"A RANDOMIZED STUDY OF EFFECTIVENESS OF ANALGESIA WITH PREEMPTIVE INTRAPERITONEAL INSTILLATION OF BUPIVACAINE AND INSTILLATION OF BUPIVACAINE AFTER THE CREATION OF PNEUMOPERITONEUM IN LAPAROSCOPIC CHOLECYSTECTOMIES"

By

DR. SPHOORTHY T M

Dissertation submitted to

BLDE UNIVERSITY, VIJAYAPUR, KARNATAKA.

In partial fulfillment of the requirements for the degree of

DOCTOR OF MEDICINE

IN

ANAESTHESIOLOGY

Under the guidance of

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DEPARTMENT OF ANAESTHESIOLOGY

B.L.D.E.U SHRI B. M. PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE.

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LIST OF ABBREVIATIONS USED

ASA	: American society of anaesthesiologists
BP	: Blood pressure
Bupi	: Bupivacaine
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	: Hour
IAP	: Intra abdominal pressure
IV	: Intravenous
IVPCA	: Intravenous patient controlled analgesia
IVRA	: Intravenous regional anaesthesia
LA	: Local anaesthetic
LC	: Laparoscopic cholecystectomy
Lido	: Lidocaine
MAP	: Mean arterial pressure
Na	: Sodium
NMDA	: N-methyl-d-aspartic acid
NO	: Nitric oxide

N_2O	: Nitrous oxide
No.	: Number
NSAID’s	: Non steroidalanti inflammatory drugs
NS	: Normal Saline
PABA	: P-amino- benzoic acid
PaCO2	: Partial pressure of arterial carbon dioxide
PACO2	: Partial pressure of alveolar carbon dioxide

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 study the efficacy of intraperitoneal Bupivacaine in reducing the initial postoperative pain when instilled as an preemptive analgesia and also to evaluate the postoperative shoulder tip pain.

AIM : This study aimed to evaluate the optimal timing of preemptive analgesia with Bupivacaine peritoneal instillation, the intensity of postoperative pain and the analgesia request rate in the initial 48 hours postoperatively.

SUBJECTS : This randomised study was conducted on 66 adult patients undergoing laparoscopic cholecystectomy under general anesthesia randomised into 2 groups of 33 each.

METHODS: It is a randomized controlled study of patients undergoing laparoscopic surgeries, where the patients were randomly allocated into two study groups- Group A and Group B. Patients allocated to *Group A* received 2mg/kg of 0.5% Bupivacaine diluted in 200ml normal saline before creation of pneumoperitoneum whereas the patients allocated to *Group B* received 2mg/kg of 0.5% Bupivacaine diluted in 200 ml normal saline after creation of pneumoperitoneum. 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 appearance of shoulder tip pain. The secondary endpoints

included the analgesia request rate in the initial 48 hours postoperatively.The statistical analysis done using Student t- test and Chi square test.

RESULTS: Significantly lower visual analog scores were observed in group A verses group B during the initial 24 hours. The patients in group A verses group B reported significantly lower pain at 4hours ($p=0.0001$) and 8hours ($p=0.0001$) postoperatively. None of the group A patients reported shoulder tip pain, whereas it was reported by most of the patients in group B. A significantly lower analgesia request rate was observed in group A verses group B ($p< 0.0423$).

CONCLUSION: Intraperitoneal instillation of Bupivacaine before the creation of pneumoperitoneum is much more effective for postoperative pain relief than when used after the creation of pneumoperitoneum.

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INTRODUCTION

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

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 postoperative pain compared to open cholecystectomy but still there is significant postoperative pain in considerable number of patients in the first 48 hours and this needs to be addressed as the necessity for postoperative analgesic may postpone discharge and increase hospital stay.

The better understanding of pain pathology following laparoscopic procedures has led to the instillation of local anaesthetics at intraperitoneal and port sites to reduce postoperative pain.[11] The use of local anaesthetics at the trocar site in combination with systemic opioids has been successful to an extent in reducing postoperative pain. The subcutaneous local anaesthetics along with opioids have shown to diminish pain scores but their duration is relatively brief (4-6 hours).[12] Furthermore, they do little to control shoulder, subscapular and generalised visceral pain.[13]

The inadequate pain control, drowsiness, postoperative nausea and vomiting, ileus, dry mouth, urinary retention and pruritis have been the major concerns to be addressed in the postoperative period as these have led to delayed return of full activities and reduced patient satisfaction.

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 pnemoperitoneum, 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 pnemoperitoneum, leading to neuropraxia of the phrenic nerve and local inflammatory stimuli such as ischemia, compression and chemical irritation stimulate the subdiaphramatic fibers. By evaluating the pathophysiology of pain it is shown that we can prevent or reduce pain by blocking the nociceptors before their stimulation by use of local anaesthetics.

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.

Decrease in postoperative pain after infiltration of local anaesthetics into the operative wound have been observed among patients who undergo herniorhaphy and

gynaecological procedures.[14,15] Postoperative catheter infusion of Bupivacaine into the subcostal incision during open cholecystectomy has been shown to decrease atelectasis, and reduce narcotic usage.[16] Continuous postoperative infusion of local anaesthetic agent into the abdominal wounds has reduced both postoperative pain and narcotic requirements.[17,18].

Local anaesthetic block generation and propogation of action potential in nerve and other excitable tissues in reversible manner, probably at the level of the passive sodium channels.[19-21] Bupivacaine is a widely used amide local anaesthetic. It is a potent agent capable of producing long duration of anesthesia and its tendency to provide more sensory than motor block has made it a popular drug for providing prolonged analgesia during laparoscopic cholecystectomies or the postoperative period. Bupivacaine is one such local anaesthetic which has a good safety profile, is long acting and free of side effects like gastritis due to NSAID's or nausea and vomiting and fear of drug dependence as in opioids.

Bupivacaine provides pain control for an average of 6 hours as it has a half-life of 2.5 to 3.5 hours.[22] There is a wide margin of safety for analgesic dose of Bupivacaine. Thus, pain relief and patient comfort during the early postoperative period becomes increasingly important, as the need for analgesic may delay discharge.

The infiltration of long-acting local anaesthetics as an adjuvant for regional or local anaesthetic techniques has shown to improvement in the management of postoperative pain. Furthermore, when administrated pre-emptively before surgery, these simple techniques are found to reduce anaesthetic, analgesic and opioid requirement postoperatively.

Many experimental and clinical studies have demonstrated the inhibitory effect of pre-emptive analgesia on the development of post traumatic hyperalgesia,

resulting in reduced post operative pain and total analgesic requirements.[23-29] The benefits of preemptively instilled local anaesthetic intraperitoneal has been concluded in 2 trials.

So the present study is a randomized trial to compare Bupivacaine solution administered in subdiaphramatic region either pre-emptively or after the creation of pnemoperitoneum regarding the effectiveness of analgesia. A greater emphasis is made on the intensity of total abdominal pain, the appearance of shoulder tip pain and the requirement of analgesics.

AIM OF THE STUDY:

To compare the effectiveness of analgesia with Bupivacaine solution administered in subdiaphramatic region pre-emptively and after the creation of pnemoperitoneum.

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.
  - The appearance of shoulder tip pain (time in hours) after surgery.

- 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.[30]

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.[31]

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.

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 gynaecological procedures. The first laparoscopic appendicectomy was done in the year 1981. The first Cholecystectomy was performed by Langenbuch on July 15, 1882 in Berlin.[32]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.[33] 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 cholecystitis

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

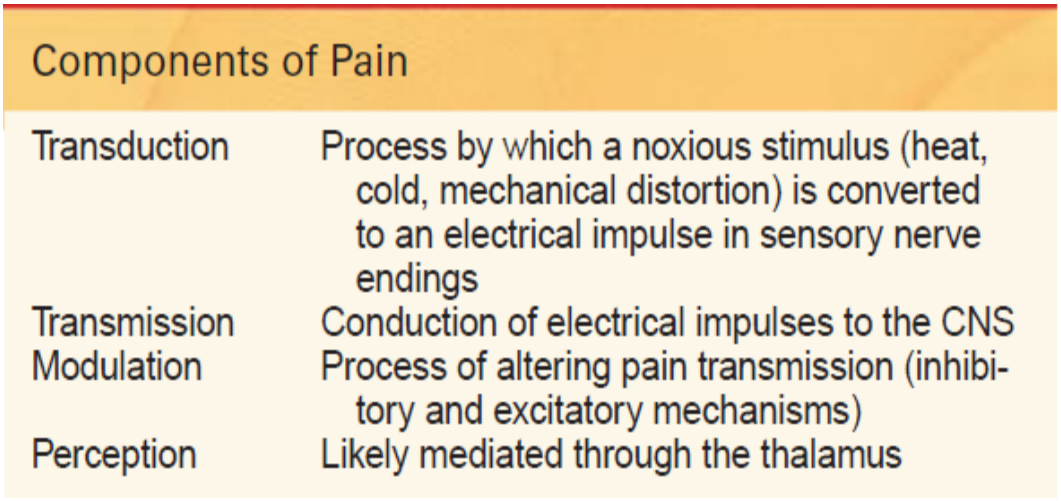
Pain is not just a sensory modality but an experience .The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage." This definition recognizes the interplay between the objective, physiologic sensory aspects of pain and its subjective, emotional and psychological components.[34]

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 behavioral 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 changes in blood pressure or heart rate.

NEURO-PHYSIOLOGY OF PAIN

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

FIGURE 1:



Components of Pain	
Transduction	Process by which a noxious stimulus (heat, cold, mechanical distortion) is converted to an electrical impulse in sensory nerve endings
Transmission	Conduction of electrical impulses to the CNS
Modulation	Process of altering pain transmission (inhibitory and excitatory mechanisms)
Perception	Likely mediated through the thalamus

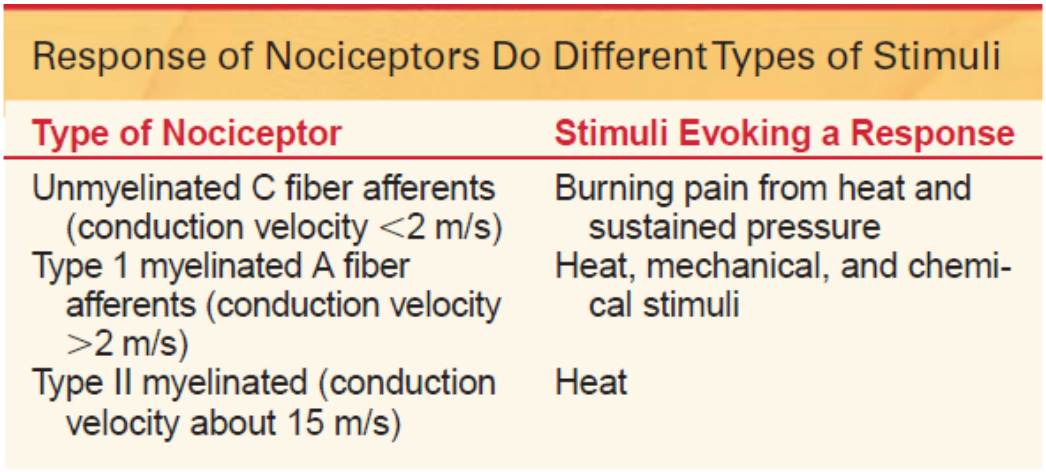
PERIPHERAL NERVE PHYSIOLOGY OF PAIN

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 end organs on the afferent neurons) and conducted by large myelinated nerve fibers, while protopathic sensation (pain) is sub served by high-threshold receptors (free nerve endings).[35]

Noxious sensations can often be broken down into two components: a fast, sharp, and well-localized sensation “first pain” which is conducted by Aδ fibers; and a duller, slower onset, and poorly localized sensation “second pain” which is conducted by C fibers. 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.

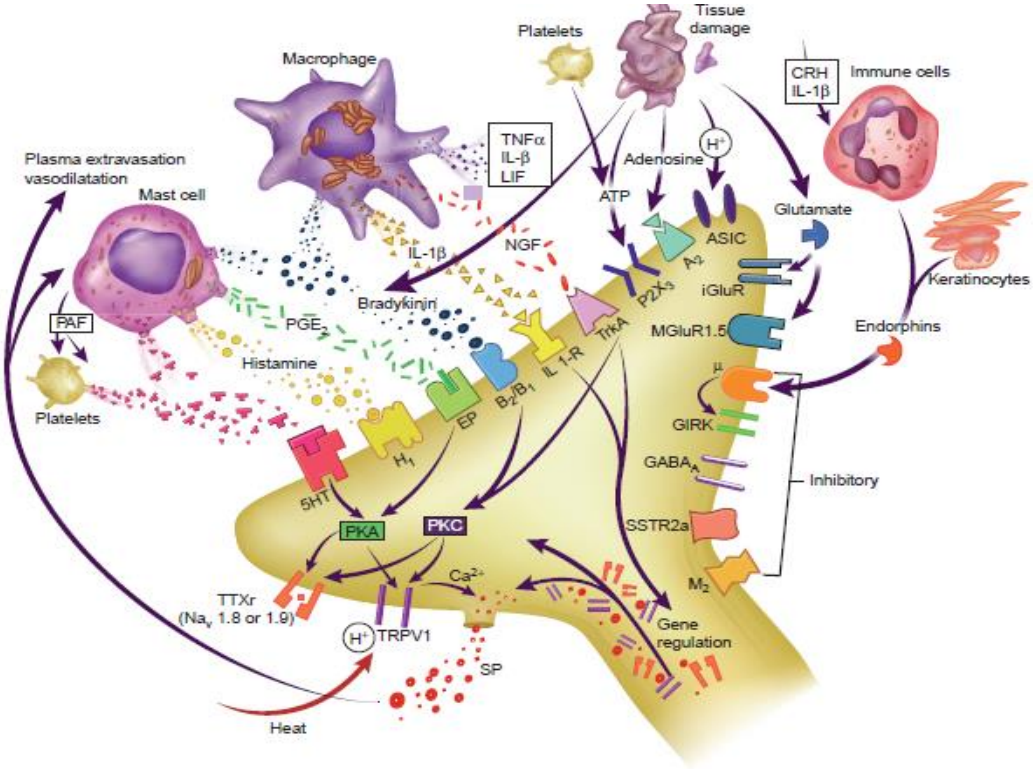
Nociceptors are either somatic that include those in skin and deep tissues (muscle, tendons, joints), or visceral nociceptors that include those in internal organs.[36]

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

1. The conditions associated with inflammation that do not resolve, resulting in sensitization of peripheral and central pain signaling 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:



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 Center for Nociception**

1. Afferent fibers 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 supra spinal brain regions if the gate is open, whereas painful stimulus is not felt if the gate is closed by the simultaneous inhibitory impulses (FIGURE: 6).

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 wind up 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: 7).

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.

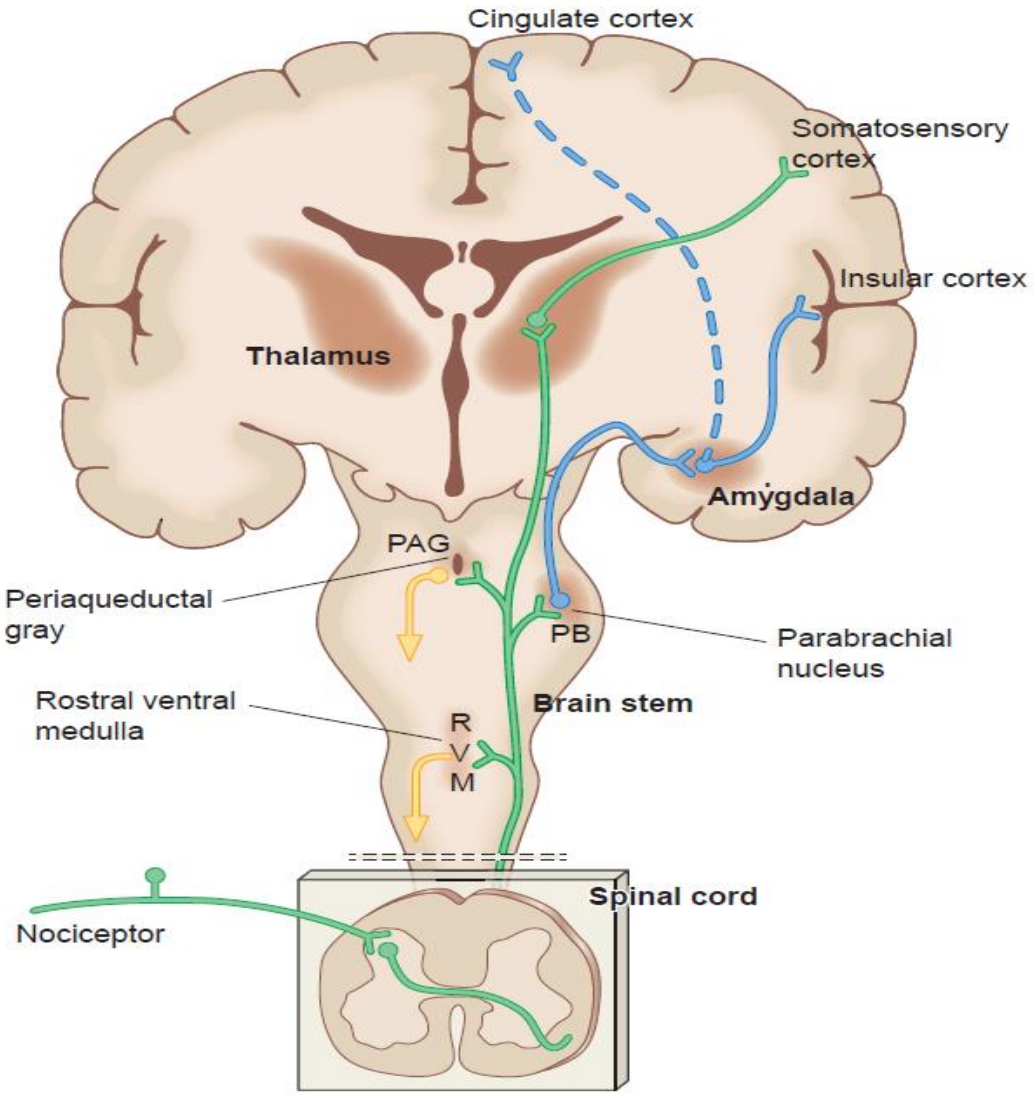
E. **Supraspinal Modulation of Nociception**

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**.

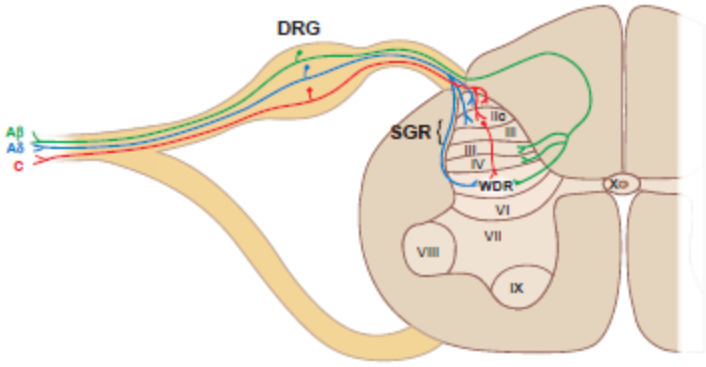
Originate from supraspinal regions and promote and suppress nociceptive transmission through the dorsal horn (FIGURE: 8).

FIGURE 4



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:



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:

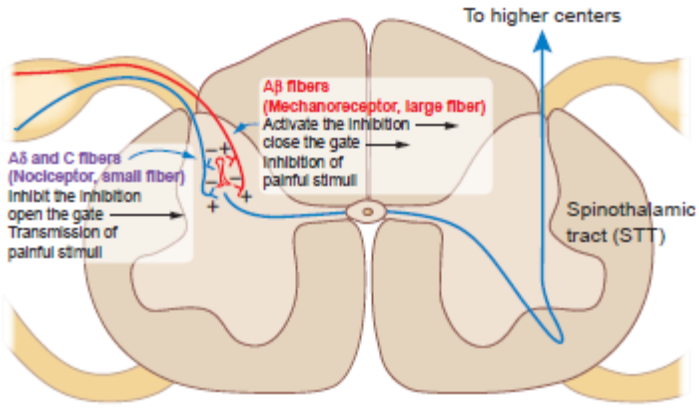
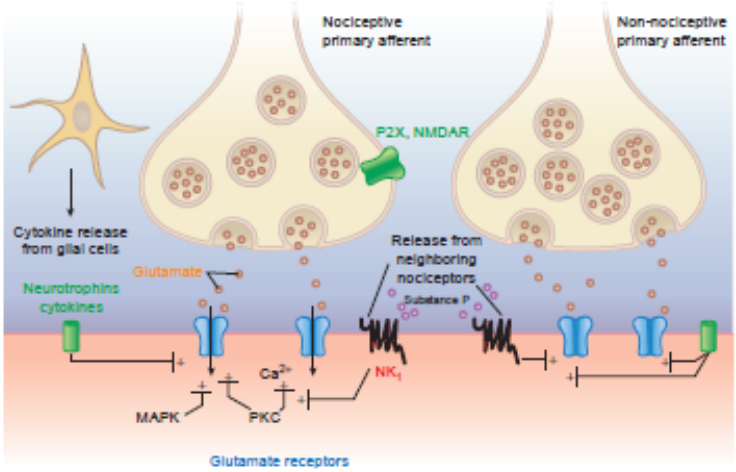


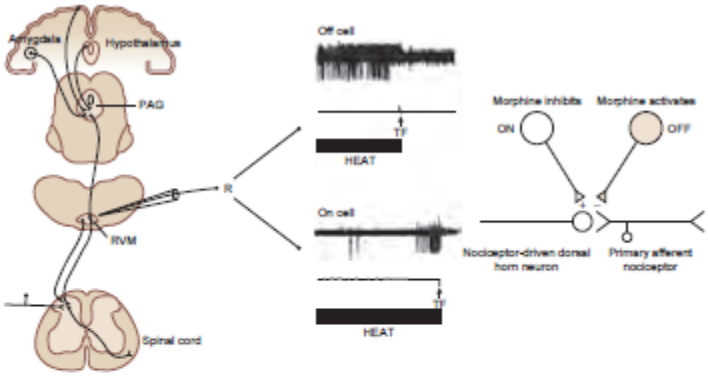
Illustration of gate theory for pain modulation in spinal dorsal horn. Lightly rubbing the skin of a painful, injured area seems to somehow relieve the pain. Large-diameter myelinated afferents (Aβ) conveying pressure and touch information have "faster" conduction speed than A-δ fibers or C fibers conveying 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 7:



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 8:



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 as to when acute pain 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 and diminishes with time and the likelihood that chronic pain will persist.

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, medicinal Cannabis) for neuropathic pain are only modestly effective.

3. The pathophysiologic processes that lead to neuropathic pain have the hallmark of a neuroinflammatory response following innate immune system activation.

B. **Visceral pain** is diffuse 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: 9)

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 fibers 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 or are normally silent wide dynamic range (WDR) neurons that can also receive 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".

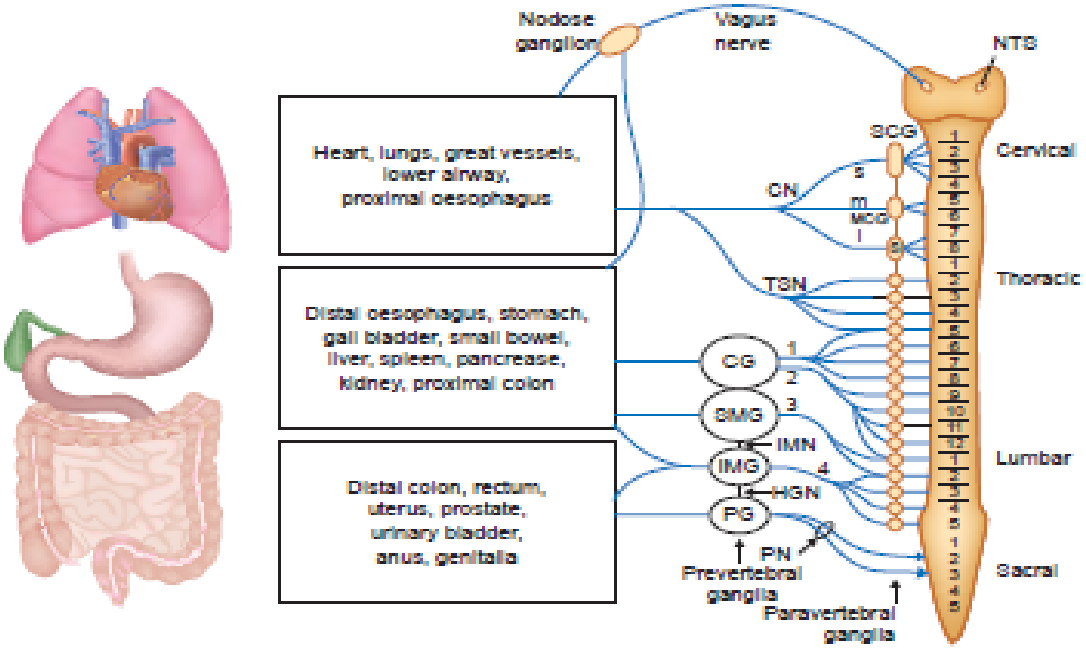
Lamina II of the gray matter of the dorsal horn of the spinal cord (also called the substantia gelatenosa) contains many interneurons and is believed to play a role in the processing and modulating nociceptive input.

Axons of most of the second order neurons cross the midline to the contralateral side of the spinal cord forming the lateral spinothalamic tract that send its fibers to the thalamus, the reticular formation, nucleus raphy and periaquidactal gray.[37,38]

THIRD ORDER NEURONS

Those are located in the thalamus and send their fibers to the somato-sensory area I and II in the cerebral cortex.[39,40]

FIGURE 9:



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.

Magnitude of the problem:

Many factors influence the occurrence, intensity, quality and the duration of postoperative pain like the site, nature and duration of operation, type of incision (thoracic and upper abdominal operations are associated with the most severe pain), the preoperative psychological, physical and pharmacological preparation of the patient, added to this the anaesthetic management and the quality of postoperative care (the attitude of the ward staff).[41]

PRE-EMPTIVE ANALGESIA, PAIN ASSESSMENT AND MANAGEMENT

Pre-emptive analgesia is defined as what is administered before surgical incision that prevent the development of central sensitization from incisional injury and inflammatory injuries (i.e., intraoperative and postoperative periods). The combination of experimental data and positive clinical trials strongly suggests that pre-emptive analgesia is a clinically relevant phenomenon. Maximum benefit is observed when there is complete blockade of noxious stimuli.[42]

Effects of postoperative pain

Moderate to severe acute pain, regardless of its site, can affect nearly every organ function and may adversely influence postoperative morbidity and mortality.

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.

(A) Cardiovascular effects:

Cardiac morbidity is a major cause of perioperative death. The realization that, in high risk populations, perioperative myocardial ischemia is most likely to occur after surgery (from day 1 to day 3 postoperatively) has led to treatment strategies designed to prevent its development.[43]

Although a variety of factors may contribute to the development of postoperative myocardial ischemia, including hypothermia, anemia, anxiety and tracheal intubation/suctioning, responses to poorly controlled pain play a prominent role. In this regard, activation of sympathoadrenal and neuroendocrine axis may have

a major impact on myocardial oxygen supply and demand. Catecholamine-induced tachycardia, enhanced contractility, increased afterload and increased preload from hypervolemia caused by enhanced release of Arginine, Vasopressin and Aldosterone, are well characterized determinants of increased oxygen demand. Increased oxygen demand, with hypervolemia, may precipitate ischemia and acute cardiac failure, especially in patients with poorly compensated coronary artery or valvular heart disease.[44]

Myocardial oxygen supply may be diminished as a result of pulmonary dysfunction, in particular, atelectasis secondary to pain-induced hypoventilation and pulmonary edema resulting from stress induced hypervolemia. Other causes of reduced oxygen supply include coronary artery constriction secondary to high circulatory levels of catecholamine and increased coronary sympathetic tone, stress induced increase in plasma viscosity and platelet induced occlusion; and serotonin induced coronary vasospasm secondary to platelet aggregation.

(B) Pulmonary effects:

Pulmonary function may be dramatically altered by surgically induced pain. The classical pulmonary response to upper abdominal surgery, include an increase in respiratory rate with decreased tidal volume, forced expiratory volume, vital capacity and functional residual capacity. These pathophysiologic alterations are characteristic of acute restrictive pulmonary disease and may be associated with clinically significant hypoxia and hypercarbia.[45]

Pain increases total body oxygen consumption and carbon dioxide production which necessitates an increase in the work of breathing. Patients with poor pain control (specially in upper abdominal and thoracic procedures) breathless deeply and have inadequate cough. This leads to further reduction in the tidal volume and

functional residual capacity which in turn can cause atelectasis, intrapulmonary shunting and hypoxemia.[46]

(C) Gastrointesinal effects:

Sympathetic hyperactivity induced by pain increases sphincter tone and decrease motility of intestine, causing ileus, pain also increases stress ulceration due to increase in gastric acid secretion.[47]

(D) Endocrinal effects:

The dominant neuroendocrine responses to pain involve hypothalamic-pitutary-adrenocortical interactions. Those interactions result in increased catecholamine and catabolic hormone release. This effect causes sodium and water retention, increased levels of blood glucose, free fatty acids and lactate. The negative nitrogen balance and protein catabolism may impede patient's convalescence.[48]

(E) Haematological effects:

The stress response causes decrease in the levels of natural anticoagulants, inhibition of fibrinolysis and increase in platelet reactivity which initiate a postoperative hypercoagulable state which in turn increases the risk of deep venous thrombosis and myocardial ischemia.

(F) Immunological effects:

The stress response potentiate postoperative immunosuppression by depressing the reticulo-endothelial system which predispose to infection.

G) Psychogenic effects:

Intense anxiety, fear and the loss of control that accompany severe tissue injury may have profound impact on the hypothalamic-pituitary axis. Sleep deprivation and reduced morale have been experienced in patients with poorly controlled postoperative pain.

In many patients, uncontrolled postoperative pain can produce a series of long-term emotional disturbances, which could impair the patient's health and cause undue fear and anxiety if subsequent surgery is required. Postoperative cognitive dysfunction occurs in up to 20% of patients after major non-cardiac surgery and may persist in about 10% of patients 3 months after surgery.[49]

Assessment of Pain

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."[50]

It is well recognized that a considerable variability both across patients and within a patient across time has been displayed between 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.[51] 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.[52]

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.[53]

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.[54]

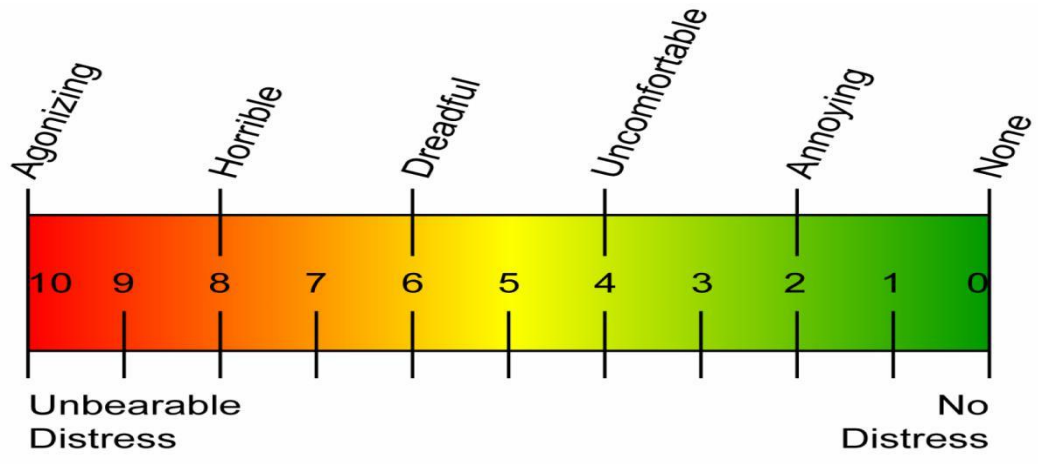
The unidimensional pain scales that can measure pain intensity and are self reported by the patients are verbal Rating Scale (VRS), numerical rating scale and

visual analogue scale (VAS) and in our hospital set up 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 centimeter. 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 10: 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 5- point scale where 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 s 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.[55]

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.[56] 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.[57] The variations in pain experiences are also greatly associated with patient's age.[58]

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 are the advantages of laparoscopy over open surgery.[59- 61] Laparoscopic surgery has the greatest advantage compared with open surgery of reduced postoperative pain. However, after laparoscopy patients frequently describe subdiaphragmatic and shoulder tip pain in addition to the discomfort of port site.[62,63] 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 hyperexcitability can be reduced or prevented.[64,65] Experimental studies have demonstrated pain hypersensitivity can result from post injury neuroplasticity and windup or expansion of receptive fields of central nervous system neurons.[66]

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".[67]

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.[68] There is still room for surgeons to improve management of post laparoscopy pain. First is patient's 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 are not likely to benefit from identical analgesic treatment.[69] 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.

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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 distention 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 distention 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 1st and 2nd postoperative day respectively. Thereafter, it normalizes to above 7.0.[70] 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.[71,72] 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.[73]

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.[72] 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 humidified gas. The exact relation between dry gas and postoperative pain is not yet determined.

B: Operational factors

1. **Wound pain**: From centre 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.[74]

2. **Wound drainage**: In the lateral aspect of the abdomen, traversing muscle layers wound drains after laparoscopic surgery are usually 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: Socio-cultural and individual factors

A study comparing the course after laparoscopic cholecystectomy in French and American patients effectively demonstrated how the socio-cultural 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, postoperative discomfort resolved within 2 weeks. A higher percentage of the Americans returned to work in a given period than did the French patients.[75]The individual postoperative pain perception and recovery time have 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 inter individual 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. However, by 24 hours after surgery 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.).[76]

Several surgical factors such as port incisions, the use of intra abdominal gas, and intra abdominal 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 regarding preparation for surgery, timing of procedures, function and roles of health-care providers, self care actions and information related to pain and discomfort) and 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 handling 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 good nursing care[53].

ACTIVE MEASURES

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

Systemic analgesics and adjuvant drugs.

Local infiltration and field block.

Regional analgesia with local anaesthetics.

Regional analgesia with combined local anaesthetics and opioid.

Electrical analgesia achieved with transcutaneous electrical stimulation or electroacupuncture.[78]

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.[79]

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-cahnnels, all of which decrease neuronal excitability[80].

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.[81]

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.[82]

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.[83] 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.[84] 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.[85]

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.[86]

PHARMACOLOGICAL PROPERTIES OF NARCOTICS:

CNS EFFECTS:

Opioids eliminates pain, depresses respiration, suppresses cough, stimulates the third nerve nucleus causing meiosis and stimulates the chemoreceptor trigger zone causing nausea and vomiting.[87]

HAEMODYNAMIC EFFECTS

Opioids cause bradycardia and decrease the sympathetic tone.[88]

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.[89]

B. NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

Non-steroidal anti-inflammatory 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 acting nociceptive 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 IV 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.[90]

D. NMDA ANTAGONISTS

A unique IV anaesthetic with analgesic like properties makes Ketamine preferred agent for induction and maintenance of anaesthesia as well as an analgesic adjuvant during local anaesthesia. Ketamine fell into disfavour in the late 1980s, as a result of its well known side-effect profile. However, because of the opioid-sparing effects and a less frequent incidence of adverse events and greater patient and physician acceptance, adjunctive use of small doses of Ketamine (0.1–0.2mgkg^{-1} IV) has been widely accepted. The use of local anaesthetics and/or opioid analgesics in combination with small-dose Ketamine has been described in several studies.[91]

Dextromethorphan, another NMDA receptor antagonist has been alleged to enhance opioid, local anaesthetic and NSAID-induced analgesia as it inhibits wind-up and NMDA mediated nociceptive responses in dorsal horn neurons. Dextromethorphan (90mg per oral) improved well-being and reduced analgesic consumption, pain intensity and sedation, as well as thermal-induced hyperalgesia in patients undergoing laparoscopic cholecystectomy or inguinal herniorrhaphy procedures.[92]

E. ALPHA-2 ADRENERGIC AGONISTS

Clonidine also improved and prolonged central neur-axial 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 (0.3mg IV) was apparently ineffective.[93]

Dexmedetomidine is a pure alpa 2-agonist that also reduces postoperative pain andopioid analgesic requirement. However, its use was associated with increased postoperative sedation and bradycardia.[94]

F. MISCELLANEOUS NON-OPIOID COMPOUNDS

Adenosine, Droperidol, Magnesium, Neostigmine and Gabapentin are non-opioid pharmacologic compounds used during the peri-operative 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 (1.2g per oral) reduced postoperative analgesic requirement significantly without increasing side effects.[95]

The antinociceptive effects of Magnesium when administered in bolus dose of $50mgkg^{-1}$ IV at induction of anaesthesia also led to improved pain control with less opioid medication and better patient satisfaction in the postoperative period. Of interest, intrathecal Magnesium was reported to prolong Fentanyl analgesia.[96]

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

relief after knee surgery. The primary adverse effects associated with neuraxial Neostigmine appear to be mild sedation and postoperative nausea and vomiting (15%–30%)[97].

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 intra-operative 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.

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, anticoagulation and bleeding diathesis.

The chief complications of interpleural analgesia are pneumothorax and local anaesthetic toxicity. Other complications of the technique include hemothorax, 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.[98]

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 sub hepatic space have been reported. Some to them failed to show analgesic effects, when 240mg of Lignocaine or 100mg 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.[99]

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 20-100mg 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 normal 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 oipiods, possibly due to reduction of vascular uptake.

IV. REGIONAL ANALGESIA WITH COMBINED LOCAL ANAESTHETICS AND OPIOIDS:

This approach assures more rapid analgesia, more effective blockade and the advantage of prolonged analgesia due to the combined actions of local anaesthetics and opioids. [100]

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.[102] 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.[103]

PHARMACOLOGY OF LOCAL ANAESTHETICS

STRUCTURE ACTIVITY RELATIONSHIP OF LOCAL ANAETHETICS:

Local anaesthetics consist of lipophilic group, usually a benzene ring, separated from a hydrophilic group, usually a tertiary amine, by an intermediate chain which includes an ester or amide linkage. Local anaesthetics are weak bases that usually carry a positive charge at the tertiary amine group at physiologic pH. The nature of the intermediate chain is the basis of classification of local anaesthetics into amide or ester. Local anaesthetics act by penetrating lipoprotein cell membrane in the non-ionized state. In order to make them suitable for injection, the non-ionized base has to be converted to the ionized state by injecting them in an acid solution as the hydrochloric salt so, tertiary amine group becomes quaternary and then they become water soluble and suitable for injection.[104]

STRUCTURAL ACTIVITY RELATIONSHIP:

A) POTENCY

An increase in the lipid solubility and/or increase in the molecular weight increase the potency of local anaesthetic. E.g. adding a butyl group to mepivacaine (less potent local anaesthetic) converts it into Bupivacaine (more potent local anaesthetic) Potency is affected by:

Fiber size: The smaller unmyelinated fibers (e.g. sensor C fibers) are more effectively blocked than the large myelinated fibers (motor A fibers).

pH: Acidic pH antagonize the block.

Frequency of nerve stimulation: Access of local anaesthetic to Na channels is enhanced by repeated opening of those channels.

1) **SPEED OF ONSET OF ACTION*:*** And this depends on:

pKa of the drug: Local anaesthetics with pKa closer to the physiologic pH have a higher concentration of the non-ionized free base that can cross the nerve cell membrane.

Molecular weight: Local anaesthetics with smaller molecular weight have more rapid onset of action.

2) **DURATION OF ACTION**

It depends on the aromatic group which affect the plasma protein binding. The higher the plasma protein binding the slower the clearance and thus the higher the duration of action. Also, higher protein binding increase the duration of affection of the local anaesthetic to the Na channels and thus prolong the action.

The myelinated nerves are protected by the myelin sheath which acts as an insulator. There is a resting potential of -70 mV on the outside of the membrane, which rises to about -55 mV , the firing threshold, before it jumps up to +20 mV to form an action potential which constitutes a change of about 90 mV . This is associated with movements of sodium ions inwards and potassium ions outwards. The membrane becomes depolarized. During recovery, the ions reverse the direction of their movements across the cell membrane. Local anaesthetics prevent the depolarization of the nerve membrane and so prevent conduction of impulses.[105]

PHARMACOKINETICS OF LOCAL ANAESTHETICS

(1) ABSORPTION

Factors that affect the absorption of local anaesthetic are:

Site of injection: Highly vascular tissues show increase in the systemic absorption of local anaesthetic and thus increase toxicity (I.V > tracheal > epidural > subcutaneous).

Presence of vasoconstrictors: Vasoconstrictors decrease the systemic absorption and thus decrease the toxicity, this is only effective in short acting local anaesthetic e.g. lignocaine.

Type of local anaesthetic: Local anaesthetics with high tissue binding are more slowly absorbed e.g. etidocaine.

1. DISTRIBUTION

Distribution of local anaesthetics is affected by:

Tissue perfusion: Highly perfused organs (brain, liver) show higher uptake than poorly perfused organs (muscles and fat) *Plasma protein binding:* the higher the protein binding the longer the time of retain of local anaesthetic in the blood.

METABOLISM

The metabolism and excretion of local anaesthetics differ depending upon their structure. Ester local anaesthetics are predominantly metabolized by pseudocholinesterase. Also one of the metabolites of ester local anaesthetics is P-amino-benzoic acid (PABA) which is highly allergenic. Patients with genetically abnormal pseudocholinesterase are at increased risk of toxic side effects.

Amide local anaesthetics are metabolized by microsomal enzymes in the liver. Decrease in hepatic function or liver blood flow will reduce the metabolic rate and predispose patients to systemic toxicity. And allergic manifestations are less common.

(4) PROTEIN BINDING

Local anaesthetics are bound to plasma proteins to varying degrees. It is assumed sometimes that drugs with the greatest degrees of protein binding are less toxic because only a small fraction of the total amount in plasma is free to diffuse into the tissues and produce toxic effects. Furthermore, even if a drug is bound to protein, it is still available to diffuse into the tissues down a concentration gradient, as the bound portion is in equilibrium with that in solution in plasma.

BUPIVACAINE

SOURCE: A synthetic drug, was prepared by A. F. Ekenstam in 1957.

CHEMISTRY: Molecular weight of the Chloride salt is 325 and that of the basefonn is 288.

MELTING POINT: 258°C

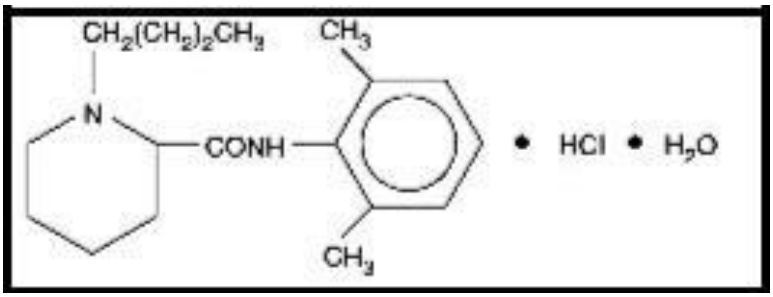
pH: Solutions containing epinephrine has a pH of about 3.5

pKa: 8.1

CHEMICAL NAME: Bupivacaine is an anilide compound. Chemical name is 1 -n-butyl-DL-piperidine-2- carboxylic acid 2,6 dimethylanilide hydrochloride.

MOLECULAR FORMULA: $C_{18}N_2OH28HCl$.

FIGURE 11: CHEMICAL STRUCTURE BUPIVACAINE



PHYSIOCHEMICAL PROPERTIES

SOLUBILITY: The base is sparingly soluble but the hydrochloride is readily soluble in water.

STABILITY AND STERILIZATION: It is highly stable and can withstand repeated autoclaving.

ANAESTHETIC PROPERTIES

POTENCY: Bupivacaine is approximately 3 -4 times more potent than Lidocaine and 8times more than Procaine.

The duration of action for local anaesthesia is 2 -3 times longer than that of Mepivacaine or Lidocaine and 20 -25% longer than that of Tetracaine.

Maximum safe dose: $3mgkg^{-1}$.

TOXIC EFFECTS OF LOCAL ANAESTHETICS

Local anaesthetic toxicity is a function of plasma free drug concentration and is influenced by the drug the dose and the injection site.

(1) Central nervous system:

The early symptoms of toxicity are numbness of the tongue and circumoral region, tinnitus and are encountered most frequently in patients on intravenous antiarrhythmic therapy. Thus, central stimulation followed by depression, hysterical behaviour, vertigo, tremor, convulsions, and respiratory failure may occur.

(2) Cardiovascular System

Local anaesthetics directly depress myocardial conduction and myocardial contractility in a dose-dependent manner, leading to hypotension, bradycardia, pallor, and sweating. This type of intoxication may be due to a rapid absorption of the drug.[106]

(3) Respiratory Depression

This may progress to apnea from medullary depression or respiratory muscle paralysis.

(4) Allergic Phenomena

Allergy rarely takes the form of bronchospasm, urticaria or angioneurotic edema.It is well documented in association with the use of ester linked agents, including dermatitis in personnel handling procaine. Allergy to amide linked agents is extremely rare.[107]

(5) Drug Interactions

Non-depolarizing muscle relaxant blockade is potentiated by local anaesthetics. Pseudocholinesterase inhibitors can lead to decrease metabolism of ester local anaesthetics. Cimetidine and Propranolol decrease hepatic blood flow and Lidocaine clearance. Opioids and adrenergic agonists potentiate local anaesthetic pain relief.

TREATMENT OF TOXICITY

Prevention of toxicity is important by avoidance of accidental intravascular injection and by avoidance of overdosing. Facilities for treatment must always be available before doing the block. The airway is maintained and oxygen administered using artificial ventilation if apnea occurs. Convulsions may be controlled with small increments doses of either Diazepam (2.5mg) or Thiopentone (50mg). Excessive doses should not be given to control convulsions, since cardiorespiratory depression may be exacerbated. If cardiovascular collapse occurs despite adequate oxygenation, it should be treated with an adrenergic drug with alpha and beta agonist properties, e.g., ephedrine 3-5 mg increments. Bretylium should be considered for treatment of ventricular arrhythmias produced by Bupivacaine.

Goldstein A et al in 2000 while comparing intraperitoneal 0.5% Bupivacaine, 0.75% Ropivacaine and saline instillation for postoperative pain relief found that local anaesthetics gave significantly good pain relief with Ropivacaine being better than Bupivacaine in both analgesia and opioid sparing effect.[108]

Many other studies during intraperitoneal instillation of 0.5% Bupivacaine with or without Adrenaline for postoperative pain relief in patients undergoing laparoscopic cholecystectomy, laparoscopic pelvic surgery and diagnostic laparoscopy. They concluded that locally instilled Bupivacaine produces significant postoperative analgesia and the requirement of analgesics was reduced.[109-112]

Palmes D et al studied the effect of intraperitoneal local anaesthesia for postoperative pain relief for two different type of surgeries and showed that local

anaesthetic was effective in reducing pain in laparoscopic fundoplication rather than laparoscopic hernia repair.[113]

Though all these studies proved that local instillation of Bupivacaine is effective in postoperative pain relief, few earlier studies have different opinion. Retzell M et al 1995 and Joris J et al 1995 studied the postoperative analgesic effect of locally instilled Bupivacaine in laparoscopic cholecystectomy patients. They opined that there is no significant postoperative pain relief in these patients.[114,115]

REVIEW OF LITERATURE

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.[13]

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.[6]

Szem J W, Hydo L, Barie P S (1996), performed randomized, double-blind, placebo-controlled study to determine the efficacy of intraperitoneal Bupivacaine in laparoscopic cholecystectomies. 55 patients were evaluated in this study. 29 patients were administered placebo (saline) and 26 patients were administered Bupivacaine (0.1%). The right hemidiaphragm, over the gallbladder serosa, over Glisson's capsule and into the subhepatic space were irrigated with 100 ml of solution prior to any dissection of the gallbladder. Postoperatively, analgesic medication usage, frequency of nausea and vomiting and pain scores were recorded during hospitalization. To continue monitoring medications and pain for the first 48 h at home, a questionnaire was given to each patient upon discharge. Postoperative pain was significantly reduced ($P < 0.05$) in the patients who received Bupivacaine, but the effect was reserved and observable only during the first 6 h after surgery but there was no significant reduction in the amount of analgesic medication, nausea, vomiting, or shoulder pain in the patients who received Bupivacaine when queried specifically. It was concluded that a noticeable benefit to patients undergoing laparoscopic cholecystectomies found with intraperitoneal Bupivacaine was transient and had little impact upon the patient's convalescence. [19]

Pasqualucci A, *et al.,* (1996) conducted a study with the purpose to assess the effectiveness of preemptive analgesia and to detect any deviation in pain intensity, in endocrine metabolic response and in the demand for postoperative analgesia between patients who received no treatment and those who received local anaesthetic before and after the surgery. In addition, to study whether the local anesthesia administered before or after surgery would give a different response. 120 patients undergoing laparoscopic cholecystectomy under general anesthesia along with topical peritoneal local anaesthetic

or saline were studied. The local anaesthetic (0.5% Bupivacaine with epinephrine) or placebo solutions were given as follows: immediately after the creation of a pneumoperitoneum and at the end of the operation. Patients were randomly prearranged to one of four groups of 30 patients each. Group A (placebo) received 20 ml 0.9% saline both before and after surgery, group B received 20 ml 0.9% saline before surgery and 20 ml local anaesthetic after surgery, group C received 20 ml local anaesthetic both before and after surgery, group P received 20 ml local anaesthetic before and 20 ml 0.9% saline after surgery. Assessment of pain was done using visual analog scale and verbal rating scale every 4 hours for the first 24 hours after surgery. Metabolic endocrine responses (blood glucose and cortisol concentrations) and analgesic requirements also were investigated.

It was concluded that postoperative pain and analgesic consumption were found to be lesser when local anaesthetic was administered before or after surgery than placebo-control condition. [10]

Tsimoyiannis E C, Siakas P, Tassis A, Lekkas E T, Tzourou H, Kambili M (1998), performed a prospective randomized study to find out the efficacy of intraperitoneal infusion of normal saline on postoperative pain following laparoscopic cholecystectomy. 300 patients were randomized to one of the 5 groups of 60 each. Group A did not receive peritoneal infusion, subhepatic drain was not placed. Group B did not receive peritoneal infusion but a subhepatic drain was placed for 24hours. Group C received normal saline 25-30 ml/kg body weight at a temperature of 37^0C infused under the right hemidiaphragm and left in the peritoneal cavity. Group D received normal saline in a room temperature was infused under the right hemidiaphragm and suctioned after the

pneumoperitoneum was deflated. Group E received normal saline infused and suctioned as in group D, but a subhepatic closed drain was left for 24 hours. Postoperatively, pain scores, analgesic medication usage, nausea and vomiting were determined at 2, 6, 12, 24, 48, and 72 hours. The result was that significant decrease in postoperative pain with subdiaphragmatic infusion of normal saline thereby resulting in pain-free patients.[115]

Cunniffe M G, McAnena O J, Dar M A, Calleary J, Flynn N, Galway (1998), conducted a study prospectively to evaluate the efficacy of intraoperative irrigation of the diaphragm with Bupivacaine to abrogate postoperative shoulder-tip pain (STP). Intraperitoneal irrigation with Bupivacaine to both hemidiaphragms at the end of surgery significantly reduces both frequency and intensity of shoulder tip pain following laparoscopic procedures thus reducing patient morbidity. [5]

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 need further technical development.[116]

M. Elhakim,M. Elkott,N. M. Ali,H. M. Tahoun (2000), evaluated the use of intraperitoneal Lidocaine in relieving postoperative pain in this double-blind study which included 59 patients. At the end of surgery, under the right diaphragmatic surface was splashed with 200 mg lidocaine diluted to 200ml with Normal Saline or the same volume of saline. Postoperative shoulder and abdominal pain intensity were recorded on a numeric grading scale and a visual analogue scale, respectively. Analgesic consumption was also recorded. Respiratory function tests before and after surgery was also compared. The results showed that in the Lidocaine group the incidence of STP was 12% with scoring 2.5±0.5 for duration of 1.6±0.01 h compared to 40% patients scoring 3.9±0.2 for duration of 17.9±0.2 h in the control group. Significantly less abdominal pain during the first postoperative day (P<0.05) Lidocaine treated patients. "No pain on deep inspiration" in 72% of patients in the Lidocaine group compared to 8% in the control group. A greater reduction in analgesic consumption for 24 h after surgery in Lidocaine group (P<0.05).So the study concluded Intraperitoneal lidocaine greatly reduces postoperative pain after a single administration.[117]

Maestroni *et al,* (2002) conducted this study to test a new method of pre-emptive analgesia. By simple randomization 60 Patients were allocated to two groups of 30 in each group. The placebo group A patients were administered 200 ml of 0.9% saline and patiernts in group B were given 5 mg/kg of a local anaesthetic solution (Ropivacaine) in 200 ml of 0.9% saline. Both administered before the creation of pneumoperitoneum. This study supported the clinical validity of pre-emptive analgesia as the pain intensity was significantly less in the group receiving Ropivacaine.[9]

Papagiannopoulou P, Argiriadou H, Georgiou M, Papaziogas B, Sfyra E, Kanakoudis F (2003), carried out this randomized, double-blind study to compared Ropivacaine and Levobupivacaine in relation to their analgesic efficacy after laparoscopic cholecystectomy for pain control. 57 ASA I and II patients scheduled for laparoscopic cholecystectomy either received local infiltration with 20ml of 0.9% saline solution (Placebo group, n = 18), 20ml of Ropivacaine 1% (Rop group, n = 20), or 20ml of Levobupivacaine 0.5% (Lev group, n = 19) administered, prior to trocar placement. Visual analogue scale (VAS) used to record pain scores. Analgesic consumption was aslso recorded. So, the study concluded that pain following laparoscopic cholecystectomy can be effectively reduced by local tissue infiltration with Levobupivacaine.[26]

Hernández-Palazón J, Tortosa JA, Nuño de la Rosa V, Giménez-Viudes J, Ramírez G, Robles R (2003), performed this double-blind, randomized study in patients undergoing laparoscopic cholecystectomy to assess the analgesic effect of the intraperitoneal administration of Bupivacaine and Morphine. At the end of the procedure, intraperitoneal injection of one of the following combinations was given. The patients in group 1 received 30 ml of NS, those in group 2 was given 30ml of Bupivacaine 0.25%, patients of group 3, 30 mL of Bupivacaine 0.25% plus Morphine 2 mg. In addition, 2 mg i.v Morphine in 2 mL saline and 2 mL saline IV given in group 2 and Groups 1, 3 respectively. VAS and VRS were used to evaluate postoperative pain for 24 hours. Metamizol administered by an IV PCA device to assess the postoperative analgesic requirement. It was concluded that pain after laparoscopic cholecystectomy effectively

controlled with intraperitoneal Bupivacaine 0.25% and IV Morphine and also reduced the analgesic requirements during the first 6 postoperative hours.[118]

A randomized, double-blind, placebo-controlled study was carried out by **M. Barczyński,A. Konturek,R. M. Herman** (2006), with the aim to assess the optimal timing of pre-emptive analgesia with Bupivacaine peritoneal instillation. Four groups of 30 each were made and patients in group A were given 2 mg/kg of Bupivacaine in 200 ml of normal saline before thye pneumoperitoneum was created, those in group B were administered 2 mg/kg of Bupivacaine in 200 ml of normal saline after the pneumoperitoneum was created. Patients in group C were administered 200 ml of normal saline before the pneumoperitoneum was created whereas patients in Group D received 200 ml of normal saline after the pneumoperitoneum was created. The postoperative pain scores visual analog scale and incidence of shoulder tip pain was noted along with the documentation of the analgesia request rate, latency of nurse-controlled analgesia activation and analgesic consumption. Although the effect of Bupivacaine peritoneal instillation is noticeable when used both before and after creation of pneumoperitoneum, it confers significantly greater benefits when used before creation of pneumoperitoneum.[29]

Boddy AP, Mehta S, Rhodes M (2006), carried out a systematic review and meta-analysis to find out the efficacy of intraperitoneal local anaesthetic technique in reducing postoperative pain following LC. 24 RCTs that met inclusion criteria were included for a systematic literature search. Quantitative analysis could be done in 16 studies due to sufficient data. Using a random effects model, the weighted mean differences (WMD) in visual analog pain score at 4 h after surgery were pooled. This

metaanalysis concluded that the intraperitoneal local anesthesia results in a statistically reduced postoperative abdominal pain.[98]

Kucuk C[1], Kadiogullari N, Canoler O, Savli S (2007), carried out this placebo-controlled study to determine the effect of local anaesthetic instillation, to compare Bupivacaine and ropivacaine in patients undergoing a laparoscopic cholecystectomy. A total of 80 patients were randomly assigned to four groups to receive the intraperitoneal instillation of 21ml of either 100mg Bupivacaine (Group B), 100mg Ropivacaine (Group R1), 150mg Ropivacaine (Group R2) or saline with Epinephrine 1/200,000 at the end of the surgery. The postoperative pain was evaluated and the analgesic requirement was also assessed. It was found that the intraperitoneal instillation of 100mg Bupivacaine, 100mg Ropivacaine, or 150mg Ropivacaine at the end of a laparoscopic cholecystectomy significantly reduced the Morphine consumption during the first 24 h. For preventing postoperative pain 150mg Ropivacaine proved to be significantly more effective than either 100mg Bupivacaine or 100mg Ropivacaine. This showed that the intraperitoneal instillation of local anaesthetic during laparoscopic cholecystectomy is a noninvasive, rapid, safe and simple analgesic technique that reduces the total Morphine consumption during first 24 h.[119]

Malhotra N, Chanana C, Roy K K, Kumar S, Riwari V, Sharma J B (2007), conducted a prospective randomized study to evaluate the effect of two doses of intraperitoneal Bupivacaine administration for pain relief after operative gynaecological laparoscopy. 52 women undergoing gynaecological laparoscopic surgery were included in the study group. Group A received 10ml (50mg) of 0.125% Bupivacaine and group B received 0.25% Bupivacaine (100 mg) intraperitoneally at the end of the procedure.

Pain was assessed at 2, 4, 6 and 8 h intervals postoperatively on a scale of 0–10. The results were compared and it was concluded that 100mg Bupivacine provided longer postoperative pain relief and that it is better than 50mg of Bupivacaine (4–6 h).[120]

Alkhamesi NA, Peck DH, Lomax D, Darzi AW, published their study in April 2007, which analysed the use of intraoperatively delivered aerosolized intraperitoneal Bupivacaine and its ability to reduce postoperative pain. 80 patients were recruited and divided randomly into four groups: control (n = 20) received no drug, aerosolized Bupivacaine (n = 20) administered to group A, aerosolized normal saline (n = 20) was administered to group B, and Bupivacaine was administered in the bladder bed (n = 20). Pain scores were documented at 6, 12, and 24 h postoperatively using pain scoring scale. It was found that aerosolized Bupivacaine appreciably reduced postoperative pain ($p < 0.05$) and thereby reduced opiate use and hospitalization.[121]

D. Palmes,S. Röttgermann,C. Classen,J. Haier,R. Horstmann, published in 2007 a randomized clinical trial which compared pre-emptive *versus* postoperative intraperitoneal LA with regard to the analgesic effect in two different types of laparoscopic surgery. 133 patients undergoing laparoscopic fundoplication or hernia repair were randomly assigned to three groups. Group A received placebo solution (50 ml 0·9 %saline), group B received LA (50ml 0·5% Lidocaine) after creation of the pneumoperitoneum and group C received LA (50ml 0·5 % Lidocaine) after the surgery. Pain was assessed at 6, 12, 24 and 48 h after surgery using a visual analogue scale (VAS) from 0 to 100. The duration of pneumoperitoneum (median 66 *versus* 46 min respectively; $p < 0{\cdot}001$) and overall pain intensity (median VAS score 46·7 *versus* 6·5; $p < 0{\cdot}001$) were higher for laparoscopic fundoplication than for hernia repair. Preoperative application of LA reduced abdominal pain (median 28·6 *versus* 74·9; $p < 0{\cdot}005$), shoulder pain (median 24·3 *versus* 43·8; $p = 0{\cdot}004$) and analgesic consumption (mean(s.d.) 11·1(5·0) *versus* 18·5(5·4)mg Piritramide per 48 h; $p = 0{\cdot}002$) after fundoplication, but had no analgesic effects after hernia repair. The study concluded that pre-emptive analgesia greatly reduced postoperative pain after laparoscopic fundoplication.[11]

Sherwinter D A, Ghaznavi A M, Spinner D, Savel R H, Macura J M, Adler H (2008), with a view to verify the safety and efficacy of On-Q pump delivery system for intraperitoneal instillation of local anaesthetics conducted a randomized clinical trial with thirty patients undergoing laparoscopic adjustable gastric banding were randomly assigned to one of two groups. On-Q pump systems filled with 0.375% Bupivacaine was administered to treatment group, while pumps filled with 0.9% normal saline were

administered to control groups. The intraperitoneally introduced pump's catheter delivered Bupivacaine or saline for the first 48 h after surgery. At preset intervals pain scores were evaluated. This trial suggested that the use of continuous intraperitoneal Bupivacaine using the On-Q pain pump system resulted in significant reduction in postoperative pain.[122]

Pappas-Gogos G, Tsimogiannis KE, Zikos N, Nikas K, Manataki A, Tsimoyiannis EC(2008), performed this trial in patients undergoing laparoscopic cholecystectomy to evaluate the use of preincisional and intraperitoneal Ropivacaine, with or without normal saline, in reducing postoperative pain. 120 patients randomized to 6 groups. Preincisional local infiltration of Ropivacaine was performed for all the patients,. Group A was infused Ropivacaine at the beginning of the LC. Group B was infused Ropivacaine at the beginning along with normal saline infusion at the end. Group C received Ropivacaine and normal saline at the end of the LC. Group D was administered Ropivacaine at the beginning and normal saline infusion at the end along with a subhepatic closed drain. Group E received Ropivacaine at the end of the LC. Group F (control group) did not receive any of these. Pain (VAS) was recorded at 2, 4, 6, 12, 24, 48, and 72 h postoperatively).This study gave a safe and valid method for reducing pain after LC i.e., preincisional infiltration of local anaesthetic and Ropivacaine infusion intraperitoneally at the beginning along with normal saline infusion at the end of the procedure.[123]

Akinci SB, Ayhan B, Aycan IO, Tirnaksiz B, Basgul E, Abbasoglu O, Aypar U, Sayek I (2008), conducted this double-blind study in sixty-one patients undergoing LC to compare intraperitoneal Tramadol with intravenous Tramadol or normal saline

with regard to the analgesic efficacy. Patients were randomized to one of three groups. All patients received an intravenous and an intraperitoneal injection after installation of the pneumoperitoneum and again before removal of the trocars. In the control group, all injections were with normal saline. In the intravenous Tramadol group, patients received intravenous Tramadol 100mg and intraperitoneal saline. In the intraperitoneal Tramadol group, patients received intravenous saline and intraperitoneal Tramadol 100 mg. Morphine was used for postoperative analgesia. Pain scores were recorded postoperatively. The intravenous Tramadol group during the first postoperative hour showed lower pain scores ($p < 0.016$). The latency of analgesia request was longer in intravenous Tramadol group (median 23 min, range 1-45), when compared with the intraperitoneal Tramadol group (10, 1-120 min, $P = 0.263$) or with the control group (1, 1-30 min, $P = 0.015$). In the intravenous Tramadol group (mean +/- SD; 3.4 mg +/- 2.5) and Morphine consumption in the intraperitoneal Tramadol group (4.4 +/- 4.3 mg) was significantly lower compared with the control group (6 +/- 2 mg) ($p = 0.044$). This study concluded that superior postoperative analgesia in the early postoperative period after laparoscopic cholecystectomy intravenous Tramadol than an equivalent dose of Tramadol administered intraperitoneally and with normal saline following laparoscopic cholecystectomy.[124]

Golubović S, Golubović V, Cindrić-Stancin M, Tokmadzić V S (2009), performed a study to measure the analgesic effect of Bupivacaine and Tramadol administered intraperitoneal in patients posted for laparoscopic cholecystectomies. 144 patients were randomized in one of four groups: Patients in Group C were administered with 50ml of saline, those in Group T were administered with 50ml of saline containing 100mg

Tramadol, Patients in Group B were administered 50ml of 0.25% Bupivacaine while the patients allocated to Group TB were given 50ml of 0.25% Bupivacaine with 100mg of Tramadol. VAS scores were recorded at half and hours, 1, 2, 4, 6 and 24 hours postoperatively. The study demonstrated that it is an effective method for management of postoperative pain after laparoscopic cholecystectomies.[125]

Papadima A, Lagoudianakis EE, Antonakis P, Filis K, Makri I, Markogiannakis H, Katergiannakis V, Manouras A (2009), conducted a study with repeated intraperitoneal instillation of Levobupivacaine for the management of pain after laparoscopic cholecystectomy. A total of 71 patients were randomized to receive either intraperitoneal analgesic (IPA group) or not (controls). At the completion of cholecystectomy, 10mL of Levobupivacaine 0.5% were infused intraperitoneally in the IPA group and 8 h postoperatively, whereas in the controls, 10mL of 0.9% NaCl were administered in the corresponding points of time. Differences in pain scores between groups were the primary end points. Opioid consumption and adverse effects were the secondary end points. At all points of time measured, the IPA group compared with controls had a lesser VAS score at rest and at movement. Moreover, in the control group patients Fentanyl consumption in the recovery room, rescue analgesia request and the Meperidine consumption was greater in the control group. This trail concluded that significant reduction in postoperative pain, following LC when Levobupivacaine was administered intraperitoneally.[126]

Alper I, Ulukaya S, Ertuğrul V, Makay O, Uyar M, Balcioğlu T (2009), conducted study to determine the effects of Levobupivacaine instilled intraperitoneally to control pain after laparoscopic cholecystectomy. Levobupivacaine 0.25% (15mL) infiltration was used prior to skin incisions for trocar insertion. After pneumoperitoneum was created, patients received intraperitoneally either 40 mL of 0.25% Levobupivacaine (LB group, n=20) or normal saline (NS group, n=20). Data of, postoperative pain relief recorded in both groups. In the first half-hour, lower postoperative pain scores period in the LB group than in the NS group ($p<0.05$). However, no significant difference between the incidence of right shoulder pain was noted between the LB group (10%) and NS group (15%). A significantly lower mean dose of Meperidine consumption and patients needing rescue Meperidine in the LB group than in the NS group ($p<0.05$). It concluded that intraperitoneal Levobupivacaine 0.25% given immediately after pneumoperitoneum into the hepatodiaphragmatic lodge and above the gallbladder demonstrated significant reduction in postoperative pain relief after laparoscopic cholecystectomy[127].

El-Labban GM, Hokkam EN, El-Labban MA, Morsy K, Saadl S, Heissam KS (2011), designed this randomised controlled study to evaluate the effect of Levobupivacaine 0.25% on post-operative pain in laparoscopic cholecystectomy. 189 patients were randomized to 3 groups. Group 1 (control group)patients did not receive any drug. Group 2 patients received intraincisional of 20ml of Levobupivacaine 0.25% while those in group 3 received 20ml of Levobupivacaine 0.25% intraperitoneally. Post-operative pain was recorded for 24 hours postoperatively.

So,the study found that postoperative abdominal pain was significantly lower with intraincisional infiltration of Levobupivacaine and that the intraperitoneal route was more effective in controlling post-operative shoulder pain.[128]

Castillo-Garza G, Díaz-Elizondo JA, Cuello-García CA, Villegas-Cabello O (2012), published a study which was carried out with the aim to assess the effect of Bupivacaine instilled at the surgical bed on relief of postoperative pain following laparoscopic cholecystectomy. 60 patients undergoing laparoscopic cholecystectomy were randomized to the placebo group (n=30) which received 20ml saline and the Bupivacaine group (n=30) which received 20ml of 0.5% Bupivacaine. Pain was assessed using visual analog scale at 0, 6, 12, and 24 hours postoperatively. Pain levels showed significant difference (P=.018) between two groups at 6 hours postoperatively. Bupivacaine group showed lower mean analgesic requirement. This study concluded that Bupivacaine irrigation at the surgical bed effectively reduced postoperative pain intensity after laparoscopic cholecystectomy.[129]

Donatsky A M, Bjerrum F, Gogenur I (2013), conducted this review with the purpose to evaluate intraperitoneal instillation (IPI) of saline and local anesthesia to minimize shoulder pain. A search of the literature was conducted using PubMed and Excerpta Medica Database (EMBASE). Eligibility criteria were: randomized clinical trials (RCT) evaluating IPI of saline and LA to minimize incidence or severity of shoulder pain after laparoscopic cholecystectomy. Only papers published in English were included. Data extracted were year of publication, number of participants and allocation, timing of IPI, and nonsignificant or significant effect on incidence or severity of shoulder pain.

Conclusion of the study was that both intraperitoneal instillation of saline and local anesthesia can be used to reduce shoulder pain severity after laparoscopic cholecystectomy. It was not possible to conclude whether the incidence of shoulder pain can be reduced with saline or local anaesthetics, due to contradictive results.[130]

Vasava M A, Patel H M, Kacheriwala S M, Duttaroy D D, Patel S J, Patel R K (2013), conducted a study with the purpose to assess the supremacy of pre-emptive analgesia with Bupivacaine 0.5% instilled before rather than after surgery for pain control following laparoscopic cholecystectomies. The purpose of this study was to assess the supremacy of pre-emptive analgesia with Bupivacaine 0.5% instilled before rather than after surgery for pain control after Laparoscopic cholecystectomy. In Group A 0.5% Bupivacaine - intraperitoneal instillation and infiltration in skin before skin incision with its optimum dosage was positioned in the gallbladder bed and sub diaphragmatic space before removal of gall bladder. In Group B, Bupivacaine 0.5% - intraperitoneal instillation with its optimum dosage was positioned in the gallbladder bed and sub diaphragmatic space after removal of gall bladder and infiltration in skin after trocar removal. 44 patients in each group were evaluated (total 88). Nature of pain Visceral, Parietal and Shoulder was assessed on VAS at 4, 8 and 24 hrs after surgery. The Intraperitoneal instillation of Bupivacaine before dissection of gall bladder shows significant reduction of visceral pain score (36.63 and 37.31 and 45.74) and shoulder pain score (38.56 and 37.13 and 38.44) compared to after removal of gall bladder (52.38 and 51.69 and 43.26) and (50.44 and 51.27 and 50.56) at 4 hrs and 8 hrs and 24 hrs assessments. In shoulder tip pain score was significantly low in group A at 24 hrs than in group B. Bupivacaine significantly reduced the parietal pain (36.74 and 37.02) in group

A as compared to Group B (52.26 and 51.98) in early post-operative period (at 4hrs and 8hrs) and it was almost equal to group B at 24hrs. The present randomized study demonstrated that intraperitoneal instillation of 0.5% Bupivacaine is superior before rather than after removal of gall bladder for postoperative analgesia and that it significantly reduced visceral, parietal as well as shoulder pain in early post-operative period. [131]

Yakoshi C, Hashimoto H, Niwa H, Kitayama M, Kudo T, Kudo M, Hirota K (2014), carried out this review to evaluate the effectiveness of analgesia and safety of rectus sheath block combined with intraperitoneal instillation using two doses of Ropivacaine in patients undergoing laparoscopic gynaecological surgery. Altogether 53 consenting women were randomized to receive intraperitoneal infiltration with 0.25% Ropivacaine or 0.5% Ropivacaine followed by rectus sheath block with 0.375% Ropivacaine. The outcomes of clinical safety were measured using plasma concentration of local anaesthetics and occurrence of toxic symptoms. The analgesic efficacy was assessed using numerical rating scales for pain and morphine consumption up to 24 hours after surgery. Patient's baseline characteristics, surgical factors, and analgesic outcomes were comparable between the two groups. Although peak plasma Ropivacaine, none of analyzed concentrations was above the toxic ones. Besides, no patients concentration of Ropivacaine was significantly higher in patients receiving 0.5% showed any symptoms of local anaesthetic toxicity. The present study showed that the combination of rectus sheath block with intraperitoneal instillation of Ropivacaine was safe and potent enough to relieve pain after laparoscopic surgery.[132]

Saghar Samimi, Arman Taheri, Fatemeh Davari Tanha (2015), published this double-blind randomized controlled study which compared the efficacy of intravenous and intraperitoneal injection of Lidocaine and normal saline in relieving postoperative pain after elective abdominal hysterectomy. For 109 patients undergoing abdominal hysterectomy were recruited to three groups :1) IV group received IV Lidocaine 2% bolus 1.5mg/kg 30 min before incision followed by Lidocaine infusion of 2mg/kg intraperitoneal injection of NS just before the wound closure , 2) IP group was given IV NS followed by intraperitoneal Lidocaine 3mg/kg , 3) P group (placebo) was administered intraperitoneal N/S and IV. At 0,2,4,8,12 and 24 hrs postoperatively pain scores were recorded. The study results showed significantly lower VAS scores in IP and IV groups than with the placebo ($p = 0.001$). This study concluded that intraperitoneally and intravenously Lidocaine administration reduced the postoperative pain.[133]

Shukla U, Prabhakar T, Malhotra K, Srivastava D, Malhotra K(2015), In their prospective, double-blind, randomised study compared the intraperitoneal administration of either Bupivacaine with Dexmedetomidine/Tramadol or Bupivacaine alone in 120 patients undergoing laparoscopic cholecystectomy randomized into three groups of 40 each. Group B patients were administered Bupivacaine 50ml 0.25% +5ml normal saline (NS) intraperitoneally, group BT patients were given Bupivacaine 50ml 0.25% + Tramadol 1mg/kg (diluted in 5ml NS) while patients in group BD were given Bupivacaine 50ml 0.25% + Dexmedetomidine μg/kg, (diluted in 5ml NS) at the end of surgery, before removal of trocar. Visual analogue scale score (VAS) was used to assess the quality of pain. Time of rescue analgesia, total dose of analgesic in the first 24 h noted. Statistical analysis was performed using Student's t-test and Chi-square test. VAS

at different time intervals, overall VAS in 24 h was significantly lower (1.80 ± 0.36, 3.01 ± 0.48, 4.5 ± 0.92), time to first request of analgesia (min) was longest (128 ± 20, 118 ± 22, 55 ± 18) and total analgesic consumption (mg) was lowest (45 ± 15, 85 ± 35, 175 ± 75) in Group BD than Group BT and Group B. The study concluded that Intraperitoneal instillation of Bupivacaine in combination with Dexmedetomidine is superior to Bupivacaine alone and may be better than Bupivacaine with Tramadol.[134]

Liu DS, Guan F, Wang B, Zhang T (2015), assessed the analgesic efficacy of Ropivacaine instilled at intraperitoneal and incisional sites at the end of the LC. 160 patients undergoing LC were recruited into four groups. Normal saline was administered intraperitoneal and incisional in group Sham. Incisional Ropivacaine and intraperitoneal NS administered in group IC. Intraperitoneal Ropivacaine and incisional NS was given in group IP. Ropivacaine instilled both intraperitoneal and incisionally in group ICP. In all the four groups, at the end of the surgery, surgical bed was sprayed with Ropivacaine through the right subcostal port and infiltrated at the four ports. Visual analogue scale (VAS) was used to assess the pain intensity at 2 h, 6 h, 24 h, and 48 h postoperatively, as well as incidence of side-effects over 48 h after LC was recorded. PACU stay, VAS score (VAS-D) at 2 h and 6 h postoperatively, morphine consumption 6 h and 24 h postoperatively, and incidence of nausea and vomiting 48 h after LC in group IC and ICP were less ($p<0.05$). Furthermore, powerful analgesic effect was noticed with intraperitoneal and incisional Ropivacaine than either intraperitoneal or incisional Ropivacaine alone ($p<0.05$). The study concluded that effective reduction in pain intensity after LC was documented with intraperitoneal and incisional Ropivacaine.[135]

Oza VP, Parmar V, Badheka J, Nanavati DS, Taur P, Rajyaguru AM (2016), carried out this study to compare the analgesic effect of Dexmedetomidine with Bupivacaine instilled intraperitoneally with Bupivacaine alone in postoperative period in patients undergoing laparoscopic surgeries. 100 patients undergoing laparoscopic surgery were randomized into two groups of 50 each. Group B was administered 50mL of Bupivacaine 0.25% (125 mg) intraperitoneally and groups B + D was given 50mL of Bupivacaine 0.25% (125 mg) + 1 μg/kg of Dexmedetomidine. At 0.5 h, 1 h, 2 h, 4 h, 6 h, and 24h postoperatively pain was assessed using visual analogue scale (VAS). The analgesic requirement was recorded. The results demonstrated that the analgesia was longer in group B+D (14.5 hr) than in group B (13.06 hr). A statistically significant difference ($p < 0.05$)was noticed in the requirement of rescue analgesic in 24 hours between the group B+D (1.76) and group B (2.56). The study hence proved that intraperitoneal instillation of Dexmedetomidine with Bupivacaine prolongs the duration of postoperative analgesia thereby needing less number of rescue analgesics.[136]

Anurag Yadava, Sunil K Rajput, Sarika Katiyar, 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.[137]

Table 1: Intraperitoneal local anaesthetic instillation in laparoscopic cholecystectomy.

Study	No of patients Treatment/ control	Bupivacaine % vol	Over all pain	Shoulder Pain	Comments.
Chundrigar et al 1993 (113)	28/30	0.25% 20ml	P < 0.05	NS	Significant at 1h and 2h post op
Pasqualucci et al 1996 (10)	30/30/30/30	0.5% 20ml preop, 0.5%20ml postop, 0.5%20ml pre and post op.	P < 0.05	--	Significant pre+post> post>pre
Szem etal 1996 (19)	26/29	0.1% 100ml intraop	P < 0.05	NS	Significant upto 6hrs
Mraovic et al 1997 (8)	40/40	0.5% 15ml preop + 15mlpostop	P < 0.05	--	Significant at 4 and 8hrs.
Weber et al 1997(138)	50/50	0.5% 10ml postop	P < 0.05	--	Significant at 2,6,and 12hrs.
Raetzell et al 1995(139)	12/12	0.25% 50ml postop	NS	NS	Evaluated at day 1,2,3.
Rademaker et al 1994(140)	15/15/15	0.25% 20ml postop (Lidocaine)	NS	NS	Evaluated at 1,2 and 4hrs
Joris et al 1995(6)	20/20	0.125% 80ml postop	NS	NS	Evaluated at 4,8,24hrs
Fornari et al 1996(141)	50/50	0.167% 60ml postop	NS	NS	Evaluated at 8,24,36hrs
Fuhrer et al 1996(142)	12/10	0.375% 41ml postop	NS	NS	Evaluated at 3,6,12,24 hrs.

NS- no significant difference between study and control group.

$p<0.05$= statistically significant difference between study and control group.

-- = Not evaluated

Listed above are 10 randomized controlled trails comparing Bupivacaine or Lidocaine with saline wherein in all trials the local anaesthetic was instilled in the right subdiaphragmatic or gall bladder region in concentrations between 0.1% and 0.5%, 10ml and 100mL at the beginning of the procedure, at the end or both (Table: 1).

Overall, 5 of the 10 trials showed improved pain relief for at least one of the evaluated pain measures. In 5 trials, overall pain scores were significantly reduced compared with the control patients.

In most studies, pain scores were only reduced early postoperatively (2-8 h). In the 5 other trials, no effect on pain scores was observed. (Table: 1)

The differences between results in the various RCTs are difficult to explain.

Although applied doses of local anaesthetics did vary, the average dose did not differ between positive and negative trials, and no clear relationship could be extracted regarding effect, dose, and application sites.

Regarding dosage of the local anaesthetic, a significant dose-response relationship was observed in the studies by Pasqualucci et al.[10]

Therefore, not surprisingly, the amount of local anaesthetic used may be of importance.

Intraperitoneal Local Anaesthetics for Postoperative Pain Relief After Laparoscopic Procedures other than laparoscopic cholecystectomy.

Four trials of a variety of procedures (diagnostic and operative gynaecological laparoscopy, sterilization, fundoplication, appendectomy, hernia repair cholecystectomy) evaluated intraperitoneal instillation of Bupivacaine50-100 mg or Lidocaine400mg.

Table 2: Intraperitoneal local anaesthetic instillation in other laparoscopic surgeries.

Study	No of patients Treatment/control	Local anaesthetic % vol	Over all pain	Shoulder pain	Comments.
Narchi et al 1991(143)	35/30	Lido/Bupi (0.5% 80ml)	--	p < 0.05	Significant at 8,12,24hrs.
Kelly et al 1996 (144)	27/30	Bupi 0.125% 50ml	p<0.05 %	--	Significant at 2hrs
Cunniffe et al 1998(5)	55/50	Bupi 0.01% 500ml	--	P < 0.05%	Significant at 4,12,24hrs
Ashraf M et al (145)	32/31	Bupi 0.125% 40ml	p<0.05 %	--	Significant t 1,2,3 hrs

p<0.05= statistically significant difference between study and control group.

NS- no significant difference between study and control group.

--- = not evaluated.

All studies showed significantly reduced pain scores.

Combined regimens with local anaesthetic for postoperative pain relief in laparoscopic procedures.

Table 3: Application of local anaesthetics at multiple sites in different laparoscopic procedures.

Study	***No of patients*** **Treatment/ control**	***Localanaesthetic*** **% vol**	***Over*** **all pain**	***Shoulder*** **pain**	**Comments.**
Cook et al 1986,(146)	30/30 l	0.5% 15ml Bupi(port site and dipped over the tube)	NS	--	Evaluated at 1 and 7hrs
Loughney et al 1994,(147)	25/22	0.5% 10 ml intraperitoneal & port site 0.5%	—	$p < 0.05$%	Evaluated at 1,2,4hrs
Benhamou et al 1994,(148)	25/25	Lido(intraperitoneal and into each mesosalphinx) 0.2% Ropivacaine	—	$p < 0.05$%	Evaluated at 2,8 12and 24hrs
Callesen et al 1999(149)	39/41	Intraperitoneal, me sosalphinx, port site)	—	$p < 0.05$	Evaluated at 1,2,3 hrs

NS- no significant difference between study and control group.

$p < 0.05$=statistically significant difference between study and control group.

---=not evaluated.

Cook and Lambert[146] evaluated port-site infiltration plus tubal application of Bupivacaine compared with no treatment and found no effect on pain outcome measures.

On the other hand, three studies comparing port-site infiltration plus intraperitoneal instillation of Bupivacaine[147], mesosalpinx infiltration plus intraperitoneal instillation of Lidocaine[148] or port-site infiltration plus mesosalpinx infiltration and

intraperitoneal instillation of Ropivacaine with placebo (95m) found significantly reduced pain scores and analgesic consumption up to 4h postoperatively (93,95) or > 24h after surgery[149] .

Only marginal effects are obtainable with intraperitoneal instillation, port-site infiltration, or visceral infiltration per se, perhaps combining these techniques would provide clinically relevant pain relief. Three of four trials with different combinations of peripheral local anaesthetic use showed improved pain relief early and also up to >24 h after laparoscopy.

Only the study by Cook and Lambert[146] showed no effect from port-site and a fallopian-tube block. However, pain was only assessed at one-half, 7, and 17 h postoperatively, and an early effect, within 4-6 h after laparoscopy, may have been overlooked.

Most convincing was the study by Callesen et al[149] in which intraperitoneal instillation, mesosalpinx, and port-site infiltration with a large dose of ropivacaine almost abolished postoperative pain up to 4 hours after surgery.

In all of these trials, laparoscopic procedures were gynaecological, diagnostic, or sterilization. Except for one recent paper of a combined somato-visceral local anaesthetic block after laparoscopic cholecystectomy, in which overall pain and incisional pain was improved up to 4 hours postoperatively.

Although laparoscopic surgery, compared with open procedures, may be associated with diminished surgical trauma response and shortened convalescence early postoperative pain after laparoscopic procedures is a frequent complaint.

Peripheral use of local anaesthetics for postoperative pain relief is, in this context, an attractive method, which in theory may improve early pain control and minimize the need for opioids. Furthermore, the fact that some laparoscopic procedures are performed on a day-care or a fast-track basis, emphasizes the importance of improving early postoperative pain relief.

Even within the same type of procedure, pain after laparoscopic surgery 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 CO_2 entrapment beneath the hemidiaphragms. In several trials, attempts have been made to differentiate between the various pain qualities and localizations however; the results and conclusions are difficult to interpret, with several authors also expressing difficulties in making this differentiation.

Accordingly, most trials only reported on overall postoperative pain. Furthermore, the literature varies in the reporting of the localization of the most severe pain. Some authors report intraabdominal pain as the most pronounced although others state incisional or shoulder-tip pain is the most painful

Convalescence after laparoscpic cholecystectomy:

Several factors such as components of the individual surgical procedures, the surgical stress response, fatigue and sleep disturbances, postoperative nausea and vomiting, sociocultural and medical traditions, and pain are likely to influence the duration of postoperative convalescence.

1. The effect of laparoscopic cholecystectomy on the surgical stress response:

Compared with open cholecystectomy, laparoscopic cholecystectomy confers advantages of reduced pulmonary dysfunction, immune response, with less increase in C reactive protein and Interleukin 6 concentrations.[9] However there is probably no significant difference in classic endocrine catabolic responses and metabolic response.[121]

2. The effect of fatigue and sleep on convalescence after laparoscopic cholecystectomy: Compared with open cholecystectomy early postoperative fatigue is less pronounced after laparoscopic cholecystectomy. In a prospective, large scale study 299 consecutive patients fatigue scores were normalized by the second day after operation and almost all the patients felt completely fit after two weeks.[133]

In the only sleep study available in patients after laparoscopic cholecystectomy, rapid eye movement sleep and oxygenation were unchanged from preoperatively during the first night after the operation [26]while there was a small decrease in slow wave sleep.

3. The effect of postoperative nausea and vomiting on convalescence: postoperative nausea and vomiting may occur in about 10-20%of patients during. the first 2-4 hours. However, during the following day up to 60% of the patients may experience nausea or nausea and vomiting have been reported to persist upto 14 days after laparoscopic cholecystectomy in about 5% of patients.[133]

4. The effect of medico cultural factors and pain on convalescence: Sociocultural factors such as patient's expectation, attitudes to treatment, and traditions within the health care system may have a major impact on the time to the resumption of work and normal activity.

In summary, the pathogenesis of prolonged convalescence after laparoscopic cholecystectomy is probably complex with medicocultutral factors having a dominant role. There is rarely a pathophysiological basis for prolonged or severe fatigue after laparoscopic cholecystectomy. Nausea and vomiting may contribute to prolonged convalescence in a few patients.

MATERIALS AND METHODS

Source of data

This study was carried out in the Department of Anaesthesiology, B.L.D.E.U's Shri B. M. Patil Medical College, Hospital and Research Centre, Vijaypur, from December 2015 to August 2017.The source of data is from inpatients of Shri B. M. Patil Medical College, Vijayapur, undergoing laparoscopic cholecystectomy under general anaesthesia. 66 patients who are willing to participate during the study period were taken and followed up for a period of 24 hours.

Mode of selection of cases & method of analysis

It is a randomized clinical trial of patients who underwent laparoscopic surgeries A total of 66 patients were allocated randomly into two groups using block randomisation method with block size 10, to receive 2 mg/kg of 0.5% Bupivacaine diluted in 200ml normal saline either before or after creation of pneumoperitoneum. Patients in Group A (n = 33) were administered with 2 mg/kg of 0.5% Bupivacaine diluted in 200ml normal saline before creation of pneumoperitoneum and those in Group B (n = 33) were administered with 2mg/kg of 0.5% Bupivacaine diluted in 200ml normal saline after creation of pneumoperitoneum.

The study was conducted using a pre-tested proforma meeting the objectives and the post operative pain is evaluated using visual analog scale for a period of 24 hours post operatively. The analysis of the study is made statistically with relevant tests.

Inclusion criteria :

- ASA Class I and II.
- Age 18 – 60 years.
- Patients with uncomplicated, symptomatic cholelithiasis.
- Consenting for study procedure.

Exclusion criteria :

- Patients with allergy to local anaesthetics.
- Pregnancy and lactation.
- Patients on prolonged administration of NSAIDS or other analgesics.
- Surgery extending beyond 3 hours duration.
- Morbid obesity (BMI > 35).
- Disturbance of central nervous system or psychiatric disease.
- Chemical substance abuse, chronic pain, chronic or recent (< 2 months) use of analgesics.
    - Hepatic or renal insufficiency.
    - Patients who fail to understand the pain evaluation scale.
    - Conversion of laparoscopic surgery into open surgery.

Intra operative findings of other causes which may be responsible for significant visceral pain.

Investigations Required :

- Hb%, Total Leucocyte Count, Differential Count, Bleeding Time, Clotting Time.
- Platelet count
- Urine routine
- Random Blood Sugar
- Blood urea and serum creatinine
- Total bilirubin
- SGOT/ SGPT
- Chest x-ray, ECG.
- HIV, HBsAg
- ECHO (If needed)

Preliminaries :

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

Equipments :

a)For the procedure :

A portable tray covered with sterile towels containing :

- Bowl containing Povidine iodine and spirit.
- Sponge holding forceps and two Mikulicz clamps.
- Towels and towel clips.
- Sterile gauze pieces
- Sterile syringes - one 100ml and one 5ml.

- The standard suction-irrigation device.
- Sterile BP handle and scalpel blade size 15.
- Inj. Glycopyrolate 0.01-0.02mg/kg, Inj. Midazolam 0.1mg/kg, Inj. Ondensetran 0.15mg/kg, Inj. Fentanyl 1-2mcg/kg, Inj. Propofol2-3 mg/kg, Inj.Succinylcholine 1-1.5mg/kg, Inj. Vecuronium0.1 mg/kg.
- Inj. Bupivacaine 0.5% and 0.25%.
- 200ml normal saline.

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.
- Non invasive blood pressure monitor by sphygmomanometer.
- Echocardiogram.

Monitoring parameters :

- Heart Rate (HR)
- Oxygen saturation (SpO_2)

Procedure : The study was undertaken. in 66 patients posted for laparoscopic surgeries s under general anesthesia assigned randomly to 2 groups, each containing 33 patients. After approval from the institute and ethical clearance from college Ethical Committee, informed consent was taken from the patients.

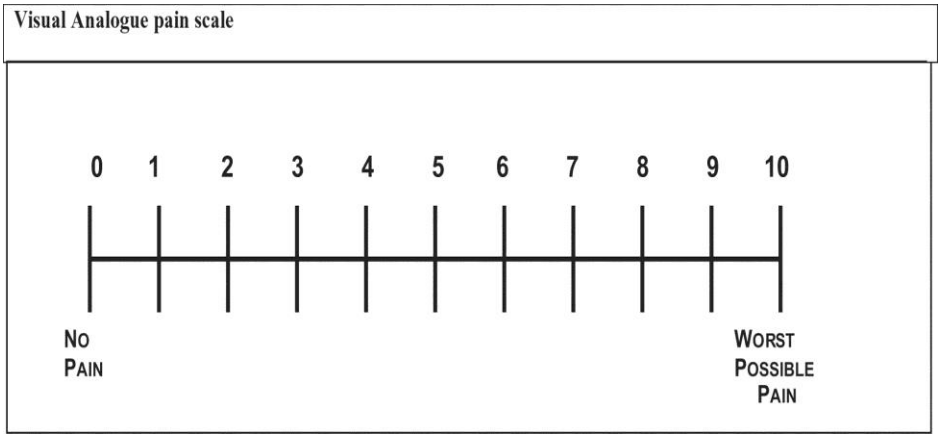
- **Group- A**: received 2 mg/kg of 0.5% Bupivacaine diluted in 200ml of normal saline before creation of pneumoperitoneum.
- **Group- B**: received 2 mg/kg of 0.5% Bupivacaine diluted in 200ml of normal saline after creation of pneumoperitoneum.
  - All patients were examined on the day before surgery and thoroughly investigated according to institution protocol and were counseled with regards to general anesthesia, local anesthesia as well as the operative procedure.
  - 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, patient was taken to operation theatre. Standard monitoring devices including ECG leads, Sphygmomanometer cuff, and pulse oximeter were connected and baseline values recorded.

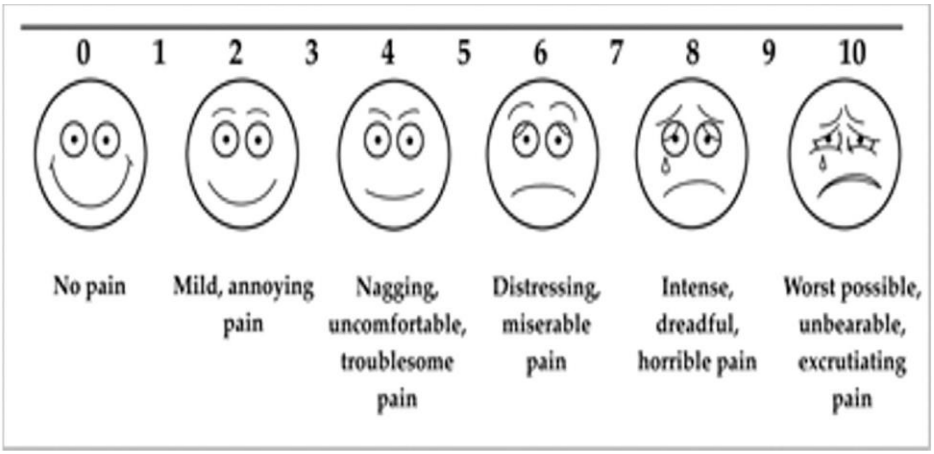
IV line secured with 20G cannula and IV Ringer's Lactate solution started at 2 ml/kg/hr and premedicated with Inj. Glycopyrolate 0.01-0.02 mg/kg, Inj. Midazolam 0.1 mg/kg**,** Inj. Fentanyl 1-2 mcg/kg, Inj. Ondensetran 0.15 mg/kg all given intravenously.

- Patients pre-oxygenated with 100% oxygen through mask.
- After induction of general anesthesia using Inj. Propofol 2-3 mg/kg IV, Inj.Succinylcholine 1-1.5 mg/kg IV, Inj.Vecuronium 0.1 mg/kg IV (loading dose), all patients were provided mechanical ventilation with Oxygen, Nitrous oxide and Isoflurane mixture . $ETCO_2$ monitored using capnography to maintain CO_2 level in the expired air within the range of 4% to 4.5%.
- In each case, a gastric tube was inserted for the duration of the procedure and removed before its termination.
- The procedure was performed by two experienced surgeons using the standard four- port surgical technique.
- Access to the peritoneal cavity was established using an open technique through a 2 cm umbilical incision, with two Mikulicz clamps lifting the abdominal wall.

Once in peritoneal cavity, patient was placed in trendelenburg position and the standard suction- irrigation device with the attached 100ml syringe was introduced through the umbilicus directed towards the liver and diaphragm, followed by spraying of infusion of 200ml of fluid (2 mg/kg of 0.5% Bupivacaine diluted with 200ml of normal saline solution for Group- A)

- Following the procedure the reversal from general anesthesia was achieved with Inj.Neostigmine 50 mcg/kg and Inj.Glycopyrolate 0.01-0.02 mg/kg IV.



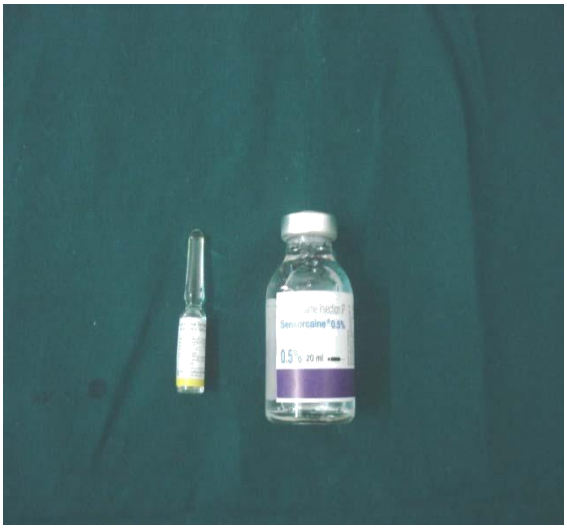


- Postoperative pain scores were obtained by an independent clinical investigator.
- The patients were aware that the scale served to analyse the intensity of pain alone, including shoulder tip pain, and is not a representation of generalized postoperative discomfort.
- All the patients received elective intravenous Inj. Diclofenac (1mg/kg) analgesia on demand and the time of demand in hours after surgery was noted and the requirement of a repeat dose of Inj. Diclofenac, if any was noted and recorded.
- A detailed statistical analysis was done including sex, age, body mass index (BMI), ASA grade, 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 and the appearance of shoulder tip pain (time in hours) after surgery.

- 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.

FIGURE 12: BUPIVACAINE 0.5% USED FOR INTRAPERITONEAL INSTILLATION .



Postoperative Period:

Patients were cared for in the recovery room according to the standard protocol and than 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. Presence of shoulder pain was also assessed during the same interval.

Patients were given 75 mg of diclofinac sodium intramuscularly on request and the total number of doses of analgesics used was recorded in a standard proforma.

STATISTICAL METHODS APPLIED

The descriptive procedures displays univariate summary statistics for several variables in a single table and calculates standardized values. Variables can be ordered by the size of their means (in ascending or descending order), alphabetically, or by the order in which the variables are selected.

The data was presented using diagrams (Qualitative data), mean +/- SD (Standard deviation) (Quantitative data) and proportion/ percentages. The Chi Square test was used to find association between the variables. The 'Student's' t test (unpaired) and Mann-Whitney U-test were used to find the significant difference between the two groups.

Chi Square Test is the test of Hypothesis testing. The Chi Square is the most important test of nonparametric technique where no assumptions about the population from which we draw a sample are made. The Greek Letter (X^2) Chi Square was first used byλ Karl Pearson (1900). According to Karl Pearson, "X^2 is the magnitude of discrepancy between observed frequencies and expected frequencies i.e. divergence of fact from the hypothesis. X^2 (Chi Square) is used in order to test " whether λ empirically obtained frequencies (fo) differ significantly from those to be expected frequencies (fe) on the basis of some Hypothesis.

Formula of X^2

$$X^2 = \frac{\sum (fo - fe)^2}{fe}$$

Where X^2 = The quantity of chi square.

$\sum$ = Summation of whole fo = Observed frequency or experimentally obtained frequency

fe = Expected frequency

The difference between observed frequencies and the expected frequencies are squared and divided by the expected number of each case and the sum of these quotients is chi square.

'**Student's t Test** : The t-test compares the actual difference between two means in relation to the variation in the data.

One-sample t-test: know the mean difference between the sample and the known value of the population mean.

Unpaired t-test: compare two population means.

Paired t-test: compare the values of means from two related samples, for example in a 'before and after' scenario.

When $t_{calc} > t_{table}$, the two value are not the same (within the confidence intervals).

The **Mann-Whitney U-test**, is a statistical comparison of the mean. The U-test is a member of the bigger group of dependence tests. Dependence tests assume that the variables in the analysis can be split into independent and dependent variables. A dependence tests that compares the mean scores of an independent and a dependent variable assumes that differences in the mean score of the dependent variable are caused by the independent variable. In most analyses the independent variable is also called factor, because the factor splits the sample in two or more groups, also called factor steps. The Mann-Whitney U-test is mathematically identical to conducting an independent

sample t-test (also called 2-sample t-test) with ranked values. Because the Mann-Whitney U-test is a non-paracontinuous level test it does not require a special distribution of the dependent variable in the analysis. Thus it is the best test to compare mean scores when the dependent variable is not normally distributed and at least of ordinal scale.

RESULTS

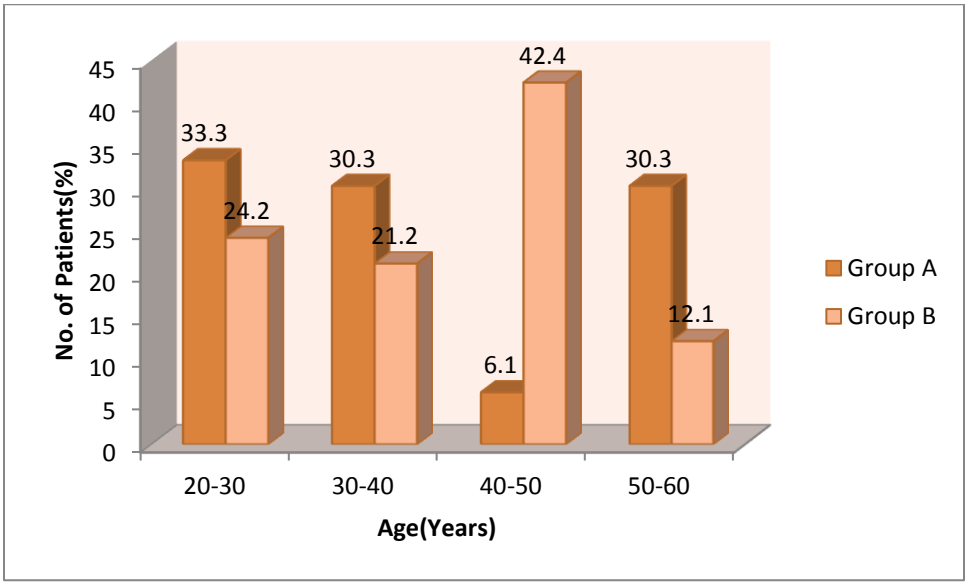
A total of sixty six patients participated in the study.

AGE AND SEX DISTRIBUTION

Table 4: Age distribution of patients

Age (years)	Group 1		Group 2	
	N	(%)	N	(%)
20-30	11	(33.3)	8	(24.2)
30-40	10	(30.3)	7	(21.2)
40-50	02	(6.1)	14	(42.4)
50-60	10	(30.3)	4	(12.1)
Total	33	(100)	33	(100)

GRAPH 1: Shows age distribution of the patients

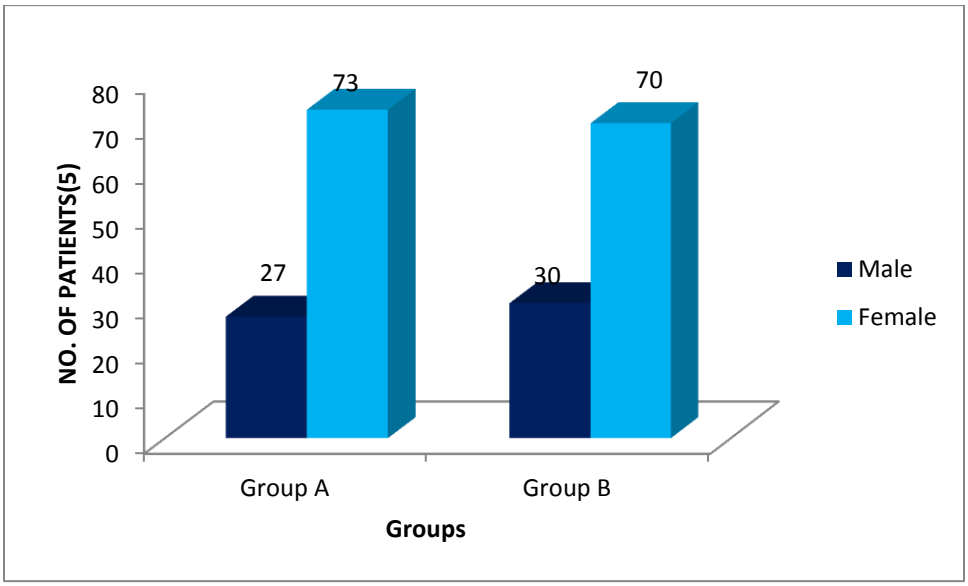


Group A comprised of 33.3%, 30.3%, 6.1%, 30.3% patients with their age between 20-30 years, 30-40 years, 40-50 years and 50-60 years respectively. The mean age of patients in group A is 40.64 and that in group B is 39.82.

Table 5: Sex distribution of patient population in the study

Gender	Group A N (%)	Group B N (%)	Chi square test p value
Male	9 (27)	10 (30)	0.7857
Female	24 (73)	23 (70)	
Total	33	33	

GRAPH 2: Shows sex distribution of patients



The male to female ratio was 0.37:1 in the group A and 0.43:1 in group B. There were 73% of females in the group A as compared 70% in the group B. This implies that sex matching was done between two group (p=0.7857).

Group A comprised of 33 patients (9 males, 24 females).

Group B consisted of 33 patients (10 males, 23 females)

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

Table 6: Comparision between the two groups for different variables in the study

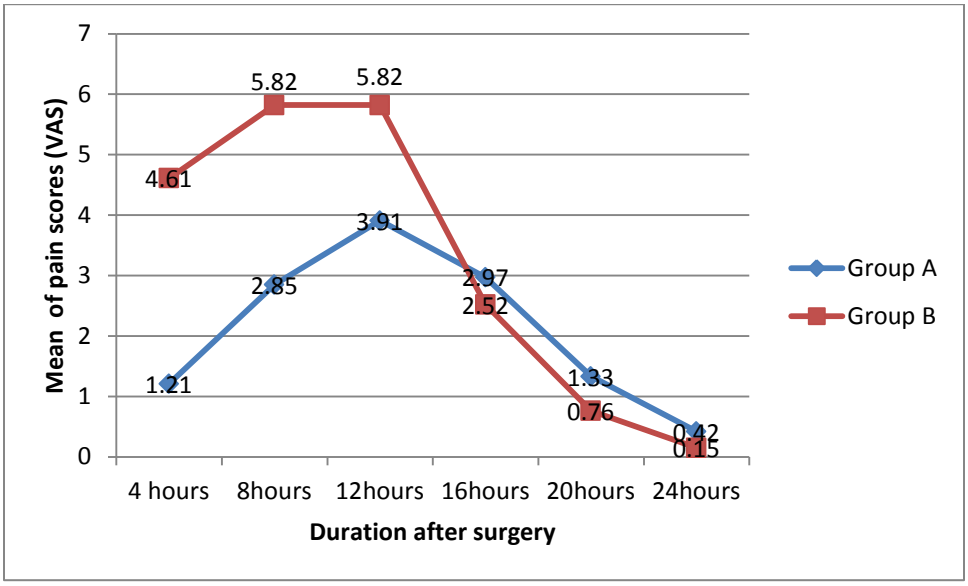
Variables	Groups	N	Mean	Std. Deviation	Unpaired t test p value
Age	A	33	40.64	12.949	0.779
	B	33	39.82	10.510	
Weight	A	33	54.85	7.023	0.130
	B	33	57.30	5.940	
Appearance of STP	A	33	No		
	B	21	414.81	99.236	
LAR in min	A	25	773.80	155.947	0.0001*
	B	33	493.94	150.425	
VAS	A	33	4.79	1.883	0.0001*
	B	33	6.58	1.347	

*Represents significant difference between two groups

Table 7: Showing the mean and standard deviation of the pain scores according to VAS at 4, 8,12,16,20, 24 hours postoperatively

Time in hours after surgery	Groups	Postoperative pain score(VAS) Mean±SD	Unpaired t test p value
4	A B	1.21± 1.409 4.61±1.999	0.0001* 0.0001*
8	A B	2.85±2.373 5.82±1.570	0.0001* 0.0001*
12	A B	3.91±1.860 5.82±1.570	0.370 0.370
16	A B	2.97±1.776 2.52±1.460	0.260 0.260
20	A B	1.33±1.267 0.76±1.119	0.055* 0.055*
24	A B	0.42±.830 0.15±0.712	0.157 0.157

GRAPH 3: Mean pain scores in VAS scales at different interval time intervals measured post operatively.



Repeated measure Unpaired t-tests showed that the overall difference in mean pain scores on VAS scales measured at different time intervals post operatively was significant between the group that received Bupivacaine before the creation of pneumoperitoneum (group A) and those that received Bupivacaine after the creation of pneumoperitoneum (group B).

The mean pain scores were significantly lower upto first 8hrs in group A in comparison with group B and further there is no significant difference in the mean pain scores in the next 16 hours of the study as it is quite evident in the graph depicted.

Mean pain scores measured at 4thhour were significantly higher in Group B than Group A.(VAS scale p value=0.0001).

Mean pain scores measured at 8th hour were significantly higher in Group A compared to Group B (VAS scale p value=0.0001).

Mean pain scores measured at 12th hour (VAS scale p value = 0.370), 16th hour (VAS scale p value = 0.260), and 24th hour(VAS scale p value= 0.157) 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 B than Group A at 16th and 24th hour. But the difference in the mean pain scores at 20th hour was significantly higher in Group B than in Group A with p value = 0.055 according to VAS scale. This can be explained by the observation that significant number of patients in Group A complained pain after the initial 12 hours whereas the patients in Group B complained of pain in the much earlier hours postoperatively. So the percentage of people complaining of pain in Group A remain high in the later part of postoperative period but the mean pain scores are not significantly different. As most of the patients in Group A first complained of pain after the initial 12 hours of the postoperative period when most of the patients in ***group B who complained of pain in the initial 12 hours were already treated for pain***. Mean pain scores of Group B were slightly lower than that of patients in Group A at 16th, 20th and 24th hour. Out of the patients complaining of pain at 20th hour most patients belonged to Group A (10%) and a significant percentage of them complained of pain for the first time so the pain scores were higher than the patients of ***group B (9%) who at 20th hour complained of pain for 2nd, 3rd or the 4th time and had already received 1 or 2 doses of analgesics,*** so the pain scores were lower resulting in p value = 0.055 indicating a significant difference again at 20th hour.

Table 8: Percentage of patients who requested analgesic doses in the initial 24 hours postoperatively in time intervals of 4 hours.

Analgesia request time(in hours)	Group A Percentage of patients who requested analgesics	Group B Percentage of patients who requested analgesics	Chi square test p value
0-4	0	1 (1.47)	0.0423*
4-8	01 (3.12)	19 (27.94)	
8-12	10 (31.25)	21 (30.88)	
12-16	10 (31.25)	17 (25)	
16-20	10 (31.25)	9 (13.23)	
20-24	01 (3.12)	1 (1.47)	
Total	32%	68%	

GRAPH 4: Percentage of patients versus analgesia request time

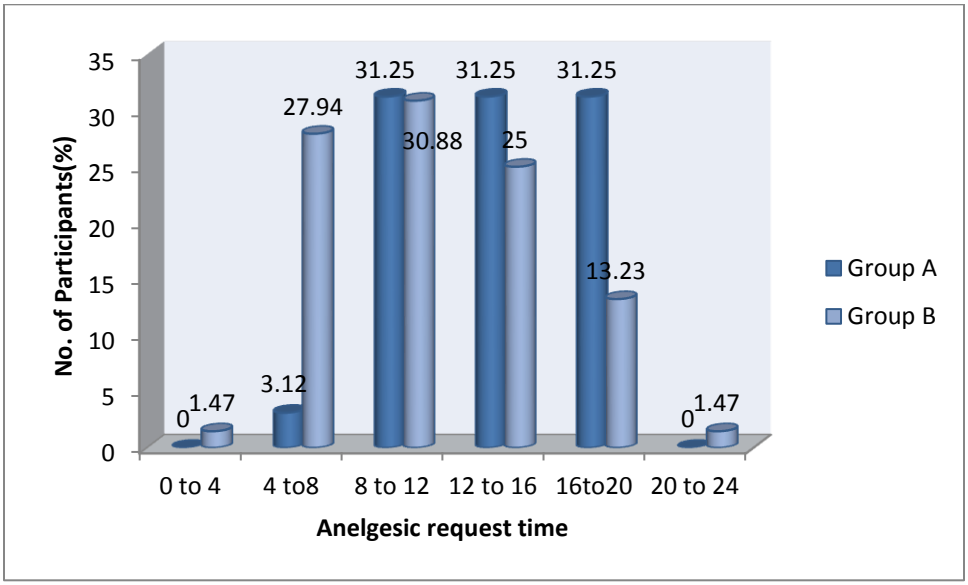
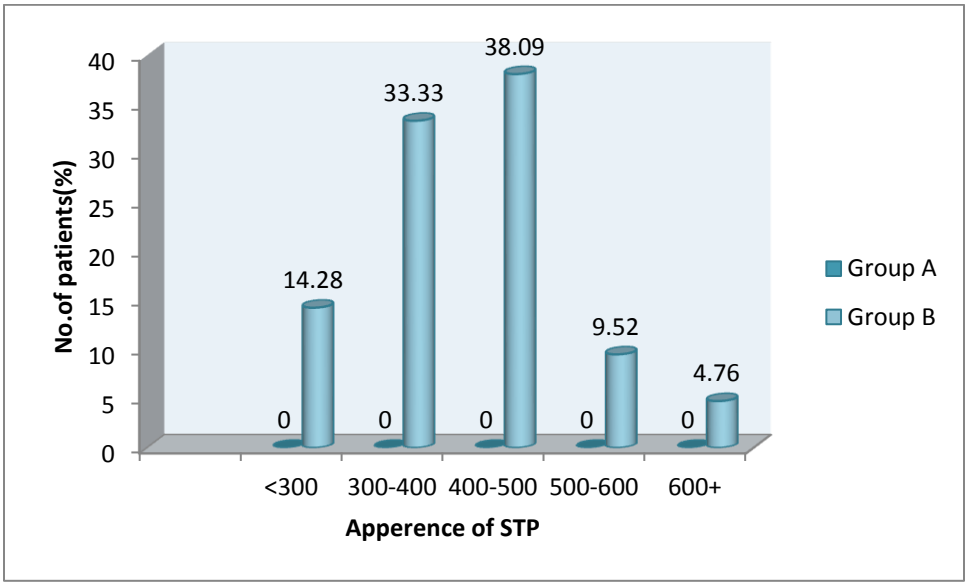


Table 9: Showing the time of appearance of STP

Time of appearance of STP in minutes	Group A N (%)	Group B N (%)
<300	0	3(14.28)
300-400	0	7(33.33)
400-500	0	8(38.09)
500-600	0	2(9.52)
600+	0	1(4.76)
Total	0	21

GRAPH 5: Showing the time of appearance of shoulder tip pain in minutes in both the groups



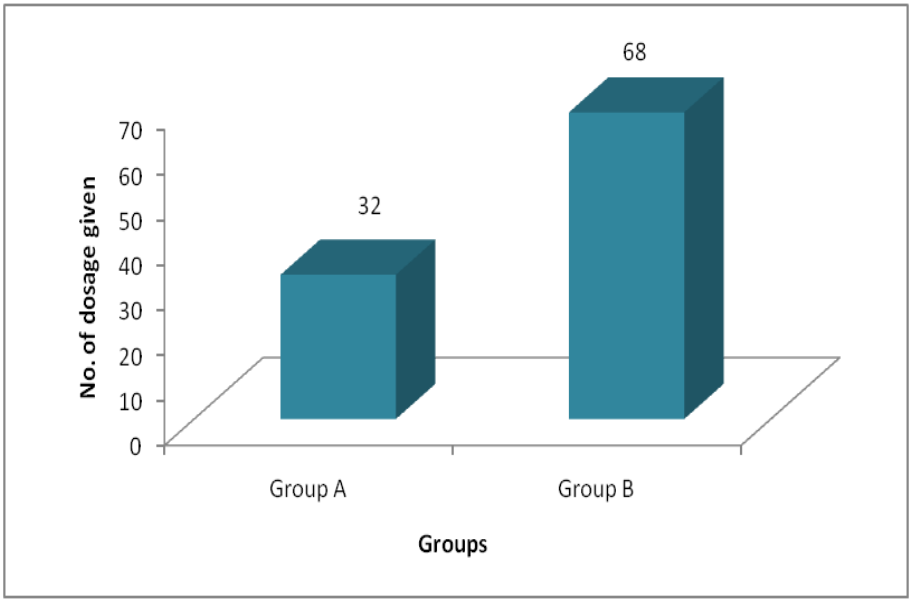
The statistical data regarding the appearance of shoulder tip pain has shown absolutely no complaints of shoulder tip pain in the patients of Group A. The appearance of shoulder tip pain noted only when the intraperitoneal instillation of Bupivacaine was done after the creation of pneumoperitoneum and higher incidence of STP was seen between 400- 500 minutes i.e., approximately between 6-9 hours.

Table 10: Average No of analgesic doses administered in 24 hrs in each group

Group A Mean(Median)±SD	Group B Mean(Median)±SD	(Mann whitney test) p value
1.39(1.0)±0.499	2.06(2)±0.899	P = 0.0006*

The average number of total analgesics used in the control group A was significantly higher compared to the other two groups Band C. But there was no significant difference among group B and C in terms of total number of analgesic dosages used (p=0.0006).

GRAPH 6: Total number of analgesic doses administered



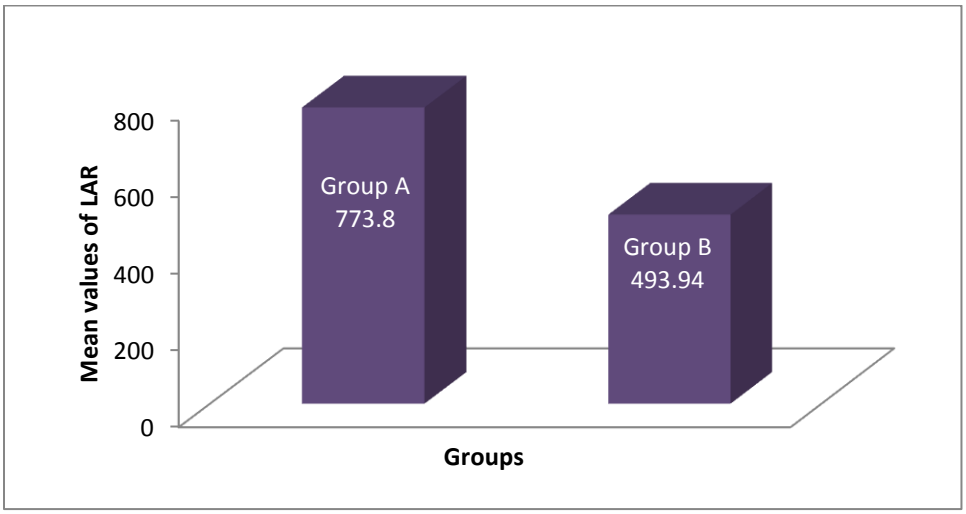
MEAN TIME OF FIRST ANALGESIC REQUEST:

Table 11.The average time at which the first analgesic was requested and administered in the two study groups (Mean values of LAR)

Group	Mean time (in minutes) postoperatively for the first request of analgesia
A	**773.8**
B	**493.94**

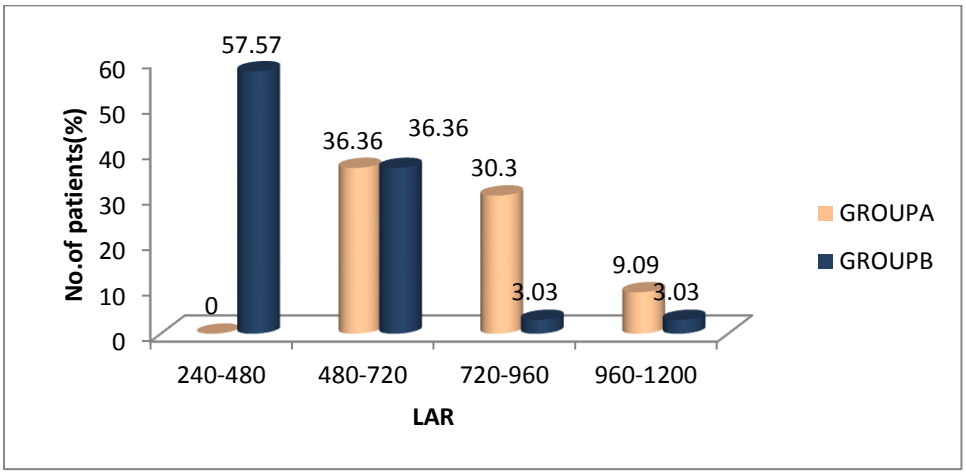
p value = 0.0001*

GRAPH 7: The average timing of the first analgesic dose in two groups



The timing of first shot of rescue analgesic was significantly shorter in group A compared to group B. In this regard there was a significant difference in group A and B with respect first dose of analgesic (p = 0.0001)

GRAPH 8: Showing the percentage of patients requesting analgesia in each group in time interval of 4 hours in the initial 24 hours postoperatively.



The statistical data has shown that higher percentage of patients from group B have requested analgesia in the initial 480 minutes i.e., 8 hours postoperatively

Table 12: Association between Duration of Surgery and LAR (Group A)

Duration of surgery	LAR (in hours)				Chi square test p value
	480-720	720-960	960-1200	Total	
30-60	2(16.7%)	1(10%)	1(33.3%)	4	0.625
60-90	4(33.3%)	3(30%)	2(66.6%)	9	
90-120	6(50%)	4(40%)	0	10	
120-150	0(%)	1(10%)	0(20%)	1	
150-180	0	1(10%)	0	1	
Total	12(100)	10 (100)	3(100)	25	

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 ($p = 0.625$).

Table 13: Association between Duration of Surgery and LAR (Group B)

Duration of surgery	LAR(in hours)					Chi square test p value
	240-480	480-720	720-960	960-1200	Total	
30-60	2(10.5%)	1(8.3%)	.0	.0	3(9.1%)	0.0001*
60-90	9(47.4%)	3(25.0%)	.0	1(100.0%)	13(39.4%)	
90-120	8(42.1%)	6(50.0%)	.0%	.0%	14(42.4%)	
120-150	0	2(16.7%)	.0%	.0%	2(6.1%)	
150-180	0	0	1(100%)	0	1(3%)	
Total	19(100%)	12(100%)	1(100%)	1(100%)	33	

*This table demonstrates that there is an association between duration of surgery and the first demand of analgesia by the patient. i.e., LAR (p = 0.0001)

The statistical analysis from the above tables correlating association between duration of surgery and the time of first demand of analgesia by the patient i.e., LAR for each group has shown that there is a strong association between the two variables in group B where Bupivacaine was instilled intraperitoneally after the creation of pneumoperitoneum and no association was found between duration of surgery and LAR when Bupivacaine was instilled intraperitoneally before the creation of pneumoperitoneum. This concludes that the duration of surgery and LAR are not related when the preemptive analgesia was given and pain stimuli was abolished.

Therefore, Bupivacaine provided a substantial reduction of pain intensity upto the first 8 – 16 hours postoperatively and this was found to be statistically significant, Further much better reduction in pain, no appeareance of shoulder tip pain, lesser

demand for analgesia and lower doses of analgesics administered when Bupivacaine was instilled intraperitoneally before creation of pneumoperitoneum.

Side effects of Bupivacaine:

No side effects were observed with the use of Bupivacaine in this study.

DISCUSSION

Although previous studies have shown that laparoscopy is associated with less pain than laparotomy it is not pain free**.** 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 insufflation of CO2 resulting in distension of abdominal wall and prolonged elevation of diaphragm.[19,140]

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, intraabdominal trauma secondary to the gall bladder removal, abdominal distention, pneumoperitoneum using carbon dioxide etc. Optimally, therefore pain should be treated multimodally. We therefore studied the effect of intraperitoneal instillation of local anaesthesia for analgesia after laparoscopic cholecystectomy.

Table 14: Randomized control studies on effect of intraperitoneal analgesia on shoulder tip and overall pain after laparoscopic cholecystectomy.

First author and Ref no	No of patients	Shoulder pain	Overall pain (incisional and visceral)
Chundrigar[113]	58	N	Y
Mraovic[8]	80	=	Y
Pasqualucci[10]	109	=	Y
Szem[19]	55	N	Y
Joris[6]	40	N	N
Raetzell[139]	24	N	N
Present study	60	Y	Y

N - bnot significant difference from placebo.

Y - significant effect in the treatment group.

= not investigated.

Out of 6 Randomized placebo controlled studies to check the effectiveness of intraperitoneal local anaesthetics, four reported reduced overall pain after intraperitoneal instillation of local anaesthetics in patient undergoing laparoscopic cholecystectomy. Our study showed modest overall analgesic effect where there was a statistically significant difference during the first 12 hours.

Our present study also showed significant reduction in shoulder tip pain but it was in contradiction with the findings of Chundrigar et al[113] and Szem et al.[19]

Bisgaard et al[116] and Michaloliakou et al[150] examined the effect of combined multiregional incisional and intraperitoneal local anaesthetic blockade in a RCT. Michaloliakou et al reported a significant reduction in overall pain during the first 24 hours postoperatively. Our study also showed a significant difference in pain intensity in the early postoperative period and the number of patients in both the studies were almost similar (Table 19).

Table15: Randomized control studies on effect of multiregional analgesia on shoulder tip and overall pain after laparoscopic cholecystectomy.

First author and Ref no	No of patients	Shoulder pain	Overall pain (incisional and visceral)
Michaloliakou[150]	59	=	Y
Bisgaard[116]	50	N	Y
Present study	63	Y	Y

N - not significant difference from placebo.

Y - significant effect in the treatment group.

= not investigated.

Bisgaard et al[116] showed a significant reduction in overall pain and narcotic requirements and it was consistent with our present study.

In our study we observed that the pain scores taken after 12hrs post operatively in study groups A were close to those in group B (not significant). (ref graph no.3 & 4).

The pain scores at 4^{th} , 8^{th} hour were significantly lower in group A compared to group B. But pain scores at 12^{th} to 24^{th} hrs gave conflicting results in terms of significance. (Table 7)

We did find an appreciable difference in total analgesic requirement between both the groups and this was consistent with the findings that of Bisgaard et al[116] in a randomized control study. Noxious stimulation lead to alterations in CNS function which influence subsequent pain experience. Local anaesthetics successfully block the noxious inputs to CNS and thus alter the pain perception in the subsequent hours and thus result in reduced pain scores and reduced analgesic usage.

If laparoscopic cholecystectomy is to be a routine ambulatory surgical procedure, the pain experienced by the patients during early postoperative period must be addressed.

Our study showed that intraperitoneal instillation of Bupivacaine diminishes the peak of pain occurring during the first 4-6 hours after the surgical procedure and significantly reduces the need for postoperative analgesia.

Any reduction in such pain is relevant, particularly if it is statistically significant, whether the lower pain score translated into increased patients comfort and compliance is questionable. However, at whatever level they functioned they did so more comfortably.

Thus, this simple, inexpensive, effective technique improves the postoperative course in hospital and can be practiced routinely in all elective laparoscopic cholecystectomy.

In our study we did not observe any side effects of Bupivacaine.

Narchi et al[143] in their study of serum concentrations of local anaesthetics (Lidocaine and Bupivacaine) following intraperitoneal administration during laparoscopy, found that the intraperitoneal use of doses of 400mg Lidocaine or 100mg Bupivacaine for perioperative analgesia was safe and solutions of Lidocaine containing Adrenaline appeared to pose even less risk than plain solutions.

Spielman et al[165]studied pharmacokinetics and pharmacodynamics of local analgesia for laparoscopic tubal ligation using 12 ml of Lidocaine 2% (240 mg), and 20 ml of Bupivacaine 0.5% (100mg) The peak concentration of Bupivacaine was not evident until 60 minutes after injection. The mean concentration was 0.44 +/- 0.15 micrograms/ml (range, 0.20 to 0.77 micrograms/ml; convulsive level, 4.5 to 5.5 micrograms/ml). These findings may justify the use of larger volumes of these local anaesthetics for more painful diagnostic laparoscopy procedures whenever adhesions or extensive manipulation is anticipated.

In our study we found a significant difference between instillation of Bupivacaine before (Group A) and after creating pneumoperitoneum (Group B).

Very small number of studies have compared the differences of pre procedure and post procedure usage of local anaesthetics.

Pasqualucci et al[10] emphasize that timing of administration of local anaesthetic is fundamental to pre-empt postoperative pain. They found that VAS pain scores and the

consumption of analgesics were significantly lower in patients receiving intraperitoneal Bupivacaine immediately after the creation of pneumoperitoneum than at the end of surgery. Their data appear to confirm that the optimum timing to reduce neuronal sensitization of the posterior horn is before nociceptive stimulation. However their study results indicate that intraperitoneal local anaesthetic blockade administered before or after surgery preempts postoperative pain relative to an untreated placebo-control condition.

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.

It was suggested that intraperitoneal injection of local anaesthetic may provide an effective block of postoperative visceral pain after laparoscopic cholecystectomy. Unfortunately, studies in which local anaesthetics have been used in this setting have provided conflicting results. Most of these initial studies have used small doses of Bupivacaine or of Lidocaine. By contrast, other recent studies that have used larger doses and concentrations have demonstrated that intraperitoneal Bupivacaine can be effective. Bupivacaine, an amide local anaesthetic has a reduced systemic and cardiac toxicity which was evaluated by several studies in doses as large as 300–375 mg for infiltration and no clinical evidence of toxicity was observed.

In our study we studied the effect of intraperitoneal instillation of Bupivacaine before and after the creation of pneumoperitoneum in reduction of postoperative pain following laparoscopic cholecystectomy.

Patients receiving intraperitoneal instillation of Bupivacaine before the creation of pneumoperitoneum showed significantly lower pain scores in early postoperative period. (p=0.0001) and table 6,7.

The difference in shoulder tip pain was strongly significant between the group that received Bupivacaine before the creation of pneumoperitoneum (group A) and those who received Bupivacaine after the creation of pneumoperitoneum (group B) Table 9; Graph 5.

The average number of doses of Diclofenac sodium given postoperatively was less in group A (p=.0006) Table 10,11, Graph 6 meanwhile the time to first requested analgesic dose was significant between the two groups A and B (p=0.001) Table 12,Graph 7.

So, we believe that intraperitoneal instillation of Bupivacaine before the creation of pneumoperutoneum is significantly effective than intraperitoneal instillation of Bupivacaine after the creation of pneumoperutoneum, in reducing postoperative pain after laparoscopic cholecystectomy. Therefore, we recommend its use as a part of analgesic technique for laparoscopic cholecystectomies.

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CONCLUSION

To conclude, Bupivacaine is effective at preventing pain in the first 4-12 hours of postoperative period after laparoscopic cholecystectomy when instilled intraperitoneally at the beginning laparoscopy giving better pain relief when intraperitoneal Bupivacaine instilled before the creation of pneumoperitoneum. Our study showed, instillation of 2 mg/kg of Bupivacaine significantly reduced the need for Diclofenac, when instilled before the creation of pneumoperitoneum compared with intraperitoneal Bupivacaine instilled after the creation of pneumoperitoneum. This technique is simple, safe, and without any adverse effects. As postoperative pain is unpredictable, local anaesthetics should be considered for instillation in all patients at the beginning and at the end of laparoscopic procedures. Bupivacaine is better choice because of its higher efficacy and larger safety margin. A systematic instillation is likely to be cost effective, because it decreases time in the postoperative units, usage of NSAIDS or opioids, and resource utilization in the ward for treatment of postoperative pain and helps patient to get a better postoperative recovery and early discharge.

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ANNEXURES

ETHICAL CLERANCE CERTIFICATE

B.L.D.E.UNIVERSITY'S
SHRI.B.M.PATIL MEDICAL COLLEGE, BIJAPUR – 586103
INSTITUTIONAL ETHICAL COMMITTEE

NO/558/2015
20/11/15

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this college met on 17/11/2015 *at* 03 pm *scrutinize the Synopsis of Postgraduate Students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected and revised version synopsis of the Thesis has accorded Ethical Clearance.*

Title "A randomized study of effectiveness of analgesia with preemptive intraperitoneal instillation of bupivacaine & instillation of Bupivacaine after the creation of pneumoperitoneum in laparoscopic Chole cystectomies"

Name of P.G. Student : Dr Sphoorthy T. M.
Dept of Anaesthesiology

Name of Guide/Co-investigator : Dr. Vidya Patil.
Professor of Anaesthesiology

DR.TEJASWINI VALLABHA
CHAIRMAN

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.

CHAIRMAN
Institutional Ethical Committee
BLDEU's Shri B.M. Patil
Medical College,BIJAPUR-586103.

SAMPLE INFORMED CONSENT FORM

B.L.D.E.U.'s SHRI B.M. PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE, VIJAYAPURA – 586103, KARNATAKA

TITLE OF THE PROJECT: "A COMPARATIVE, RANDOMIZED, PROSPECTIVE STUDY OF PREEMPTIVE INTRAPERITONEAL INSTILLATION OF BUPIVACAINE WITH INSTILLATION OF BUPIVACAINE AFTER THE CREATION OF PNEUMOPERITONEUM IN LAPAROSCOPIC CHOLECYSTECTOMIES"

INVESTIGATOR : **Dr. SPHOORTHY. T. M.**
Department of Anaesthesiology
Email: sphoorthytm@gmail.com

PG GUIDE : Dr.VIDYA PATIL
Professor
Department of Anaesthesiology
B.L.D.E. University's Shri B. M. Patil Medical College Hospital Centre and Research Sholapur Road,
VIJAYAPURA

PURPOSE OF RESEARCH:

I have been informed that this study is **"A COMPARATIVE, RANDOMIZED, PROSPECTIVE STUDY OF PREEMPTIVE INTRAPERITONEAL INSTILLATION OF BUPIVACAINE WITH INSTILLATION OF BUPIVACAINE AFTER THE CREATION OF PNEUMOPERITONEUM IN LAPAROSCOPIC CHOLECYSTECTOMIES"** I have been explained about the reason for doing this

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

PROCEDURE:

I understand that I will be doing **"A COMPARATIVE, RANDOMIZED, PROSPECTIVE STUDY OF PREEMPTIVE INTRAPERITONEAL INSTILLATION OF BUPIVACAINE WITH INSTILLATION OF BUPIVACAINE AFTER THE CREATION OF PNEUMOPERITONEUM IN LAPAROSCOPIC CHOLECYSTECTOMIES".**

RISKS AND DISCOMFORTS:

I understand that I/my ward may experience some pain while giving general anesthesia and intraperitoneal instillation of local anesthesia 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 **"A COMPARATIVE, RANDOMIZED, PROSPECTIVE STUDY OF PREEMPTIVE INTRAPERITONEAL INSTILLATION OF BUPIVACAINE WITH INSTILLATION OF BUPIVACAINE AFTER THE CREATION OF PNEUMOPERITONEUM IN LAPAROSCOPIC CHOLECYSTECTOMIES".**

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.Sphoorthy. T. M is available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during the course of this study, which might influence my continued participation.

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

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

REFUSAL OR WITHDRAWL OF PARTICIPATION:

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

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

INJURY STATEMENT:

I understand that in the unlikely event of injury to me/my ward, resulting directly 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. Sphoorthy T.M

(Guide) (Investigator)

STUDY SUBJECT CONSENT STATEMENT:

I confirm that Dr. Sphoorthy T.M 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

_____

_____

PROFORMA

STUDY: "A RANDOMIZED STUDY OF PREEMPTIVE INTRAPERITONEAL INSTILLATION OF BUPIVACAINE WITH INSTILLATION OF BUPIVACAINE AFTER THE CREATION OF PNEUMOPERITONEUM IN LAPAROSCOPIC CHOLECYSTECTOMIES".

Serial No. Group [A] Group [B]

Name: I.P. No. :

Age : Hospital:

Sex: DOA: DOS:

Preoperative diagnosis:

Proposed surgery:

PRE- ANAESTHETIC EXAMINATION

Chief Complaints:

Past History

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

Previous anaesthetic 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:

Temperature: Height:

Teeth: BMI:

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:

Total bilirubin: Platelet count: Blood group/Rh typing:

SGOT/ SGPT: Serum Electrolytes: BT/ CT:

X-Ray chest: ECG: ECHO:

Any other:

Pre-operative baseline

HR

BP

Premedication :

ASA Grade :

Anaesthetic Technique: Generalanesthesia along with intraperitonal instillation of bupivacainewith normal saline either before or after the creation of pneumoperitoneum.

Drug and Dosage:

Duration of surgery:

Adverse effects (If any):

INTRA OPERATIVE MONITORING:

PR: ECG:

BP: ECHO:

POST OPERATIVE MONITORING:

1. The time lapse between the operation and

   the first demand of analgesics by the patient (in minutes):

2. The intensity of post operative pain on the visual

   analogue scale (VAS) at the time first demand of analgesia:

3. The appearance of shoulder tip pain (time in minutes after surgery):

4. Postoperative pain scores in the initial 24 hours recorded every 4^{th} hourly.

Time after surgery in hours	VAS score
4	
8	
12	
16	
20	
24	

5. Analgesia request time in the initial 24 hours postoperatively.

Analgesia request time in hours after surgery	No. of doses of analgesics administered
0-4	
4-8	
8-12	
12-16	
17-20	
20-24	

KEY TO MASTER CHART

Sl No.	**:**	Serial number
IP No.	**:**	Inpatient number
VAS	**:**	Visual Analogue Scale
STP	**:**	Shoulder tip pain
LAR	**:**	The time of first demand of analgesia by the patient (Latency of analgesia request)
Y/N	**:**	Yes/No