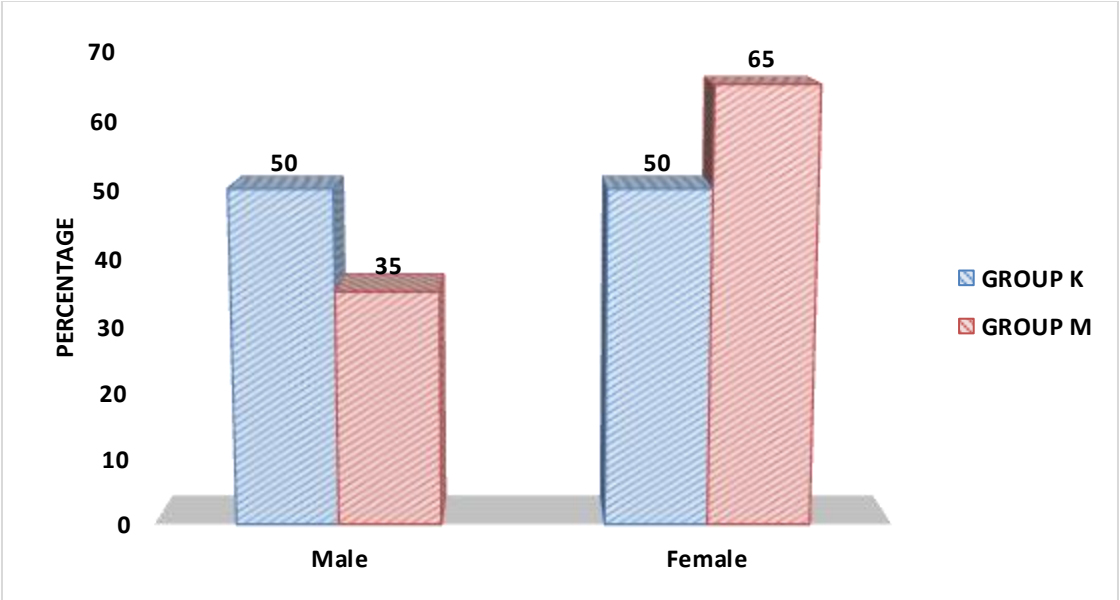


Group K comprised of 5%, 20%, 30%, 20% & 25% patients with their age between 20-30 years, 30-40 years, 40-50 years and 50-60 years respectively. The mean age of patients in group K is 40.65 and that in group M is 39.88.

TABLE NO 3: DISTRIBUTION OF CASES ACCORDING TO SEX AMONG THE STUDY GROUPS

SEX	GROUP K		GROUP M		p value
	N	%	N	%	
Male	20	50	14	35	0.175
Female	20	50	26	65	
Total	40	100	40	100	

GRAPH 3: DISTRIBUTION OF CASES ACCORDING TO SEX AMONG THE STUDY GROUPS



There were 50% of females in the group K as compared 65% in the group K. The p value was 0.175, therefore there was no significant difference in the sex distribution in both the groups This implies that sex matching was done between the two groups.

Group K comprised of 40 patients (20 males, 20 females).

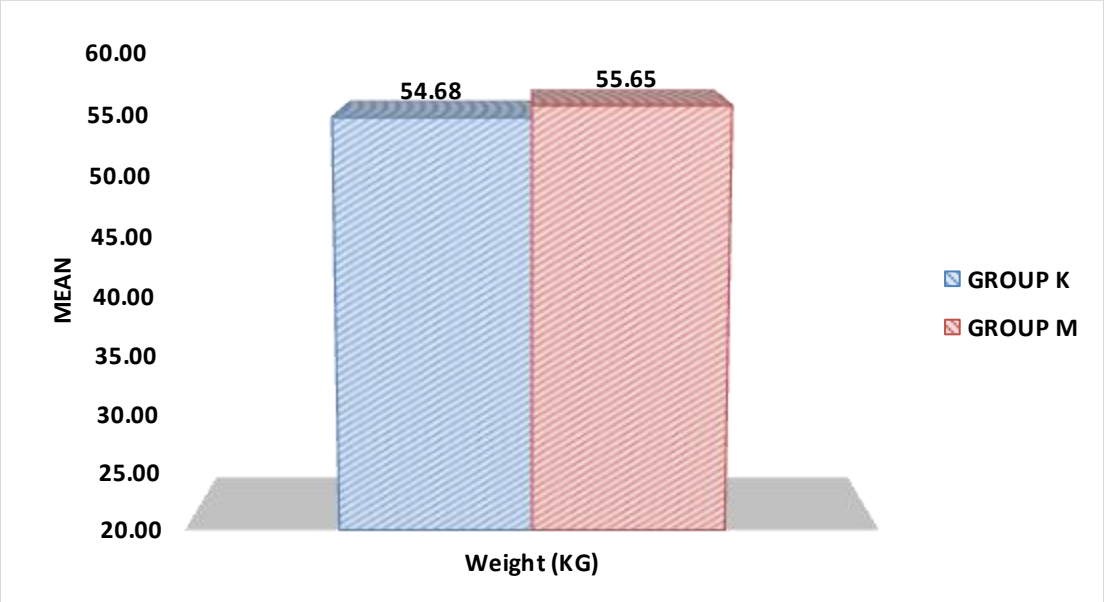
Group M consisted of 40 patients (14 males, 26 females)

The patients in both groups were similar in respect to age and sex distribution.

TABLE NO 4: COMPARISON OF MEAN WEIGHT AMONG THE STUDY GROUPS

PARAMETERS	GROUP K		GROUP M		p value
	Mean	SD	Mean	SD	
Weight (KG)	54.68	11.46	55.65	7.81	0.658

GRAPH 4: COMPARISON OF MEAN WEIGHT AMONG THE STUDY GROUPS



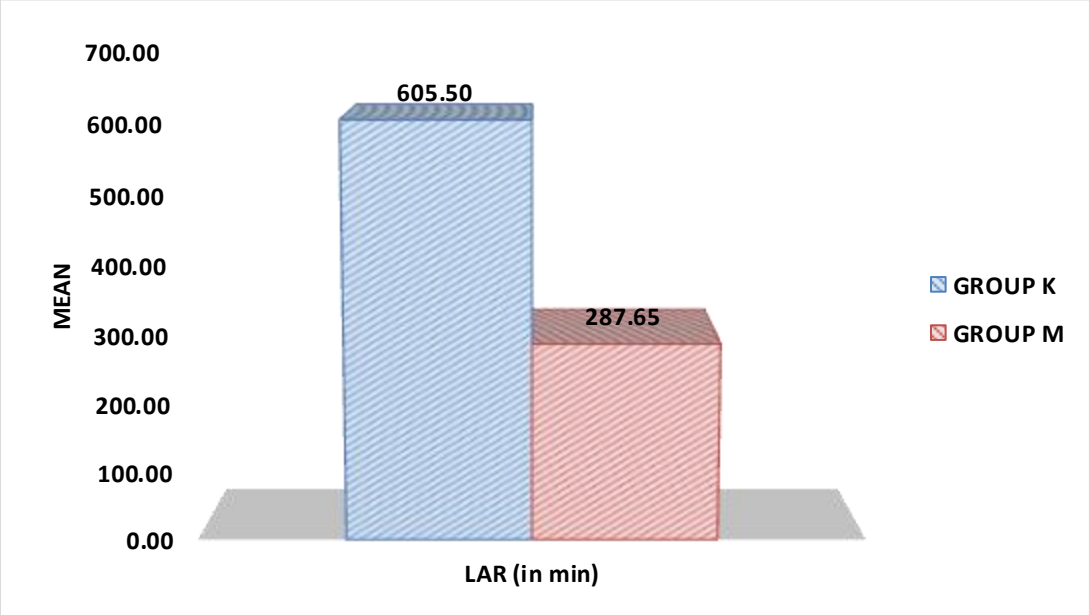
The mean weight among the study groups i.e group K and group M were 54.68 kg and 55.65 kg respectively, the p value being 0.658. hence there was no significant difference between two groups.

TABLE 5: COMPARISON OF MEAN LAR AMONG THE STUDY GROUPS

PARAMETERS	GROUP K		GROUP M		p value
	Mean	SD	Mean	SD	
LAR (in min)	605.50	143.47	287.65	130.19	<0.001*

Note: * significant at 5% level of significance (p<0.05)

GRAPH 5: COMPARISON OF MEAN LAR AMONG THE STUDY GROUPS



The timing of first shot of rescue analgesic was significantly shorter in group K compared to group M. In this regard there was a significant difference in group A and B with respect first dose of analgesic (p = 0.001)

TABLE 6: COMPARISON OF MEAN DURATION OF SURGERY AMONG THE STUDY GROUPS

PARAMETERS	GROUP K		GROUP M		p value
	Mean	SD	Mean	SD	
Duration of Surgery (min)	88.90	24.04	101.38	32.52	0.055

This table illustrates that there is no association between duration of surgery and the time of first demand of analgesia by the patient i.e., LAR (p = 0.055).

GRAPH 6: COMPARISON OF MEAN DURATION OF SURGERY AMONG THE STUDY GROUPS

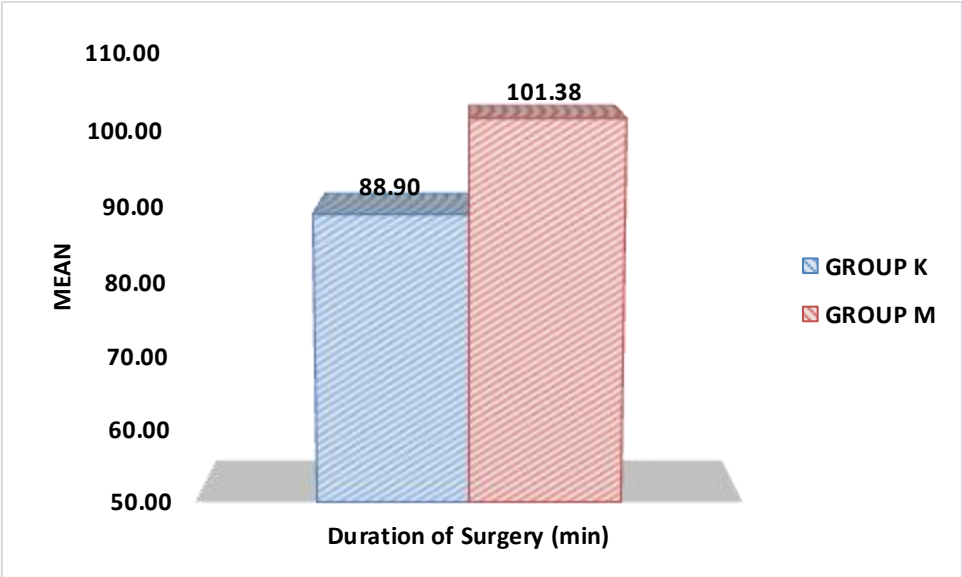


TABLE 7: COMPARISON OF MEAN INTENSITY OF PAIN AT FIRST DEMAND OF ANALGESIA AMONG THE STUDY GROUPS

PARAMETERS	GROUP K		GROUP M		p value
	Mean	SD	Mean	SD	
Intensity of pain at first demand of analgesia (VAS)	6.00	0.99	6.33	1.05	0.157

In the above table, the mean intensity of pain at first demand of analgesia among the two study groups were compared. The results were 6.00 and 6.33 for group K and group M respectively which not statistically significant (p value 0.157)

GRAPH 7: COMPARISON OF MEAN INTENSITY OF PAIN AT FIRST DEMAND OF ANALGESIA AMONG THE STUDY GROUPS

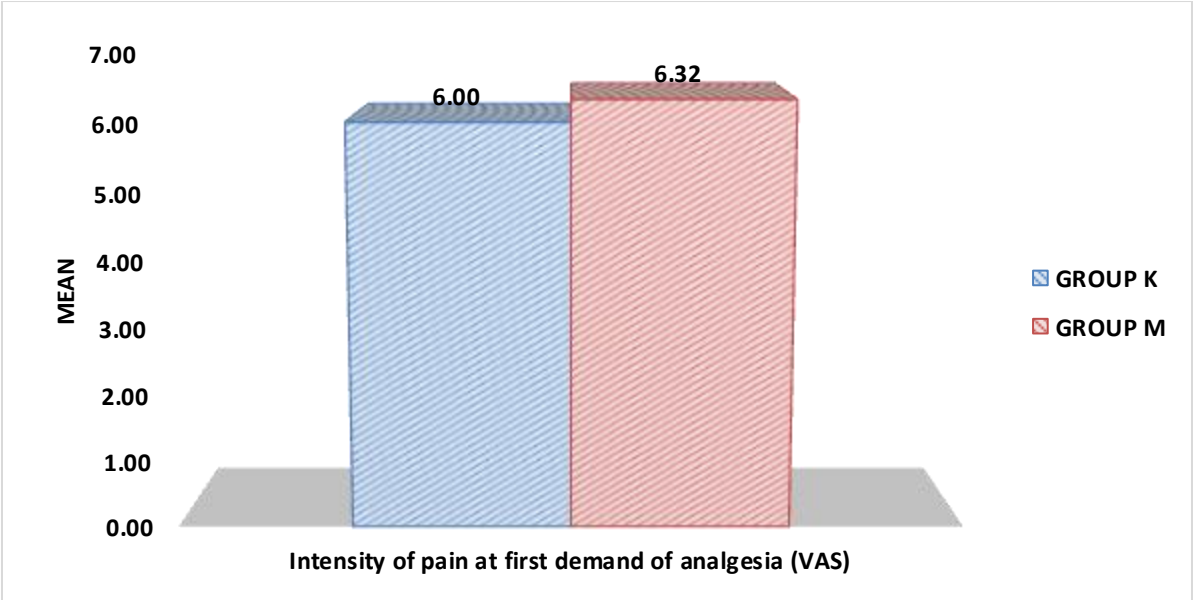
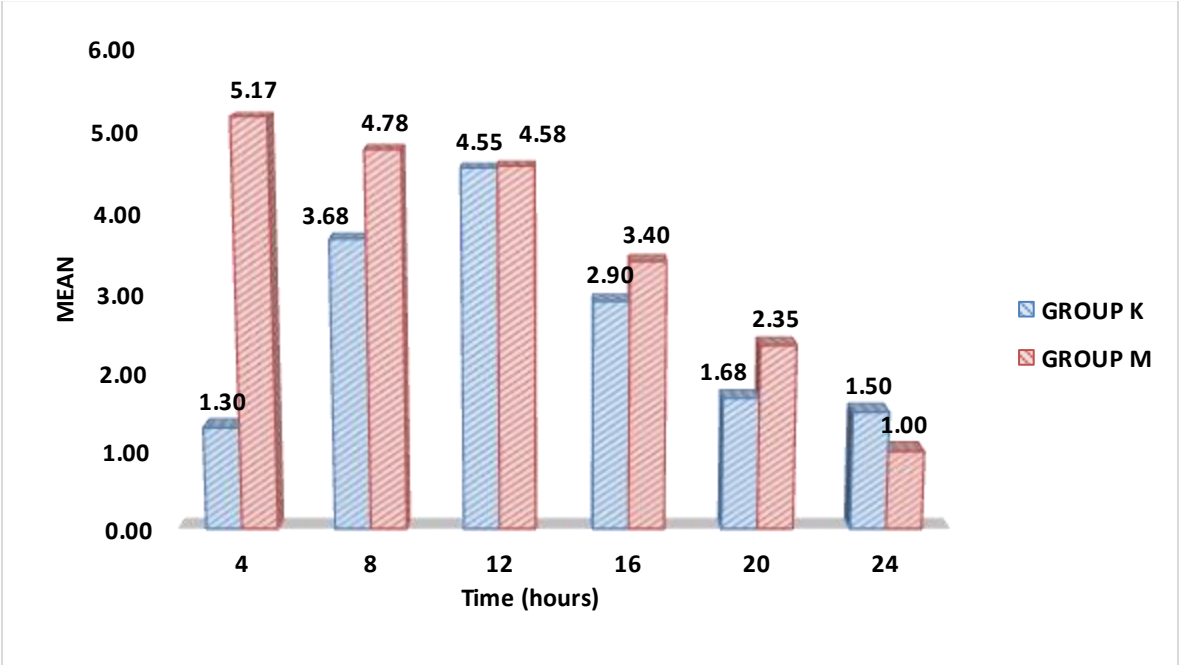


TABLE 8: COMPARISON OF MEAN POST OPERATIVE PAIN SCORE AMONG THE STUDY GROUPS

Time (hours)	Post operative pain score				p value
	GROUP K		GROUP M		
	Mean	SD	Mean	SD	
4	1.30	1.40	5.18	1.77	<0.001*
8	3.68	2.57	4.78	1.82	0.030*
12	4.55	1.85	4.58	1.71	0.95
16	2.90	1.92	3.40	2.22	0.284
20	1.68	1.90	2.35	2.37	0.164
24	1.50	1.95	1.00	1.71	0.226

Note: * significant at 5% level of significance ($p<0.05$)

GRAPH 8: COMPARISON OF MEAN POST OPERATIVE PAIN SCORE AMONG THE STUDY GROUPS



The mean pain scores were significantly lower upto first 8 hours in group K in comparison with group M and further there is no significant difference in the mean pain scores in the next 24 hours of the study as it is quite evident in the graph depicted.

Mean pain scores measured at 4^{th} hour were higher in Group M than Group K.(VAS scale p value <0.001).

Mean pain scores measured at 8^{th} hour were significantly higher in Group M compared to Group K (VAS scale p value=0.030).

Mean pain scores measured at 12^{th} hour (VAS scale p value = 0.95), 16^{th} hour (VAS scale p value = 0.284), 20^{th} hour (VAS scale p value=0.164) and 24^{th} hour (VAS scale p value= 0.226) were not significantly different in the two groups.

The graphical representation of the mean pain scores illustrates that the mean pain scores were slightly but not significantly higher in Group M than Group K at 12^{th} , 16^{th} , 20^{th} & 24^{th} hour.

A significant number of patients in Group K complained pain after the initial 8 hours whereas the patients in Group M complained of pain in the much earlier hours postoperatively. So the percentage of people complaining of pain in Group K remain high in the later part of postoperative period but the mean pain scores are not significantly different.

TABLE 9: COMPARISON OF ANALGESIA REQUEST TIME AMONG THE STUDY GROUPS

Analgesia request time	GROUP K		GROUP M		p value
	N	%	N	%	
0 to 4	0	0	24	60	<0.001*
4 to 8	14	35	19	47.5	0.256
8 to 12	21	52.5	20	50	0.823
12 to 16	7	17.5	16	40	0.026
16 to 20	11	27.5	15	37.5	0.34
20 to 24	4	10	4	10	1

Note: * significant at 5% level of significance ($p<0.05$)

The statistical analysis from the above tables showed that in the initial 0-4 hours people from group K demanded absolutely no rescue analgesia while in group M, 24 people had to be given rescue analgesia on demand. The calculated p value was <0.001 ,which was a significant difference. But in the later period, when the demand for rescue analgesia was compared among the two groups , the difference was not found statistically significant. Therefore, Ketamine provided a substantial reduction of pain intensity up to the first 4 hours postoperatively and this was found to be statistically significant.

FIGURE 9: COMPARISON OF ANALGESIA REQUEST TIME AMONG THE STUDY GROUPS

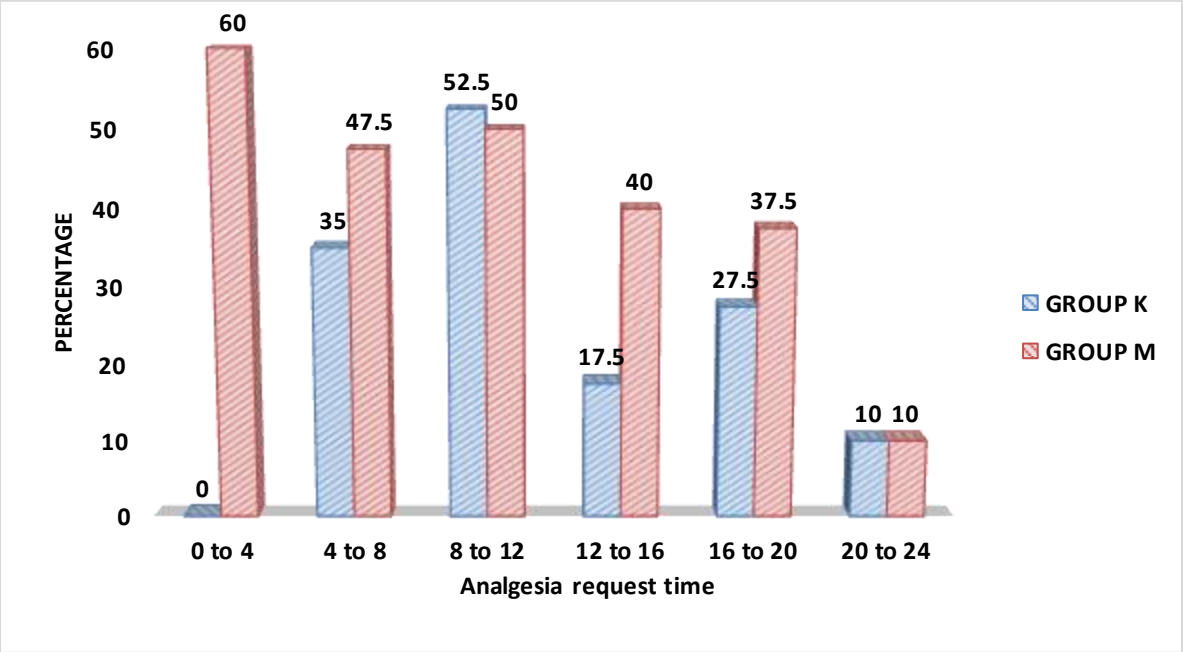


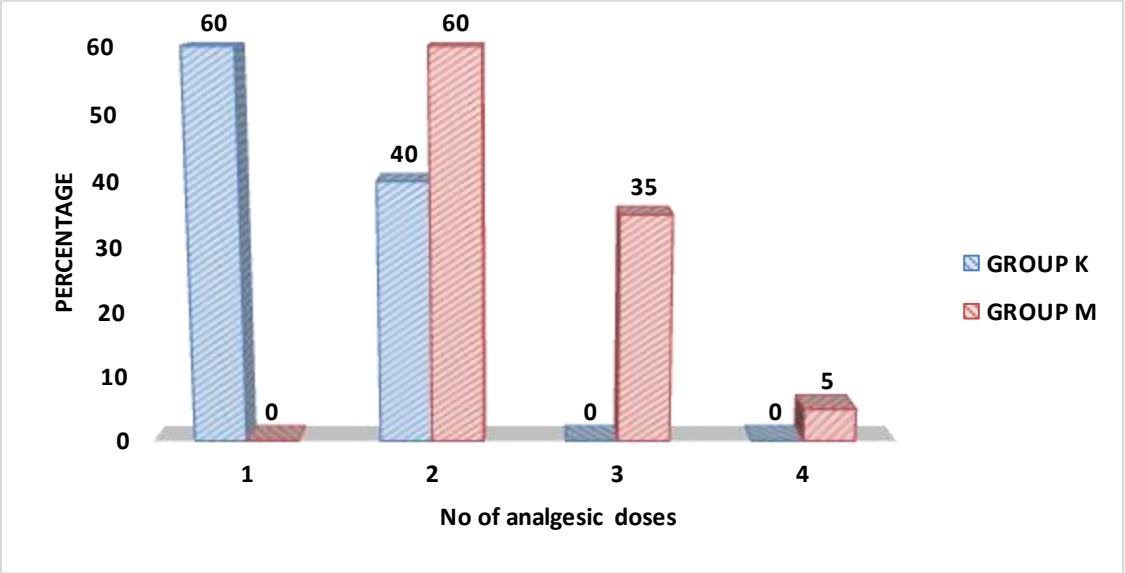
TABLE 10: COMPARISON OF NO OF ANALGESIC DOSES ADMINISTERED IN 24 HRS AMONG THE STUDY GROUPS

No of analgesic doses administered in 24 hrs	GROUP K		GROUP M		p value
	N	%	N	%	
1	24	60	0	0	<0.001*
2	16	40	24	60	
3	0	0	14	35	
4	0	0	2	5	
Total	40	100	40	100	

Note: * significant at 5% level of significance ($p<0.05$)

The above table shows comparison of total number of rescue analgesic doses administered in 24 hours. In group K, 24 people required only one dose of rescue analgesia and 16 people required two doses of rescue analgesia in a period of 24 hours. But in group M, 24 people required two doses, 14 people required three doses and 2 people required four doses. According to this, the total number of analgesic doses were lower in Ketamine group when compared to Magnesium group ($p < 0.001$).

FIGURE 10: COMPARISON OF NO OF ANALGESIC DOSES ADMINISTERED IN 24 HRS AMONG THE STUDY GROUPS



DISCUSSION

DISCUSSION

Although previous studies have shown that laparoscopy is associated with less pain than laparotomy it is not pain free. [1-9] Patients undergoing Laparoscopic cholecystectomy suffer considerable pain on the day of surgery frequently requiring analgesics.

Controversy exists about the principal source of pain after laparoscopic procedure. Some clinicians maintain that placement of trocars through the abdominal wall is the primary source; whereas others believe that most pain arises from intraperitoneal dissection and insufflations of CO2 resulting in distension of abdominal wall and prolonged elevation of diaphragm.[70]

Early pain after laparoscopic cholecystectomy is a complex process and includes different pain components secondary to different pain mechanisms, such as surgical trauma to the abdominal wall, intra-abdominal trauma secondary to the gall bladder removal, abdominal distension, pneumoperitoneum using carbon dioxide etc. Optimally, therefore pain should be treated multimodally. We therefore studied the effect of intravenous infusions of Ketamine and Magnesium sulphate on post-operative analgesia

Different drugs have been used as an adjuvant for post-operative pain management. The N-methyl D-aspartate (NMDA) receptor is found in many parts of the body, including the nerve endings, and it plays a well-defined role in pain modulation. NMDA receptor antagonists, such as, magnesium sulphate, and Ketamine, have been previously investigated as a possible adjuvant for postoperative analgesia.[5-12]

The use of Magnesium as an adjuvant for peri-operative analgesia is based on the properties of NMDA receptor antagonist and calcium channel blocker.[5,8,9,10,13]

However, although the basic mechanism of analgesic effect of Magnesium is unclear, it is presumed that its antagonism of NMDA receptor prevents the induction of central sensitization due to peripheral nociceptive stimulation and abolishes hypersensitivity.

Murphy *et al* [113] demonstrated that the perioperative infusion of magnesium sulfate was associated with a decrease in postoperative opioid consumption. In addition, they also found that perioperative magnesium sulfate infusion was associated with a decrease in visual analog scale pain scores up to 4-6 hours after surgery. However in our study the latency for first analgesic request by group M was less than 4 hours.

Muge Arikan[10], et al conducted a randomised, double blind, placebo-controlled, clinical study to compare the effects of Magnesium and Ketamine on postoperative pain and morphine consumption. Total morphine consumption for 48 h was significantly lower in group K than in Group M, (Sample size n=120). Our study also showed a significant difference in pain intensity in the early postoperative period.

H. Kara et al[13] conducted this study to determine whether perioperative infusion of magnesium would reduce postoperative pain and anxiety. Patients were evaluated pre- and postoperatively for anxiety. Fentanyl consumption and total morphine requirements were significantly decreased in the Magnesium group compared to the control group. Postoperative anxiety scores and sedation were similar between groups.

Zakine *et al*[110] compared Ketamine infusion during the intraoperative period alone with that for the perioperative period (intraoperative plus postoperative, 48h). The authors demonstrated that low dose Ketamine improved postoperative analgesia, reduced morphine consumption and incidence of nausea. **Remerand et al** [111] showed that an IV bolus at the beginning of surgery followed by a 24hr infusion decreased

morphine consumption in patients undergoing total hip arthroplasty. **Akhavanakbari *et al*** [112] demonstrated that adding Ketamine to morphine in IV-PCA reduced pain score and morphine consumption. However in our study for rescue analgesia injection Diclofenac was used and we could demonstrate decrease in total number of rescue analgesia doses for a period of 24 hours in Group K when compared to Group M.

In this study, Ketamine has been used only for the intra operative period without pre- or postoperative administration. In line with the previous studies, we found that the rescue analgesia was less in Ketamine group, and the use of the low dose (0.05 mg/kg/h) of Ketamine was not associated with any psychotic effects.

SUMMARY

SUMMARY

Laparoscopic cholecystectomy is the preferred surgical technique for uncomplicated cholecystectomy, because of an improved postoperative course. Although laparoscopic cholecystectomy, compared with the open procedure may be associated with diminished surgical trauma and shortened convalescence, early postoperative pain after laparoscopic procedures is a frequent complaint. Furthermore, the fact that laparoscopic cholecystectomy is performed on a fast-track basis, emphasizes the importance of improving early postoperative pain. Pain after laparoscopic cholecystectomy may vary in quality and localization and is reported in several trials to be incisional, intraabdominal, or referred (shoulder tip). The etiology is complex, including damage to abdominal wall structures, the induction of visceral trauma and inflammation, and peritoneal irritation because of CO2 entrapment beneath the hemidiaphragms. Acute pain is typically associated with neuroendocrine stress response that is proportional to pain intensity, and it has been hypothesized that a reduction in surgical stress responses (endocrine, metabolic and inflammatory) will lead to a reduced incidence of postoperative organ dysfunction and thereby to an improved outcome. The latter suggests that effective postoperative pain management is not only human but a very important aspect of postoperative care. Uncontrolled postoperative pain has an adverse sequel of delayed resumption of normal pulmonary function, restriction of mobility (thus contributing to thromboembolic complications), nausea and vomiting, increase in the systemic vascular resistance, cardiac work, and myocardial oxygen consumption through an increase in the catecholamine release induced by the stress response.

In this study we compared the analgesic effects of Ketamine and Magnesium sulphate given perioperatively as continuous infusions following a bolus dose. The

mean pain scores were significantly lower upto first 8 hours in group K in comparison with group M and further there is no significant difference in the mean pain scores in the next 24 hours of the study (VAS scale p value=0.030) (TABLE 8)

The mean intensity of pain at first demand of analgesia among the two study groups were compared. The results were 6.00 and 6.33 for group K and group M respectively which not statistically significant (p value 0.157) (TABLE 7).

The statistical analysis showed that in the initial 0-4 hours people from group K demanded absolutely no rescue analgesia while in group M, 24 people had to be given rescue analgesia on demand. The calculated p value was <0.001 ,which was a significant difference. But in the later period, when the demand for rescue analgesia was compared among the two groups , the difference was not found statistically significant. Therefore, the total number of analgesic doses were lower in Ketamine group when compared to Magnesium group ($p < 0.001$). (TABLE 9)

CONCLUSION

CONCLUSION

To conclude, Ketamine is effective at preventing pain in the first 4-8 hours of post operative period after laparoscopic cholecystectomy .This study showed that the latency of analgesic request was significantly more for Ketamine and also perioperative Ketamine infusion significantly reduced the need for Diclofenac, compared with perioperative Magnesium sulphate infusion. Ketamine is still one of the most advantageous adjuvant drugs for treating postoperative pain.

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BIBLIOGRAPHY

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ANNEXURES

ANNEXURE-I

ETHICAL CLEARANCE CERTIFICATE

Institutional Ethical Committee
BIJAPUR-586 103.
OUTWARD
No. 61/2016
Date. 06/10/16
B.L.D.E.U's Shri B.M. Patil Medical College

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

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this college met on 04-10-2016 at 03 pm to scrutinize the Synopsis of Postgraduate Students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected & revised version synopsis of the Thesis has been accorded Ethical Clearance.

Title "Comparison of postoperative analgesia with Intravenous infusion of Magnesium Sulphate & Ketamine after induction of general anaesthesia in patients undergoing laparoscopic cholecystectomy."

Name of P.G. student Dr. Neha. S. Ardwikar
Dept of Anaesthesiology

Name of Guide/Co-investigator Dr Vidya. A. Patil
Prof of Anaesthesiology

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

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

ANNEXURE-II

INFORMED CONSENT FORM

B.L.D.E's (DEEMED TO UNIVERSITY)

SHRI B.M. PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE, VIJAYPUR – 586103, KARNATAKA

TITLE OF THE PROJECT

"Comparison of postoperative analgesia with Intravenous infusion of Magnesium Sulphate and Ketamine after induction of general anaesthesia in patients undergoing laparoscopic cholecystectomy "

PRINCIPAL INVESTIGATOR : **Dr. NEHA S ARWIKAR**
Department of Anaesthesiology
Email: nsarwikar@gmail.com

PG GUIDE: GUIDE : **Dr.VIDYA PATIL**
Professor
Department of Anaesthesiology
B.L.D.E's (DEEMED TO BE UNIVERSITY) Shri B. M. Patil Medical College Hospital Centre and Research Sholapur Road, Vijaypur

PURPOSE OF RESEARCH:

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

RISKS AND DISCOMFORTS:

I understand that I/my ward may experience some pain while receiving general anaesthesia and I understand that necessary measures will be taken to reduce these complications as and when they arise.

BENEFITS:

I understand that my/my wards participation in this study will help in finding out appropriate medication for analgesia following the surgery.

CONFIDENTIALITY:

I understand that medical information produced by this study will become a part of this hospital records and will be subjected to the confidentiality and privacy regulation of this hospital. Information of a sensitive, personal nature will not be a part of the medical records, but will be stored in the investigator's research file and identified only by a code number. The code key connecting name to numbers will be kept in a separate secure location.

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

REQUEST FOR MORE INFORMATION:

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

If during this study, or later, I wish to discuss my participation in or concerns regarding this study with a person not directly involved, I am aware that the social worker of the hospital is available to talk with me and that a copy of this consent form will be given to me to keep for careful reading.

REFUSAL OR WITHDRAWL OF PARTICIPATION:

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

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

INJURY STATEMENT:

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

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

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

Date: DR.VIDYA PATIL DR. NEHA S ARWIKAR

(Guide) (Investigator)

STUDY SUBJECT CONSENT STATEMENT:

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

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

_____ _____

(Participant) Date

_____ _____

(Witness to above signature) Date

ANNEXURE – III

PROFORMA

STUDY: "Comparison of postoperative analgesia with Intravenous infusion of Magnesium Sulphate and Ketamine after induction of general anaesthesia in patients undergoing laparoscopic cholecystectomy"

Serial No. Group [M] Group [K]

Name: I.P. No. :

Age : Hospital:

Sex: DOA: DOS:

Preoperative diagnosis:

Proposed surgery:

PRE- ANESTHETIC EXAMINATION

Chief Complaints:

Past History:

Presence of any co-morbid condition – DM/ HTN/ IHD/ CVD/Asthama/ Bleeding disorders/ Drug allergy/ Any other:

Previous anesthetic exposure:

Present medication/ Previous drug therapy:

Family History:

General Physical Examination:

Pallor/ Icterus/ Cyanosis/ Clubbing/ Lymphadenopathy/ Pedal edema

Pulse rate: Blood Pressure:

Respiratory rate: Weight:

Teeth:

Jaw movement:

Mallampatti grade:

Systemic Examination :

Cardiovascular system: Central Nervous system:

Respiratory system: Others:

INVESTIGATIONS :

Hemoglobin: TLC/ N/ L/ M/ E: Random Blood Sugar:

Blood Urea: Serum.Creatinine: Urine routine:

Platelet count: Blood group/Rh typing: BT/ CT:

X-Ray chest: ECG:

Any other:

Pre-operative baseline

HR:

BP:

Premedication :

ASA Grade :

Anesthetic Technique: General anesthesia

Drugs and Dosages:

Duration of surgery:

Adverse effects (If any):

INTRA OPERATIVE MONITORING:

PR:

BP:

POST OPERATIVE MONITORING:

1. The time lapse between the operation and the first demand of analgesics by the patient.
2. Total requirement of analgesic doses for a period of 24 hrs

TABLE - 1

Number of patients requiring analgesics in 24 hours duration postoperatively.

Time in hour	2	4	6	8	10	12	14	16	18	20	22	24
GROUP M												
GROUP K												

KEY TO MASTER CHART

LAR : Latency of analgesia request

VAS: Visual Analogue Score

ASA: American Society of Anesthesiologists

M: Male

F: Female

SL No: Serial number

IP No: Inpatient Hospital number

MASTER CHART- Group M

Sl No	Name	IP No.	Age (Yrs)	Sex (M/F)	Weight (KG)	LAR (in min)	Duration of Surgery (in min)	Intensity of pain at first demand of analgesia (VAS)	Post operative pain score (Time in hours)						Analgesia request time						No of analgesic doses administered in 24 hrs	ASA GRADE
									4	8	12	16	20	24	0 to 4	4 to 8	8 to 12	12 to 16	16 to 20	20 to 24		
1	Shantamma	18877	38	F	55	240	135	6	6	3	8	4	2	5	1		1			1	3	I
2	Renuka	22323	40	F	65	365	70	7	3	7	3	2	5	0		1			1		2	I
3	Shashikumar	36161	24	M	65	120	70	7	7	4	5	2	5	0	1		1		1		3	I
4	Mallanna	25683	60	M	68	70	120	6	6	6	4	5	1	3	1	1		1			3	I
5	Laxmi	36631	30	F	52	130	85	8	8	6	4	4	5	0	1	1			1		3	II
6	Kashinath	1782	60	M	58	230	145	6	6	4	3	8	4	0	1			1			2	I
7	Mallamma	24944	45	F	53	480	135	7	4	7	5	3	0	0		1	1				2	II
8	Shakuntala	428055	18	F	52	185	105	7	7	4	8	2	5	3	1		1		1		3	I
9	Kamala	22457	44	F	59	490	70	5	4	4	5	1	6	0			1		1		2	I
10	Shilabai	20337	60	F	59	380	70	5	5	5	3	1	6	0	1	1			1		3	II
11	Rudrappa	41308	46	M	54	230	80	8	8	6	4	2	0	3	1	1					2	I
12	Rachappa	410	29	M	68	240	160	6	7	3	4	6	2	0	1			1			2	I
13	Yashoda	23513	55	F	56	440	160	6	3	6	4	5	2	0		1		1			2	II
14	Bhimashankar	1991	50	M	53	455	105	5	4	5	3	0	6	0		1			1		2	I
15	Mohammad	2629	46	M	62	210	65	7	7	4	5	3	5	0	1		1		1		3	I
16	Divya	2626	38	F	48	420	95	5	3	5	4	7	0	0		1		1			2	I
17	Navya	2904	54	F	52	180	100	7	7	4	5	2	2	2	1		1				2	I
18	Bharati	4089	38	F	60	480	75	6	3	6	4	7	0	0		1		1			2	I
19	Veda	23511	30	F	59	480	75	6	2	6	4	5	0	0		1		1			2	I
20	Neelabai	6500	43	F	60	450	105	6	3	6	3	6	2	0		1		1			2	I
21	Parvati	10068	36	F	60	190	60	6	6	3	5	5	0	0	1		1	1			3	I
22	Sharanama	10927	26	F	60	300	105	6	4	6	5	0	2	3		1	1				2	I

23	Iramma	11449	25	F	54	350	115	6	6	3	5	2	0	0	1		1				2	I
24	Yallawwa	12393	35	F	48	185	110	6	7	4	5	0	0	5	1		1			1	3	I
25	Laxmibai	13166	35	M	45	140	45	5	5	4	6	0	6	0	1		1		1		3	I
26	Jyotika	12850	24	F	42	130	95	6	6	0	2	5	2	0	1			1			2	I
27	Deepa	11683	33	M	52	126	80	6	6	4	5	4	2	0	1		1	1	1		4	I
28	Anita	10546	22	M	46	110	40	5	5	4	7	1	5	0	1		1		1		3	I
29	Indirabai	7804	60	F	54	240	75	8	8	4	5	3	0	0	1		1				2	II
30	Sainath	5255	32	M	50	360	120	6	4	6	4	5	0	0		1		1			2	I
31	Anita	4452	32	F	62	300	100	8	4	8	4	5	0	0		1		1			2	I
32	Yamanavva	2365	52	F	65	465	85	8	3	8	3	5	0	1		1		1			2	I
33	Padmini	14216	40	F	50	220	150	6	6	3	8	4	2	0	1		1		1		3	I
34	Shivppa	13365	60	M	68	345	110	5	2	5	0	5	2	2		1		1			2	II
35	Devappa	12800	48	M	58	220	125	5	5	1	2	6	0	0	1			1			2	I
36	Parvati	2005	55	F	50	180	105	5	6	4	5	0	0	0	1		1				2	II
37	Ganesh	23631	36	M	64	215	90	6	6	3	8	0	0	3	1		1				2	I
38	Dilshad	35745	20	F	30	440	185	8	4	8	6	4	2	0		1	1		1		3	I
39	Chandrabhaga	6720	40	F	60	235	95	8	8	4	6	4	7	5	1		1		1	1	4	I
40	Bharati	4089	38	F	50	480	140	8	3	8	4	3	6	5		1			1	1	3	I

Group K																						
Sl No	Name	IP No.	Age (Yrs)	Sex (M/F)	Weight (KG)	LAR (in min)	Duration of Surgery (in min)	Intensity of pain at first demand of analgesia (VAS)	Post operative pain score (Time in hours)						Analgesia request time						No of analgesic doses administered in 24 hrs	ASA GRADE
									4	8	12	16	20	24	0 to 4	4 to 8	8 to 12	12 to 16	16 to 20	20 to 24		
1	Drupathi	13617	55	F	50	675	126	7	4	7	0	0	0	4		1					1	I
2	Yallawa	29586	30	F	50	600	70	6	0	0	6	2	0	6			1			1	2	I
3	Mallappa	10504	26	M	62	620	70	6	0	0	6	4	2	6			1			1	2	I
4	Malkawwa	36277	50	F	60	755	95	6	0	3	6	5	0	0			1	1	1		2	I
5	Sujata	9021	40	F	48	630	90	7	1	4	7	5	1	1			1		1		2	I
6	Tukaram	9298	55	M	56	510	75	6	0	6	4	0	2	4			1				1	I
7	Neelamma	16406	32	F	60	620	90	7	1	4	7	0	2	5			1			1	2	I
8	Renuka	35358	30	F	50	360	120	6	0	6	1	0	2	4		1					1	I
9	Somappa	33322	45	M	51	440	60	6	3	6	4	2	0	3		1					1	I
10	Jayashree	30874	20	F	43	670	110	5	0	3	5	3	0	0			1				1	I
11	Siddalingayya	29930	36	M	64	630	65	8	4	8	6	4	1	0			1		1		2	I
12	Sunil	24429	30	M	65	860	65	8	3	4	7	6	3	3			1	1			2	I
13	Laxmi	21800	28	F	50	690	113	8	2	8	3	1	0	4		1					1	I
14	Ishwar	10920	43	M	68	685	45	6	3	6	4	4	6	0		1			1		2	I
15	Jayashree	10032	37	M	50	730	65	5	1	1	3	5	2	0				1			1	I
16	Tulsidas	7441	60	M	65	435	110	7	2	7	3	1	0	0		1					1	II
17	Priya	6587	33	M	52	627	87	5	0	0	3	5	2	0				1			1	I
18	Shankar	6159	60	M	55	465	105	6	0	0	6	0	5	2		1			1		2	II
19	Anand	5757	26	M	58	490	90	7	2	4	7	0	1	0			1				1	I
20	Yamanawwa	3657	55	F	45	550	60	6	1	1	6	3	0	0			1				1	II

21	Sunanda	2199	33	F	55	465	120	7	4	7	5	5	3	3		1			1		2	I
22	Manjula	1138	35	F	56	650	120	5	0	3	5	3	0	0			1				1	I
23	Bheemji	43369	50	F	70	665	105	6	0	4	6	4	2	0			1		1		2	I
24	Salima	40859	45	F	48	570	90	5	0	3	5	2	0	0			1				1	I
25	Nagraj	40931	35	M	67	480	90	5	3	6	3	5	0	0		1			1		2	I
26	Hanumanth	36161	44	M	54	670	60	5	0	0	6	1	3	3			1				1	I
27	Vijaylaxmi	36259	40	F	50	745	55	5	0	0	2	5	1	1				1			1	I
28	Gangamma	31319	57	F	53	668	120	7	0	0	7	4	2	5			1			1	2	I
29	Fayaz	29087	49	M	67	480	135	6	0	6	4	5	6	1		1			1		2	I
30	Siddagondappa	25613	60	M	62	525	70	5	0	2	5	3	0	2			1				1	II
31	Sujata	25511	30	F	50	380	60	5	3	5	2	0	6	0		1			1		2	I
32	Shankremma	11443	35	M	F	1080	60	4	0	0	2	5	3	1				1			1	I
33	Shivanad	21863	41	F	67	735	105	6	3	3	6	4	2	0			1				1	I
34	Irappa	5019	40	M	63	375	125	7	3	7	3	3	0	0		1					1	I
35	Janabee	3282	30	F	48	470	105	5	2	6	3	0	0	0		1					1	I
36	Manjula	138	35	F	50	670	90	5	2	4	5	3	6	0			1		1		2	II
37	Ramachandra	43527	60	M	55	665	75	6	2	2	6	4	0	0			1				1	II
38	Subhash	42735	60	M	65	450	70	5	0	5	3	2	2	2		1					1	II
39	Pramodgouda	41364	15	M	48	705	110	7	1	4	7	3	0	0			1				1	I
40	Sarojini	17178	57	F	57	730	80	6	2	2	3	5	2	0				1			1	II