"COMPARISON OF PREINCISIONAL PORT SITE INFILTRATION OF 0.5% LEVOBUPIVACAINE V/S 0.5% ROPIVACAINE FOR POST OPERATIVE PAIN RELIEF IN PATIENTS UNDERGOING LAPAROSCOPIC APPENDICECTOMY - A ONE YEAR HOSPITAL BASED DOUBLE BLIND RANDOMISED CONTROLLED TRIAL"

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ENDORSEMENT

This is to certify that the dissertation entitled **"COMPARISON OF PREINCISIONAL PORT SITE INFILTRATION OF 0.5% LEVOBUPIVACAINE V/S 0.5% ROPIVACAINE FOR POST OPERATIVE PAIN RELIEF IN PATIENTS UNDERGOING LAPAROSCOPIC APPENDICECTOMY - A ONE YEAR HOSPITAL BASED DOUBLE BLIND RANDOMISED CONTROLLED TRIAL"** is a bonafide research work done by **REG NO.BA0114005**.

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LIST OF ABBREVIATIONS USED

ASA	-	American society of Anaesthesiologists
BMI	-	Body mass index
CNS	-	Central nervous system
CO_2	-	Carbon dioxide
CVS	-	Cardiovascular system
DBP	-	Diastolic blood pressure
E	-	Eosinophils
ECG	-	Electrocardiogram
ED_{50}	-	Effective Dose 50
$EtCO_2$	-	End tidal carbon dioxide
GIT	-	Gastrointestinal tract
Hb	-	Haemoglobin
HR	-	Heart rate
Inj.	-	Injection
IV	-	Intravenous
Kgs	-	Kilograms
L	-	Lymphocytes
M	-	Monocytes
MAP	-	Mean arterial pressure
Mg	-	Milligrams
Mins	-	Minutes
MPG	-	Mallampati Grading
N	-	Neutrophiles

PR	-	Pulse rate
RBS	-	Random blood sugar
RR	-	Respiratory rate
SBP	-	Systolic blood pressure
SPO_2	-	Saturation percentage of oxygen
Sr	-	Serum
Temp	-	Temperature
TLC	-	Total Leucocyte count
VAS	-	Visual Analogue Scale
α	-	Alpha
β	-	Beta

ABSTRACT

BACKGROUND: It is well known that laparoscopic surgeries cause less post operative pain, allow early ambulation and discharge, than open surgeries. However laparoscopic surgery is not completely pain free. Administration of local anaesthetic into the wound before incision (pre-emptive analgesia) has been found to reduce post operative pain following laparoscopic surgery. Bupivacaine is a commonly used long acting amide local anaesthetic for local infiltration. To overcome the associated cardiotoxicity and neurotoxicity, Levobupivacaine and Ropivacaine which are less cardiotoxic and neurotoxic are being used for local infiltration (port site) for post operative pain relief.

OBJECTIVE: To compare the efficacy of preincisional portsite infiltration of 0.5%Levobupivacaine v/s 0.5% Ropivacaine for post operative pain relief in patients undergoing laparoscopic appendicectomy.

METHODOLOGY: The present study was conducted at , KLE'S Dr. Prabhakar Kore Hospital and Medical Research Centre, Nehru nagar, Belagavi 590010, on 60 adult patients undergoing elective laparoscopic appendicectomy under General Anaesthesia between January 2015 to December 2015.Patients were divided into 2 groups, Group 1 and Group 2 by computer generated randomisation table. After induction of general anaesthesia Group 1 patients received 14ml of 0.5% Levobupivacaine preincisional port site infiltration and Group 2 patients received 14ml of 0.5% Ropivacaine preincisional port site infiltration, 6ml at the umbilical port and 4 mL at each working port. Laparoscopic appendicectomy was done according to standard protocol.

In the post operative period anaesthesia resident blinded to the drug used assessed for post operative pain at 0, 1,2,3,4,5,6,10,14,18,24 hours using VAS pain scale. If VAS>3 rescue analgesia in the form of Inj Tramadol 2mg/kg was given. Time of first rescue analgesia as well as total opioid consumption at the end of 24hrs was noted.

RESULTS: The mean VAS scores were comparable (less than 3) in both the groups at different time intervals post operatively ($p > 0.05$). The maximum VAS score recorded was 6 at 0^{th} hour in both group1 and group 2. The number of patients requiring rescue analgesia were 5 in group 1 and 6 patients in group 2. The total amount of rescue analgesic consumed over 24 hours in the form of Inj. Tramadol IV was 126 $\pm$ 14.76 in group 1 and 122$\pm$ 12.77 in group 2 and was comparable ($p = 0.641$).

CONCLUSION: Preincisional portsite infiltration with both 0.5% levobupivacaine and 0.5% ropivacaine are equally effective in providing postoperative pain relief in patients undergoing laparoscopic appendicectomy.

KEYWORDS: Preincisional portsite infiltration, 0.5% levobupivacaine, 0.5% ropivacaine, laparoscopic appendicectomy, postoperative pain.

CONTENTS

LIST OF TABLES

LIST OF GRAPHS

LIST OF FIGURES

LIST OF PHOTOGRAPHS

INTRODUCTION

It is well known that laparoscopic surgeries cause less post operative pain, allow early ambulation and discharge, than open surgeries.[1,2,3] That is why laparoscopic appendicectomy is being increasingly done rather than open appendicectomy. However laparoscopic surgery is not completely pain free.

The exact etiology of pain after laparoscopic surgeries is still unclear, however, it appears to be multifactorial and the causes include, abdominal wall trauma by trocar entrances, diaphragmatic irritation secondary to CO_2 insufflation and pneumoperitoneum, type and temperature of insufflated gas, residual intraperitoneal gas, intraabdominal trauma, microruptures of the parietal peritoneum due to abdominal distension, chemical irritation of the peritoneum, etc. In order to reduce postoperative pain after the laparoscopy, several methods such as parentral or peroral opioids and NSAIDs, rectus sheath block, intraperitoneal infiltration of the local anesthetics or opioids, the use of intramuscular morphine injections, patient-controlled analgesia, and injection of local anesthetics into the port sites are suggested.[4,5,6,7,8]

Various modalities have been tried to treat post operative pain following laparoscopic appendicectomy. Administration of local anaesthetic into the wound before incision (pre-emptive analgesia) has been found to reduce post operative pain in both laparoscopic cholecystectomy and laparoscopic appendicectomy.[5,6]

Bupivacaine is a commonly used long acting amide local anaesthetic for local infiltration. It provides adequate analgesia but is associated with cardio and neurotoxicity especially when used in higher concentrations or on inadvertent intravascular injection.[5]

To overcome this shortcoming, levobupivacaine, which contains the levorotatory isomer and is less cardiotoxic and neurotoxic when compared to Bupivacaine was introduced.[10]

To overcome various shortcomings associated with the use of local anaesthetic agents like systemic toxicity, short duration of action, another newer local anaesthetic, Ropivacaine was introduced, which combines the anaesthetic potency and long duration of action of bupivacaine with a toxicity profile intermediate between bupivacaine and lidocaine.[9] Ropivacaine shows marked differential blockade. In equal doses it will provide similar sensory blockade to bupivacaine but less motor blockade.[9] It has also been successfully used for reduction of post-operative pain by port site infiltration.[10]

However very few studies have compared levobupivacaine and ropivacaine.

Hence this study is conducted to compare the efficacy of preincisional port site infiltration of 0.5% levobupivacaine v/s 0.5% ropivacaine for post operative analgesia in patients undergoing laparoscopic appendicectomy.

OBJECTIVE

To compare the efficacy of preincisional portsite infiltration of 0.5% Levobupivacaine v/s 0.5% Ropivacaine for post operative pain relief in patients undergoing laparoscopic appendicectomy.

REVIEW OF LITERATURE

The first operation for acute appendicitis was performed in 1759 by J. Mestivier. He described the case of a 45-year-old patient admitted to St. Andrew Hospital in Bordeaux for a mass localized on the right side of the umbilical area. The mass was fluctuant and was opened, but the patient died later. [11]

The first successful appendicectomy was performed in 1735 by Claudius Amyand. Later in 1981 Kurt Semm performed the first laparoscopic appendicectomy which became a new gold standard in surgical treatment of acute as well as chronic appendicitis.[12]

Laparoscopic appendicectomy has now been improved and standardized[13]. Laparoscopic appendicectomy has some advantages, including decreased postoperative pain, better aesthetic result, a shorter time to return to usual activities, and lower incidence of wound infections or dehiscence. This procedure is cost-effective but may require more operative time and skill as compared with open appendicectomy. In addition, patients who underwent open appendicectomy returned to work later and had more complications.[14]

History of post operative pain relief

H. David Reines, defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage." Acute pain is a normal and predictable physiologic response to an adverse chemical, thermal, or mechanical stimulus; it is associated with surgery, trauma, or acute illness and is usually experienced for a limited and defined period of time.[15]

Knowledge of the history of pain management appears to begin with the case of a 5000-year-old cadaver that apparently experienced sciatic pain and had markings showing that treatment was attempted. "Pain has been part of our culture for a long time," said Dr. Reines. "It is a central metaphor of Judeo-Christian thought and sometimes believed to be a test of faith." [15]

A tincture of opium, or laudanum, was used as early as 1680 for the treatment of pain. "By the early 1800s," continued Dr. Reines, "pain was no longer considered to be something that people had to suffer. At that point, it was believed that a skilled surgeon could operate fast enough so that patients weren't in total agony." Morphine was isolated from heroin in 1803, but modern anesthesia use began around 1846 with the use of ether and chloroform.[15]

Pain treatment has evolved over the years. The first spinal anesthetic was performed just before the turn of the twentieth century, and cocaine was also used in the late 1800s for local anesthesia of the eye. A number of peripheral blocks were described and used by surgeons prior to World War II. "The use of intravenous (IV) drugs didn't arrive until the 1930s and were used a lot in World War II and thereafter," explained Dr. Reines. The use of morphine and cocaine was followed by meperidine and codeine and then fentanyl, oxycodone, and hydromorphone. In the 1950s and 1960s, most pain medication was given either subcutaneously or intramuscularly, and meperidine was used frequently. The use of patient-controlled IV (IV PCA) pain medication was proposed in 1979. In the 1980s, use of intrathecal opioids, epidurals, and continuous spinals began; by the 1990s, nonsteroidal anti-inflammatory drugs (NSAIDs) were being used for augmentation in a multimodal approach, followed by

preemptive pain management and the advent of new technologies such as a fentanyl patch.[15]

The etiology of pain after laparoscopic surgeries appears to be multifactorial and the causes are, abdominal wall incision at trocar entrances, pneumoperitoneum, diaphragmatic irritation secondary to CO_2 insufflation, type and temperature of insufflated gas , residual intraperitoneal gas, intraabdominal trauma, microruptures of the parietal peritoneum due to abdominal distension, chemical irritation of the peritoneum, etc.[4]

Various modalities have been tried to treat post operative pain. In order to reduce postoperative pain after the laparoscopy, several methods such as parentral or peroral opioids and NSAIDs, rectus sheath block, intraperitoneal infiltration of the local anaesthetics or opioids, patient-controlled analgesia, and injection of local anaesthetics into the port sites are suggested.[4] Among these the post site infiltration of local anaesthetics is a simple and effective method.

A study was done by So Ra Ahn, Dong Baek et al; 75 patients who underwent SILS-A (single incision laparoscopic surgery-appendecectomy) were enrolled in the study. The patients were randomly assigned to two groups: conventional SILS-A group (C-SILS-A) or wound infiltrated with 0.5% bupivacaine in SILS-A group (W-SILS-A). Forty-five patients were in the C-SILS-A, and 30 patients were in the W-SILS-A. Patients with perforated appendicitis were excluded. The clinical outcomes were compared between the groups by using the verbal numerical rating scale (VNRS). Clinical outcomes were similar in both study groups except for the pain score. The W-SILS-A group showed significantly lower numbers of additional pain killers and lower VNRS scores 1, 6, and 12 hours after surgery than the C- SILS-A

group. They concluded that portsite infiltration of 0.5% bupivacaine is a technically simple and effective method of reducing early postoperative pain following SILS-A.[16]

Another study was done by Yu-Yin Liu, Chun-Nan Yeh,et al; which studied the efficacy of port site infiltration with 1.0% of Ropivacaine in comparison with normal saline for post operative analgesia in patients undergoing laparoscopic cholecystectomy. Total 72 patients were randomized into two groups of 36 patients each. One group received ropivacaine (Ropi group) infiltration at the port sites at the end of laparoscopic cholecystectomy and the other received normal saline. A visual analogue scale (VAS) was used to assess postoperative pain when the patient awakened in the operating room, 6 and 24 hours (hrs) after surgery, and before discharge. The amount of analgesics used was recorded. Ropivacaine group registered significantly lower VAS scores($p<0.001$)than the placebo group in the 1st 24hr. Regarding analgesic use, the amount of meperidine used after laparoscopic cholecystectomy were lower in patients undergoing laparoscopic cholecystectomy with local anaesthetic infiltration. This group also had a shorter hospital stay[9].

In another study done by F.Cantore et al; to compare the efficacy of pre versus post operative trocar site local infiltration with levobupivacaine in reducing pain after laparoscopic cholecystectomy, 50 patients were enrolled and were randomized into 2 groups :pre group (pre incisional infiltration) and post group (post operative infiltration). All the operations were performed with the same technique. In the pre group the mean intravenous dose of Ketorolac post operatively was 124 mg while in the post group was 339 mg . This difference was statistically significant. Their study demonstrated that infiltration of the trocar site with long acting local anaesthetic is extremely effective for the treatment of post operative pain after

laparoscopic cholecystectomy. Pre incisional local infiltration seems to be better in terms of pain perception and intravenous post operative analgesic consumption.[17]

In another study done by Goldstein, Andrei, et al; for preventing Postoperative Pain by Local Anesthetic Instillation After Laparoscopic Gynecologic Surgery,a total of 180 patients were randomly assigned into three groups to receive an intraperitoneal instillation of 20 mL of either bupivacaine 0.5% (Group B), Ropivacaine 0.75% (Group R) or saline (Group S) at the end of surgery. All patients received analgesia with acetaminophen and Ketoprofen IV infusions. Pain was assessed by using a 0–10 graded numerical scale (NS) every 5 min in the postanesthesia care unit and IV morphine was administered if NS was >4. Assessment of pain was continued every 4 h on the ward, and subcutaneous morphine was injected if needed to keep the NS score < 4. Postoperative nausea and vomiting (PONV) was rated on a 4-point scale. The morphine consumption at wake-up and over the first 24 h was significantly lower ($P < 0.05$) in Group B (mean, 0.92 mg at wake-up; 3.08 mg over 24 h) and in Group R (mean, 0.25 mg at wake-up; 0.69 mg over 24 h), than in Group S (mean, 4.18 mg at wake-up; 12.93 mg over 24 h). The morphine-sparing effect of Ropivacaine was significantly greater than that of bupivacaine. Both local anesthetics were effective in the prevention of PONV. They concluded that local anesthetics should be instilled in all gynecologic patients at the end of all laparoscopic procedures.[18]

In another study done by P.Papagiannopoulou, H. Argiriadou et al; on controlling post laparoscopic cholecystectomy pain, total 57 patients of ASA grade I&IIwere randomly assigned to receive local infiltration with 0.9%saline solution (placebo n=18), Ropivacaine 1.0% (Ropi group n=20) or levobupivacaine 0.5% (Levo group n=19). The local anaesthetic was administered prior to trocar placement, using

the same technique and same volume (20ml) of the drug. Postoperative pain was rated at 2hr, 4hr and 24hr postoperatively by VAS score. Cumulative analgesic consumption and adverse effects were also recorded. The Levo and Ropi groups did not differ significantly in their VAS score at 2hr postoperatively, but the Levo group experienced significantly($p<0.001$) less pain than the placebo and ropi group at 4hr and 24hr post operatively. The Ropi group registered significantly lower VAS scores ($p<0.001$) than the placebo group at 4hr postoperatively. Additionally, the consumption of analgesics was significantly lower in the Levo group than the Ropi and placebo groups. They concluded that local infiltration with Levobupivacaine is more effective than Ropivacaine in reducing the postoperative pain associated with laparoscopic cholecystectomy.[19]

Port site infiltration has been found to be useful in reducing opioid requirement in the post operative period following laparoscopic surgery.[2] This modality of analgesia is cost effective, with least systemic side effects and convenient compared to other modalities.[20]

The practice of preincisional port site infiltration of local anaesthetics in preventing post operative pain in patients undergoing laparoscopic surgeries is not commonly practiced.

Levobupivacaine is a recently introduced local anaesthetic agent which has better safety profile as compared to bupivacaine.[10]

Few studies have compared the efficacy of port site infiltration with bupivacaine 0.5% ,0.25% and ropivacaine 1.0% in laparoscopic surgeries. [9,16,22] No studies have compared Levobupivacaine 0.5% and Ropivacaine 0.5%.especially when used for preincisional portsite infiltration in laproscopic appendicectomy.

Recent studies have shown 0.5% Levobupivacaine and 0.5% Ropivacaine to be equipotent especially when used in peripheral nerve blocks.[10] At higher concentration, Levobupivacaine might be more potent than Ropivacaine.

In a study by Marcel A et al; levobupivacaine, ropivacaine, and bupivacaine were administered in a combined psoas compartment–sciatic nerve block (PCSNB) for total hip arthroplasty and the extent of sensory and motor blockade, postoperative analgesic efficacy was compared .Patients were randomly assigned to receive either 50 mL levobupivacaine 3 mg/mL, 50 mL ropivacaine 4.5 mg/mL or 50 mL bupivacaine 3 mg/mL with epinephrine. Postoperative, the pain intensity at rest, the degree of motor block (Modified Bromage Scale) and the extent of sensory block (pin prick test) were recorded at 4, 8, 12, 24, and 48 hours following initial injection. The postoperative pain intensity was low and did not differ between groups, except for a significantly lower pain intensity in group ropivacaine compared with group levobupivacaine at 4 hours. They found that levobupivacaine, bupivacaine and ropivacaine are equally effective for PCSNB in patients undergoing total hip arthroplasty.[23]

Ingelmo et al; performed a prospective, randomized, double-blind study to determine the minimum local analgesic concentrations of a caudal single shot of ropivacaine and levobupivacaine in children and to describe the upper dose-response curve. In phase 1, 80 boys were randomized to receive either ropivacaine or levobupivacaine. In the second phase a further 32 patients were randomly allocated to receive caudal anesthesia with doses designed to delineate the upper dose-response range (the 50% effective dose [ED50]-ED95 range).

They found that there was no significant differences in ED50 values for caudal ropivacaine and levobupivacaine. The ED50 for levobupivacaine estimated from the Dixon Massey method was 0.069% (95% CI 0.056%-0.082%) and for ropivacaine was 0.075% (95% CI 0.058%-0.092%). Estimated by isotonic regression the ED50 and ED95 respectively of levobupivacaine were 0.068 (0.04-0.09) and 0.20% (95% CI 0.16%-0.24%). For ropivacaine ED 50 and ED95 were 0.066 (0.033-0.098) and 0.225% (95% CI 0.21%-0.24%). Therefore in children receiving one minimum alveolar anesthetic concentration of sevoflurane, there were no significant differences in the ED50 for caudal levobupivacaine and ropivacaine. They concluded by saying that that caudal levobupivacaine and ropivacaine have a similar potency.[24]

Very few studies have compared the efficacy of preincisional port site infiltration of local anaesthetics as a mode of post operative analgesia in patients undergoing laparoscopic appendicectomy. Levobupivacaine being a newer drug, a direct comparison between 0.5%Levobupivacaine and 0.5% Ropivacaine in preventing post operative pain in patients undergoing laparoscopic appendicectomy is missing. Thus this study was undertaken to fill the knowledge gap.

BASIC SCIENCES

PAIN

Pain is the most common symptom that brings patient to a physician. 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, or described in terms of such damage."** This definition recognizes the interplay between the objective, physiologic sensory aspects of pain and its subjective, emotional and psychological components.[25]

The term nociception is derived from Latin word (noci) which means harm or injury. It is used to describe neural responses to traumatic or noxious stimuli. All nociception produces pain, but not all pain results from nociception. Many patients experience pain in the absence of noxious stimuli. It is therefore clinically useful to divide pain into two categories.

Pain is clinically divided into acute pain, which is primarily due to nociception and chronic pain, which may be due to nociception, but in which psychological and behavioral factors often play a major role.

Acute Pain

Acute pain is caused by noxious stimulation due to injury, a disease process, or the abnormal function of muscle or viscera. It is usually nociceptive. Nociceptive pain serves to detect, localize, and limit tissue damage. Four physiological processes are involved namely transduction, transmission, modulation, and perception. This type of pain is typically associated with a neuroendocrine stress response that is proportional to the intensity of pain. Its most common forms include post-traumatic,

postoperative, and obstetric pain as well as pain associated with acute medical illnesses, such as myocardial infarction, pancreatitis, and renal calculi. Most forms of acute pain are self-limited or resolve with treatment in a few days or weeks. When pain fails to resolve because of either abnormal healing or inadequate treatment, it becomes chronic.[26]

Two types of acute pain are differentiated based on origin and features 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 localized and described as sharp, pricking, throbbing or burning sensation. Visceral pain on the other hand is due to nociceptive input arising from internal organ or one of its covering. It is usually dull diffuse pain, which is frequently associated with abnormal sympathetic or parasympathetic activity causing nausea, vomiting, sweating and /or changes in blood pressure or heart rate.[27]

1.Somatic pain — Somatic pain is classified into superficial and deep. Superficial somatic pain is due to nociceptive input arising from skin, subcutaneous tissues, and mucous membranes. It is characteristically well localized and described as a sharp, pricking, throbbing, or burning sensation. Deep somatic pain arises from muscles, tendons, joints, or bones. It usually has a dull, aching quality and is less well localized.[26]

2. Visceral pain — Visceral acute pain is due to a disease process involving an internal organ or its covering (eg, parietal pleura, pericardium, or peritoneum). Four subtypes are described: (1) true localized visceral pain, (2) localized parietal pain, (3) referred visceral pain, and (4) referred parietal pain. True visceral pain is dull, diffuse, and usually midline. It is frequently associated with abnormal sympathetic or

parasympathetic activity causing nausea, vomiting, sweating, and changes in blood pressure and heart rate. Parietal pain is typically sharp and often described as a stabbing sensation that is either localized to the area around the organ or referred to a distant site . The phenomenon of visceral or parietal pain referred to cutaneous areas results from patterns of embryological development and migration of tissues, and the convergence of visceral and somatic afferent input into the central nervous system. Thus, pain associated with disease processes involving the peritoneum or pleura over the central diaphragm is frequently referred to the neck and shoulder, whereas pain from disease processes affecting the parietal surfaces of the peripheral diaphragm is referred to the chest or upper abdominal wall.[26]

Chronic Pain

Chronic pain is pain that persists beyond the usual course of an acute disease or after a reasonable time for healing to occur, this healing period can vary from 1 to 6 months. Chronic pain may be nociceptive, neuropathic, or mixed. A distinguishing feature is that psychological mechanisms or environmental factors frequently play a major role. Patients with chronic pain often have attenuated or absent neuroendocrine stress responses and have prominent sleep and mood disturbances. Neuropathic pain is classically paroxysmal and lancinating, has a burning quality. When the sympathetic system plays a major role, it is often termed sympathetically maintained pain. The most common forms of chronic pain include those associated with musculoskeletal disorders, chronic visceral disorders, lesions of peripheral nerves, nerve roots, or dorsal root ganglia (including diabetic neuropathy, causalgia, phantom limb pain, and postherpetic neuralgia), lesions of the central nervous system (stroke, spinal cord injury, and multiple sclerosis), and cancer pain. The pain of most musculoskeletal disorders (eg, rheumatoid arthritis and osteoarthritis) is primarily

nociceptive, whereas pain associated with peripheral or central neural disorders is primarily neuropathic.[26]

Pain may also be classified according to pathophysiology as nociceptive or neuropathic pain, etiology as arthritis or cancer pain, or the affected area such as headache or low back pain. Such classifications are useful in the selection of treatment modalities and drug therapy. Nociceptive pain is caused by activation or sensitization of peripheral nociceptors, specialized receptors that transduce noxious stimuli. Neuropathic pain is the result of injury or acquired abnormalities of peripheral or central neural structures.

Many factors influence the occurrence, intensity, quality and 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 post operative care.[27]

NEURO-PHYSIOLOGY OF PAIN

Nociceptors

Sensation is often described as either protopathic (noxious) or epicritic (non-noxious). Epicritic sensation (light touch, pressure, proprioception, and temperature discrimination) is characterized by low-threshold receptors (specialized endorgans on the afferent neurons) and conducted by large myelinated nerve fibers while; protopathic sensation (pain) is sub served by high-threshold receptors (free nerve endings).[28]

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.[29-31,32]

Several types of pain receptors are recognized

1. Mechano-nociceptors, which respond to pinprick.
2. Silent nociceptors, which respond only on the presence of inflammation.
3. Polygonal mechano-heat receptors which is more prevalent and respond to excessive pressure, extreme of temperature, and pain producing substances.[29]

Nociceptors are either somatic that include those in skin and deep tissues (muscle, tendons, joints), or visceral nociceptors that include those in internal organs.[28-30]

Pain pathway

Pain is conducted along three neuron pathways; from the periphery to the cerebral cortex. [28-30,32]

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) for example, 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). [28-30,32]

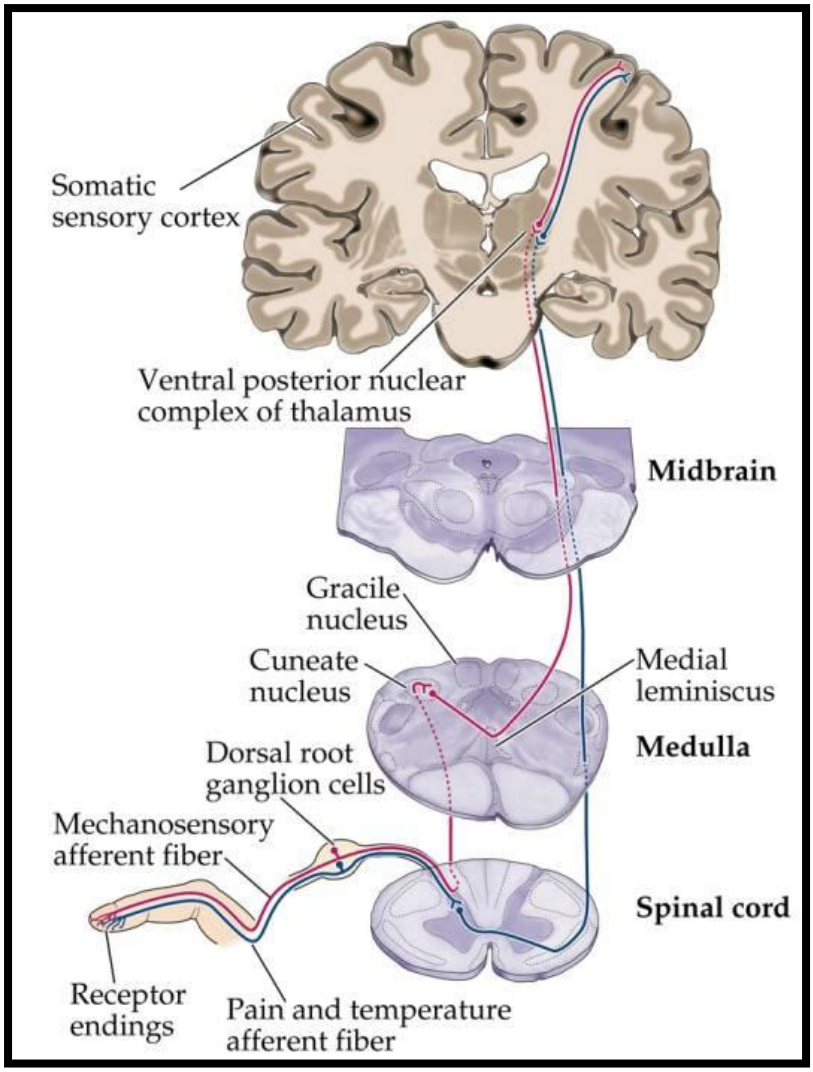

Figure 1: Pain pathway[28-30,32]

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 and are normally silent or wide dynamic range (WDR) neurons that can receive also non-noxious afferent input. WDR neurons are more prevalent in the dorsal horn and are

responsible for the increased intensity of firing in response to same stimulus "wind-up".[30,31]

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 processing and modulating nociceptive input.[30,31]

Axons of most of the second order neurons cross the midline to the contra-lateral side of the spinal cord forming the lateral spinothalamic tract that send its fibers to the thalamus, the reticular formation, nucleus raphe and periaquiductal gray.[30,31]

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.[30-33]

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 lead to an improved outcome. The latter suggests that effective postoperative pain management as a very important aspect of postoperative care.[34]

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 one to day three postoperatively) has led to treatment strategies designed to prevent its development.[35]

Although a variety of factors may contribute to the development of postoperative myocardial ischemia, including hypothermia, anaemia, 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.[36]

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.[37]

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, vital capacity, forced expiratory volume and functional residual capacity. Those pathophysiologic alterations are characteristic of acute restrictive pulmonary disease and, as such, may be associated with clinically significant hypoxia and hypercarbia.[37]

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) breath less deeply and have inadequate cough which leads to further reduction in the tidal volume and functional residual capacity, which in turn can cause atelectasis, intrapulmonary shunting and hypoxemia.[34]

c. Gastrointestinal 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.[38]

d. Endocrinal effects

The dominant neuroendocrine responses to pain involve hypothalamic-pituitary-adrenocortical interactions. These interactions result in increased catecholamine and catabolic hormone release. This effects cause sodium and water retention, and increased levels of blood glucose, free fatty acids and lactate. The negative nitrogen balance and protein catabolism may impede patient's convalescence.[39]

e. Hematological 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. This hypercoagulability causes a series of other events such as deep venous thrombosis and myocardial ischemia.[30]

f. Immunological effects

The stress response potentiate postoperative immunosuppression; the extent of which correlates with the extent of surgery. Stress response has been reported to depress the reticulo-endothelial system which predispose to infection.[40]

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. Behavioral responses associated with poorly controlled pain include sleep deprivation and reduced morale.[41]

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.[34]

h. Development of chronic pain

Recently, it is accepted that neuropathic pain can develop after surgery, be persistent, and be the basis for ongoing suffering for the patient. The diagnosis of neuropathic pain can be obtained from the presenting features of burning, stinging or

shooting pain, despite apparent tissue healing with a relative lack of response to doses of opioids used in the postoperative period.[42]

Lastly, optimizing treatment of acute postoperative pain can improve health-related quality of life, while poor postoperative pain control may intervene with patient's activities of daily living.

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).

Behavioral

- 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.[35]

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.

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.

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.

Of most of the methods of pain scoring VAS and VRS are the most commonly used in the single dimension method.

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 labeled “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 (for example, 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.[43]

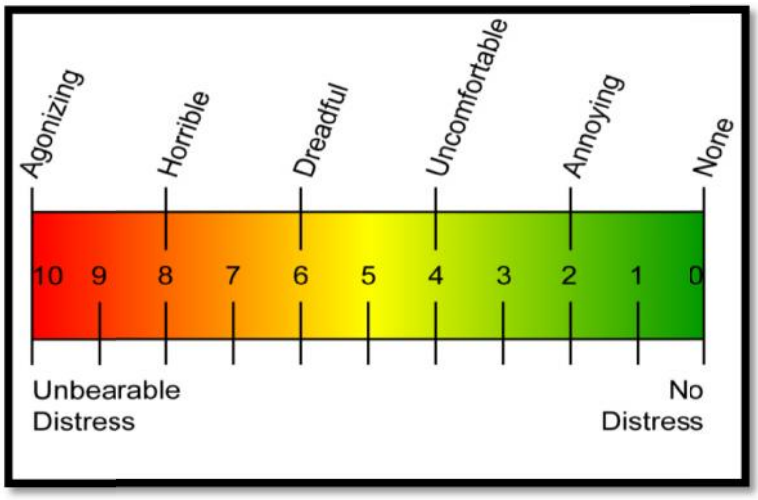

Fig. 2. Visual analogue scale

MANAGEMENT OF POSTOPERATIVE PAIN

Prophylactic measures

The incidence, severity, and duration of pain and suffering during the postoperative period can be decreased by proper preoperative and postoperative surgical and psychological care. Although the accepted definition of pain emphasizes the cognitive, emotional response to tissue damage, the role of psychological techniques in the relief of acute pain has been minimized. Psychoeducational care has beneficial effects on recovery, postoperative pain and psychological distress after surgery.

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

Optimal surgical care also helps to decrease the severity of postoperative pain. Skillful and gentle handling of tissues while carrying out the operation and observance of other surgical principles assist to minimize trauma. Proper postoperative care help to decrease the magnitude of postoperative pain which involves continuing psychological support, proper care of wounds, early ambulation, and of course good nursing care.

Active measures

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

1. Systemic analgesics and adjuvant

a. Narcotics

b. Non-steroidal anti-inflammatory drugs

c. NMDA antagonists

d. Alpha-2 adrenergic agonists

e. Miscellaneous non-opioid compounds

2. Local infiltration and field block - Regional analgesia with local anaesthetics

a. Continuous segmental epidural block

b. Intrapleural instilation

c. Intraperitoneal instilation

d. Infiltration of the incision site

3. Regional analgesia with neuro-axial opioids and local anaesthetics

4. Regional analgesia with combined local anaesthetics and opioids

5. Electrical analgesia achieved with transcutaneous electrical stimulation or electroacupuncture.[29]

Pain after laparoscopic surgeries

Laparoscopic approaches to surgery have increased dramatically over the past several years. However laparoscopic procedures are not pain free and pain occurs after laparoscopy, but is usually less and shorter compared to the same conventional surgical procedure.[3]

Mechanism of pain in laparoscopic surgeries

Early postoperative pain is the most prevalent and dominant complaint that requires strong analgesia including opiates after elective laparoscopic surgeries. For that reason, many efforts have been made to improve postoperative analgesia, but postoperative pain, however, does not completely disappear and several studies have shown that port site incision and visceral pain is the major component. Nonetheless, pain may be moderate or even severe for some patients during the first 24 postoperative hours, and has frequently been treated with nonsteroidal anti-inflammatory drugs (NSAIDs) or opioid treatment.[3,4]

The exact etiology of pain after laparoscopic surgeries is still unclear, however, it appears to be multifactorial and the causes include, abdominal wall trauma by trocar entrances, diaphragmatic irritation secondary to CO_2 insufflation and pneumoperitoneum, type and temperature of insufflated gas, residual intraperitoneal gas, intraabdominal trauma, microruptures of the parietal peritoneum due to abdominal distension, chemical irritation of the peritoneum, etc.[4]

Therefore, abdominal distention should 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 correlation between the width of the gas bubble and pain score, and this pain can be reduced by the aspiration of the gas under the diaphragm.[44]

Factors associated with gaseous pneumoperitoneum

1. Neuropraxia of the phrenic nerve

It has been suggested that distention of the diaphragm during gas insufflations and the resultant phrenic nerve neuropraxia possibly contribute to postoperative pain, which may include the related C4 dermatome.[45]

2. The type of insufflated gas and intraabdominal pH

The phrenic nerves may be damaged by the acid milieu created by the dissolution of CO_2. The intraperitoneal pH when CO_2 gas is insufflated has been measured to be 6.0 immediate postoperatively. On the first postoperative day, the pH rises to 6.4 to 6.7, and on the second postoperative day to 6.8 to 6.9. Thereafter it normalizes to above 7.0.[46]Similar values were found when argon gas was substituted.

3. Residual intraabdominal gas

Several reports have indicated that residual intraabdominal gas after laparoscopy causes pain. Carbon dioxide dissolution, intraabdominal acidosis, and the consequent peritoneal irritation occur for a longer period if the gas is not evacuated at the end of the laparoscopic procedure. Residual gas also may result in a loss of peritoneal surface tension and support to the abdominal viscera, thus contributing to postoperative pain.[47]

4. Temperature of gas

The effect of gas temperature on postoperative pain after gynaecologic laparoscopic procedures has been investigated in a prospective randomized study of standard insufflation gas (20^0 C) versus gas at body temperature. This study found that pain reduction was significantly greater for those patients in whom warmed gas was used, especially with respect to diaphragmatic and shoulder tip pain, with the lasting effect of three days.[45]

5. Humidity of gas

A prospective randomized controlled trail was conducted at the Queen Elizabeth Hospital, Adelaide, to investigate the outcome when humidified gas was insufflated during laparoscopic cholecystectomy instead of standard dry gas.[48] This study demonstrated significantly reduced postoperative pain in patients who underwent humidified gas insufflation. The humidified insufflations showed a trend of less post operative analgesic consumption, along with shorter hospital stay and earlier return to work. The exact relation between dry gas and postoperative pain is not yet determined, but other animal studies have observed that dry gas insufflation is implicated in ultrastructural damage to exposed membranaes, an effect that was not seen with the use of humidified gas.[48]

Management of post operative pain after laparoscopic surgeries

In order to decrease the postoperative pain after the laparoscopy, some methods such as rectus sheath block, intraabdominal drain placement in order to throw out CO_2 pneumoperitoneum, intraperitoneal infiltration of the local anesthetics or opioids, the use of intramuscular morphine injections, patient-controlled analgesia, and injection of local anesthetics into the port sites are suggested[4].

When the condition of the insufflated gas and intra abdominal pressure are optimized the major source of pain which remains are pain from port site incision and visceral pain. As there is no much visceral and tissue manipulation or handeling in laparoscopic appendicectomy,the major source of pain remains is port insertion site.

LEVOBUPIVACAINE

INTRODUCTION

The search for newer anesthetic agents with safer clinical profile has always been one of the primary needs in anesthesiology practice. Regional anesthesia techniques have seen numerous modifications over the last two decades with the advent of many new and safer local anesthetics.

Bupivacaine, the widely used local anesthetic in regional anesthesia is available in a commercial preparation as a racemic mixture (50:50) of its two enantiomers, Levobupivacaine, S (−) isomer and dextrobupivacaine, R(+) isomer.[49]

Severe central nervous system (CNS) and cardiovascular adverse reactions reported in the literature after inadvertent intravascular injection or intravenous regional anesthesiahave linked to the R(+) isomer of Bupivacaine.[49]

Levobupivacaine is a levorotatory (S(−) isomer) isomer of comercially available racemic mixture of Bupivacaine.[49]

The levorotatory isomers like Levobupivacaine were shown to have a safer pharmacological profile, with less cardiac and neurotoxic adverse effects due to its faster protein binding rate.

Levobupivacaine is being used extensively in almost all modes of regional anaesthesia: infiltration, peripheral nerve blocks, spinal anaesthesia, epidural anaesthesia as well as caudal epidural blocks in paediatric patients.[50]

CHEMICAL STRUCTURE

Levobupivacaine ([2S]-1-butyl-N-2 6-dimethylphenyl] piperidine-2-carboxamide) is an amino-amide local anesthetic drug belonging to the family of n-alkyl substitute pipecoloxylidide. Its chemical formula is C_{18} H_{28} N_2 O[49].

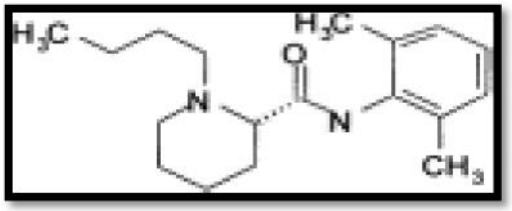

Figure 3 : Chemical structure of levobupivacaine

Structure – Activity relationship

Levobupivacaine being more lipophilic (because of butyl group) it is very potent and produces longer lasting blocks. pKa of Levobupivacaine hydrochloride is 8.1 at 36ºC.

Anesthetic Potency

Lipid solubility of a local anaesthetic correlates well with it's potency and toxicity. Compounds which are more lipophilic penetrate the nerve cell membrane more readily. Thus fewer molecules are required to produce the desired conduction blockade. The order of potency when used in subarachnoid block is Bupivacaine>Levobupivacaine>Ropivacaine. Hydrophobicity appears to be a primary determinant of intrinsic anesthetic potency and Levobupivacaine is highly hydrophobic, hence is very potent.[49,50]

Onset of Action

The onset of conduction blockade is dependent on the dose or concentration of the local anesthetic.

Differential Sensory Motor Blockade

Levobupivacaine in low concentration (0.125%) produces acceptable analgesia with only mild muscular weakness.[49]

Pharmacokinetics

The concentration of Levobupivacaine in blood is determined by the amount injected, the rate of absorption from the site of injection, the rate of absorption from the site of injection, the rate of tissue distribution and the rate of biotransformation and excretion of Levobupivacaine.[49,50]

Absorption

The site of injection, dose and addition of a vasoconstrictor determine the systemic absorption of Levobupivacaine. The maximum blood level of Levobupivacaine is related to the total dose of drug administered from any particular site. Absorption is faster in areas of high vascularity.[50]

Distribution

The two-compartment model can describe this. The rapid distribution phase α is believed to be related to uptake by rapid equilibrating tissue i.e., tissues that have high vascular perfusion. The slow distribution phase β is mainly a function of distribution to slowly equilibrating tissue, biotransformation and excretion of the compound.

More highly perfused organs show higher concentrations of the drug. Levobupivacaine is rapidly excreted by lung tissue. Though skeletal muscle does not show any particular affinity for Levobupivacaine it is the largest reservoir of the drug.[50]

Distribution Characteristics

- T1/2 α 2-7 minutes (uptake by rapid equilibrium tissue)
- T1/2 β 28 minutes (distribution by slowly perfused tissues)
- T1/2 γ 3-5 hours (metabolism and elimination)
- VDSS 72 liters (volume of distribution at steady state)

Clinical Pharmacology

1. Anaesthetic potency: Hydrophobicity is a major determinant of intrinsic anaesthetic potency and Levobupivacaine being highly hydrophobic, is very potent.
2. Onset of action: It depends on the pH of the drug and its concentration.
3. Differential sensory/motor blockade: Levobupivacaine 0.25 to 0.75% produces adequate analgesia with less of motor blockade.

Factors influencing anaesthetic activity

1. ***Dosage of Levobupivacaine:*** As the dosage of Levobupivacaine is increased, the probability and duration of satisfactory analgesia will increase and the onset of block will be shortened. Administering either large volume or a more concentrated solution can increase the dosage.[49,50]

2. ***Addition of vasoconstrictors:*** Addition of adrenaline does not significantly increase the duration of action of Levobupivacaine.

3. ***Site of action:*** The latency and duration are long when given for brachial block, epidural block and subarachnoid block.

4. ***Compounding of local anaesthetics:*** The basis for this practice is rapid onset of one agent. e.g., lidocaine and longer duration of action of other agent, e.g. Levobupivacaine.

5. ***Carbonation and pH adjustment:*** The success of any local anaesthetic depends upon the quantity of drug that can be absorbed on to the axon membrane of the target nerves. This in turn depends upon the ability of the drug to penetrate tissue barrier around the nerve. Alkalinisation of local anaesthetic solution improves the penetration power and more availability of diffusible base of the local anaesthetic. When pH of the solution is equal to pKa of local anaesthetic solution, half of the drug is present as ionized water-soluble cation and rest half as lipid soluble unionized base since this non-ionised soluble form is permeable to nerve cell membrane; it has a major role in penetration.[49,50]

Alkalinisation of local anaesthetic solution acts by

- A direct depressant effect of CO_2 on the axon.
- Concentrating local anaesthetic inside the nerve trunk (diffusion trapping).
- Converting local anaesthetic to the active cation through its effects on pH at the site of action inside the nerve.

The addition of sodium bicarbonate to Levobupivacaine increases the pH of the solution without affecting its chemical stability.[49,50]

Actions

Levobupivacaine produces the same adverse effects as seen with racemic bupivacaine and other local anesthetics. The cardiac toxicity and unwanted CNS effects, may be lower than bupivacaine. Allergic reactions are rare and range in severity from urticaria to anaphylactoid-like reaction.

Levobupivacaine has a safety margin of 1.3, which means toxic effects are not seen until the concentration rises by 30%. The concentration necessary to produce cardiac and neurotoxicity is higher for levobupivacaine than for racemic bupivacaine. There are three case reports of successful resuscitation after inadvertent intravenous injection.

Central Nervous System

Levobupivacaine readily crosses the blood brain barrier causing CNS depression following higher doses. The initial symptoms involve feeling of light-headedness and dizziness followed by visual and auditory disturbances. Disorientation and occasional feeling of lightheadedness may occur. Objective signs are usually excitatory in nature, which includes shivering, muscular twitches and tremors, initially involving muscles of the face (perioral numbness) and part of extremities. At still higher doses cardiovascular or respiratory arrest may occur. Acidosis increases the risk of CNS toxicity from Levobupivacaine, since an elevation of $PaCO_2$ enhances cerebral blood flow, so that more anesthetic is delivered rapidly to the brain.[49]

Autonomic nervous system

Levobupivacaine does not inhibit the Nor Adrenaline uptake and hence has no sympathetic potentiating effect. Myelinated preganglionic B fibers have a faster conduction time and are more sensitive to action of Levobupivacaine. When used for conduction blockade, all local anesthetics, particularly Levobupivacaine produces higher incidence of sensory than motor fibers.

Cardiovascular System

The primary cardiac electrophysiological effect of a local anesthetic is a decrease in the maximum rate of depolarization in Purkinje fibers and ventricular muscle. This action by Levobupivacaine is far greater compared to Lignocaine. Also, the rate of recovery of block is slower with Levobupivacaine. Therefore there is complete restoration of V_{max} between action potential particularly at higher rates. Therefore Levobupivacaine is highly arrythmogenic. Levobupivacaine reduces the cardiac contractility. This is by blocking the calcium transport. Low concentration of Levobupivacaine produces vasoconstriction whereas high doses cause vasodilatation.[49,50]

Respiratory System

Respiratory depression may be caused if excessive plasma level is reached which in turn results in depression of medullary receptor center. Respiratory depression may be also caused by paralysis of respiratory muscles of diaphragm as may occur in high spinal or total spinal anesthesia.[49,50]

Biotransformation And Excretion

Levobupivacaine undergoes enzymatic degradation primarily in the liver. The excretion occurs primarily via the kidney. Renal perfusion and factors affecting urinary pH affect urinary excretion. Less than 5% of Levobupivacaine is excreted via the kidney unchanged through urine. The major portion of injected agent appears in urine in the form of 2, 6 pipecolyoxylidine which is a de-alkylated metabolite of Levobupivacaine. Renal clearance of the drug is related inversely to its protein binding capacity and pH of urine.[49,50]

Adverse effects are encountered in clinical practice mostly due to overdose, inadvertent intravascular injection or slow metabolic degradation.

ADVERSE EFFECTS

Levobupivacaine produces the same adverse effects as seen with racemic bupivacaine and other local anesthetics. The cardiac toxicity and unwanted CNS effects, may be lower than bupivacaine. Allergic reactions are rare and range in severity from urticaria to anaphylactoid-like reaction.

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Central Nervous System: Nervousness, dizziness, blurring of vision or tremors, drowsiness, convulsions and respiratory arrest.

Cardiovascular System: Myocardial depression, hypotension, arrhythmia, ventricular type conduction defect, SA node depression and cardiac arrest.

Allergic reactions:Urticaria, bronchospasm, hypotension.

Other: Constriction of pupil and tinnitus

ADVANTAGES OVER OTHER LOCAL ANAESTHETICS

It has a lower systemic toxicity than bupivacaine and a better,cardiostable profile. Levobupivacaine has been developed to offer a safer alternative to bupivacaine while retaining the desirable blocking properties of racemic bupivacaine.[49,50]

ROPIVACAINE

INTRODUCTION

Ropivacaine is a newer amino amide local anaesthetic which belongs to the group with longer duration of action . It was first synthesized in 1957 by Ekenstam ,but introduced for clinical practice only since 1996. It belongs to the same group as bupivacaine i.e pipecoloxylidide local anaesthetic.

It was found that cardiotoxicity was more with butyl derivatives of pipecoloxylidides like bupivacaine than propyl derivatives. Ropivacaine is a pure S – enantiomeric form of pipecoloxylidides. Ropivacaine has been available for over three decades , but it is a new entrant in the Indian market. [51,52]

It is becoming popular among anaesthesiologists and is being used in almost all modes of regional anaesthesia such as infiltration , peripheral nerve blocks , spinal anaesthesia , epidural anaesthesia as well as caudal epidural blocks in paediatric patients.

CHEMICAL STRUCTURE

Ropivacaine is an amino amide local anaesthetic agent , chemically described as S-(-)-1-propyl-2',6'-pipecoloxylidide hydrochloride monohydrate. It's molecular formula is $C_{17}H_{26}N_2O•HCl•H_2O$ and it has a molecular weight of 328.89. [51,52]

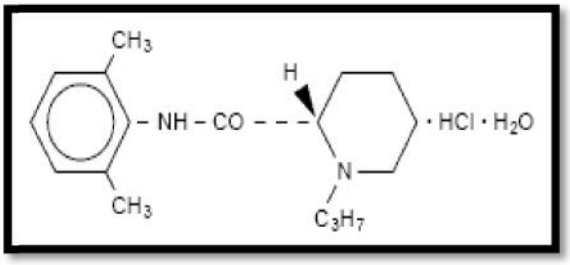


Figure 4: chemical structure of Ropivacaine

PHYSICAL PROPERTIES

Ropivacaine is a white crystalline powder . At 25°C ropivacaine hydrochloride has a solubility of 53.8 mg/mL in water and a distribution ratio of 14:1at pH 7.4. The pKa of ropivacaine is 8.07 which is very similar to that of bupivacaine (8.1) .

However , ropivacaine has a much lesser lipid solubility as compared to Bupivacaine and Levobupivacaine This can be explained on the basis of presence of a propyl (3 Carbon) side chain in ropivacaine as compared to a butyl (4 Carbon) side chain in the other two local anaesthetics. This lower lipid solubility of ropivacaine has a significant effect on the block characteristics of ropivacaine. [51,52]

MECHANISM OF ACTION

Ropivacaine reversibly inhibits the voltage gated sodium channels present on the nerve cell membranes and prevents the influx of sodium ions into the cells, thus blocking the generation and conduction of nerve impulses.

Almost all local anaesthetic agents block the unmyelinated C and myelinated Aδ fibres, which transmit pain impulses, at the same rate.

The rate of blockade of motor fibres i.e Aα and Aβ depends upon the physio chemical properties like pKa and lipid solubility of the local anaesthetic . As ropivacaine is less lipid soluble than bupivacaine , the Aα and Aβ blockade is slower and hence motor blockade is less potent . Studies of lumbar epidural block in humans have confirmed that equal volumes and concentrations of bupivacaine and ropivacaine produce similar degree of sensory block but the motor block produced by ropivacaine is slower in onset, lesser in intensity and shorter in duration. [51,52]

PHARMACOKINETICS

Absorption :

The systemic concentration of ropivacaine depends on the total dose and concentration of drug given, the route of administration, the patient's haemodynamic state and the vascularity of the site of administration. [51]

Distribution :

After intravascular infusion, ropivacaine has a steady state of distribution of 41 ± 7 litres. It is 94% protein bound, mainly to α1-acid glycoprotein. In case of continuous epidural infusion of ropivacaine the plasma concentration can rise due to increased protein binding and reduced clearance. Ropivacaine can easily cross the placenta. [51,52]

Metabolism and excretion :

Ropivacaine is extensively metabolized by the liver, predominantly by the cytochrome P_{4501A} mediated aromatic hydroxylation to produce 3 – hydroxyl

ropivacaine. After a single IV dose, approximately 37% of the total dose is excreted in the urine as both free and conjugated 3-hydroxy ropivacaine. An additional unquantified amount of 2 – hydroxyl – methyl ropivacaine has also been identified.

Ropivacaine metabolites are mainly excreted via kidney. After I.V administration 86% of the dose is excreted in urine of which only 1% is in unchanged form. Following I.V administration ropivacaine has a mean ± SD total plasma clearance of 387 ± 107 mL/min, an unbound plasma clearance of 7.2 ± 1.6 L/min and a renal clearance of 1 mL/min. [51,52]

PHARMACODYNAMICS

Central Nervous System & CardioVascular System :

Ropivacaine has a higher threshold for both cardiac and neuro toxicity as compared to bupivacaine due to its lower lipid solubility and stereo - selective properties. This holds good for both isomers of ropivacaine which have been shown to be less cardio depressant than respective bupivacaine isomers in animal studies. [51] CNS toxicity occurs earlier than cardiac toxicity on iv infusion in healthy volunteers.

Potency :

Lipid solubility of a local anaesthetic correlates well with it's potency and toxicity. Compounds which are more lipophilic penetrate the nerve cell membrane more readily . Thus fewer molecules are required to produce the desired conduction blockade . [51,52]

ADVERSE EFFECTS

Excessive plasma levels are due to over dosage, unintentional intravascular injection or slow metabolic degradation. The mean doses at which CNS symptoms of toxicity begin to occur in human beings are 4.3 and 0.6µg/mL of total and free plasma concentrations respectively. [51,52]

- **Cardiovascular system toxicity:** Syncope, postural hypotension, non-specific ECG abnormalities which include wide QRS complexes , increased conduction time and reduced contractility.

- **Central nervous system toxicity:** Tremor, Horner's syndrome, dyskinesia, neuropathy, vertigo, convulsion and coma. Because of depressant effect of ropivacaine on medulla, excitatory stage of CNS might not occur.

- **Gastrointestinal system toxicity:** Fecal incontinence, tenesmus, nausea, vomiting

ADVANTAGES OVER OTHER LOCAL ANAESTHETICS

It has a lower systemic toxicity than bupivacaine and a better cardiostable profile, thus lower incidence of cardio and neuro toxicity are noted. Ropivacaine produces a more differential blockade allowing better separation between sensory and motor block and is therefore a better choice for use in post operative pain relief. When compared to bupivacaine it produces less dense motor blockade of shorter duration. Ropivacaine has been developed to offer a safer alternative to bupivacaine while retaining the desirable blocking properties of racemic bupivacaine. [51,52]

MATERIALS AND METHODS

The present study was conducted at, KLE'S Dr. Prabhakar Kore Hospital and Medical Research Centre, Nehrunagar, Belagavi 590010, on patients undergoing laparoscopic appendicectomy under General Anaesthesia between January 2015 to December 2015.

Study design

A one year double blind randomised controlled trial.

Study Period

One year from January 2015 to December 2015.

Sample size

A total sample size of 60 cases.

Sample size calculation

Using the formula, sample size =

$$\text{Sample Size (n)} = \frac{2 \times (Z\alpha + Z\beta)2(S12+S22)}{(X1 - X2)2}$$

Level of significance was taken as 5%

Power of the test used was taken as 80%

type I error rate $\alpha = 0.05$ and

type II error rate $\beta = 0.2$

Taking the level of significance at 5%(α=0.05), power of the test as 80%(β=0.2), and using one sided test we get $Z\alpha$=1.65 and $Z\beta$=0.84

S1 is S.D of 1.0 % Ropivacaine[5]

S2 is S.D of 0.5 % levobupivacaine[6]

X1 is mean VAS score at 4 hours post operative period with 1%ropivacaine[5]

X2 is mean VAS score at 4 hours post operative period with 0.5% levobupivacaine [6]

Hence, Zα = 1.65

Zβ = 0.84

S1= 1.35

S2 = 0.84

X1=3.4

X2 = 1.05

$$\text{Sample Size (n)} = \frac{2X(1.65+0.84)2(1.35+0.84)}{(3.4-1.05)2}$$

n = 4.9

As the sample size obtained by the formula was very low, by thumb rule 30 patients were included in each group.

Selection criteria:

Inclusion criteria:

1) ASA grade I and II.

2) Age between 18 to 60 years.

3) Patients undergoing laparoscopic appendicectomy under General Anaesthesia.

Exclusion criteria:

1) Patients not willing to give consent.

2) Patients with known allergic reactions to local anaesthetics.

3) Patients in whom time from port site infiltration to endotracheal extubation is more than 2 hours.

Methodology

After obtaining approval from ethical committee and written informed consent from patients satisfying inclusion and exclusion criteria, 60 adult patients undergoing elective laparoscopic appendicectomy were included in the study.

A thorough Pre-Anaesthetic Evaluation was done. Investigations such as Complete blood count, Random Blood Sugar, Blood Urea, Serum Creatinine were advised. Chest-radiography and Electrocardiography was advised, if the patient was more than 40 years of age. Patients were advised overnight fasting and procedure was explained.

Patients were divided into 2 groups by computer generated randomisation table. Group 1 patients received 14ml of 0.5% Levobupivacaine preincisional port site infiltration and Group 2 patients received 14ml of 0.5% Ropivacaine preincisional port site infiltration.

On the day of surgery base line vitals were recorded. Under strict aseptic precaution 18 or 20 gauge IV cannula was secured. Patient was shifted into the OT and standard monitors like pulseoxymeter, NIBP, ECG, were connected.

Following preoxygenation, patient was premedicated with Inj.Glycopyrrolate 0.005mg/kg iv, Inj.Midazolam 0.05mg/kg iv and Inj Pentazocine 0.5mg/kg. Induction of anaesthesia was done with Inj.Thiopentone sodium 5mg/kg iv sufficient to obtund the eye-lash reflex, followed by Inj.Vecuronium 0.1 mg/kg iv. Tracheal intubation was performed by an experienced anaesthesiologist with an appropriate sized

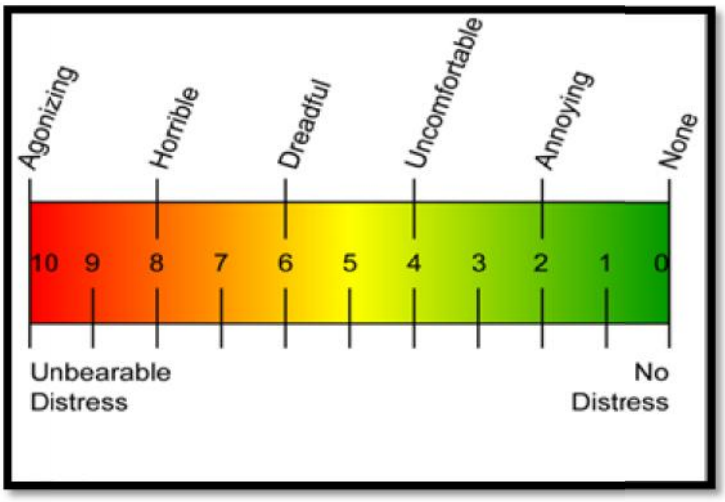
endotracheal tube. Immediately after intubation, cuff of the endotracheal tube was filled with a volume of room air required to prevent a palpable air leak. Anaesthesia

was maintained with 0.5MAC Halothane, Vecuronium and supplemented with Oxygen 33% in Nitrous oxide. Intracuff pressure was maintained throughout the procedure to prevent palpable air leak.

Patient was painted with povidone iodine and surgical spirit sequentially. Parts were draped. Study drug was prepared in identical 20ml syringes by an anaesthesia resident containing 14ml of the study drug. An anaesthesiologist who is blinded to the study drug infiltrated the drug at the port site before the ports were inserted, 6ml at the umbilical port and 4mL at each working port under strict aseptic precautions. Laparoscopic appendicectomy was done according to standard protocol,by a well trained surgical team. Intra op vitals recorded.

Residual neuromuscular relaxation with vecuronium was antagonized with Inj. Neostigmine iv (0.05mg/kg body weight) and Inj. Glycopyrrolate iv (0.01mg/kg body weight) on completion of surgery.

In the post operative period anaesthesia resident blinded to the drug used, assessed for post operative pain at 0, 1,2,3,4,5,6,10,14,18,24 hours using VAS pain scale.



Visual Analogue Scale (VAS)

If VAS>3 rescue analgesia in the form of Inj Tramadol 2mg/kg was given. Total Opioid consumption at the end of 24 hrs was noted. Adverse effects if any of local anaesthetics as well opioids was noted.

Statistical Analysis

The data was entered into the Microsoft Excel Spreadsheet. The data was analyzed using SPSS statistical software version 20.0. Student's unpaired 't' test was used to compare quantitative variables in both groups and the qualitative variables was compared using student's paired 't' test for each group independently. The categorical data are compared using Chi square test. . Non- parametric data was analyzed by using Mann Whitney Test All data were expressed as mean +_ standard deviation. A probability ('p' value) of less than or equal to 0.05 at 95% confidence interval was considered as statistically significant.

RESULTS

The present study was conducted to compare the efficacy of preincisional portsite infiltration of 0.5%Levobupivacaine v/s 0.5% Ropivacaine for post operative pain relief in patients undergoing laparoscopic appendicectomy.

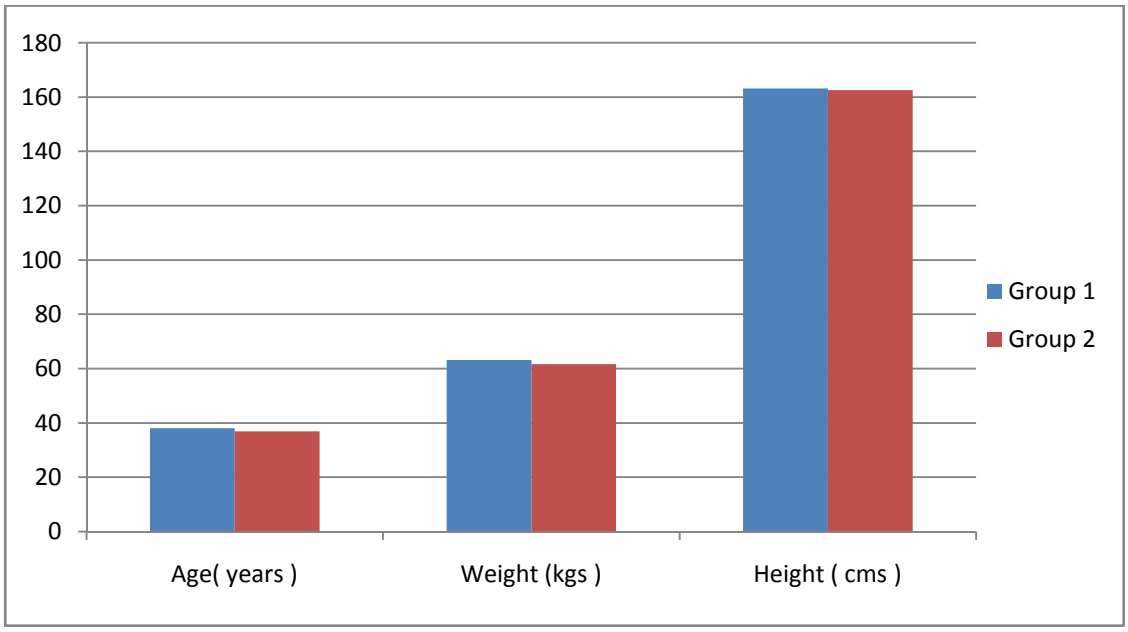
60 patients were enrolled for the study, keeping in mind the inclusion and the exclusion criteria. 30 patients in Group 1 (0.5% Levobupivacaine) and 30 patients in Group2 (0.5% Ropivacaine).

DEMOGRAPHIC DATA

Table 1: Mean Age, Weight and Height

	Group 1		Group 2		p value
	Mean	Standard Deviation	Mean	Standard Deviation	
Age(years)	38.1	10.44	36.9	11.54	0.650
Weight(kgs)	63.2	7.70	61.7	6.02	0.415
Height(cms)	163.1	7.13	162.5	7.81	0.783

Graph 1: Mean Age, Weight and Height



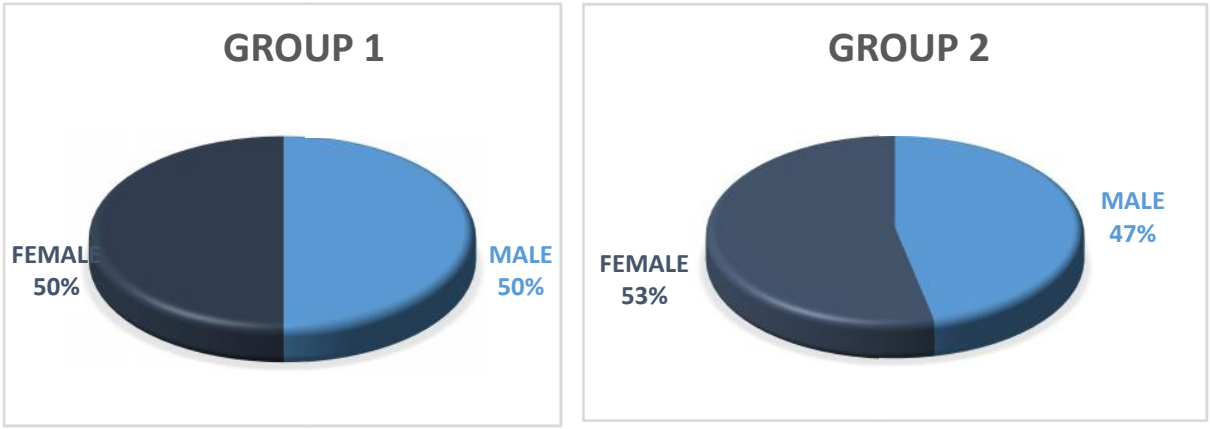
In our study we found no statistically significant difference between group 1and group 2 with regards to mean age (38.1 ± 10.44 and 36.9 ± 11.54 years respectively; p = 0.650), mean weight (63.2± 7.70 and 61.7 ± 6.02 kgs respectively; p = 0.415) and mean height (163.1 ± 7.13 and 162.5 ± 7.81 cms respectively; p =0.783)

Table 2: Percentage of male and female

	Group 1		Group 2	
	Number	Percent	Number	Percent
Male	15	50	14	47
Female	15	50	16	53
Total	30	100	30	100

p=0.742

Graph 2: Percentage of male and female



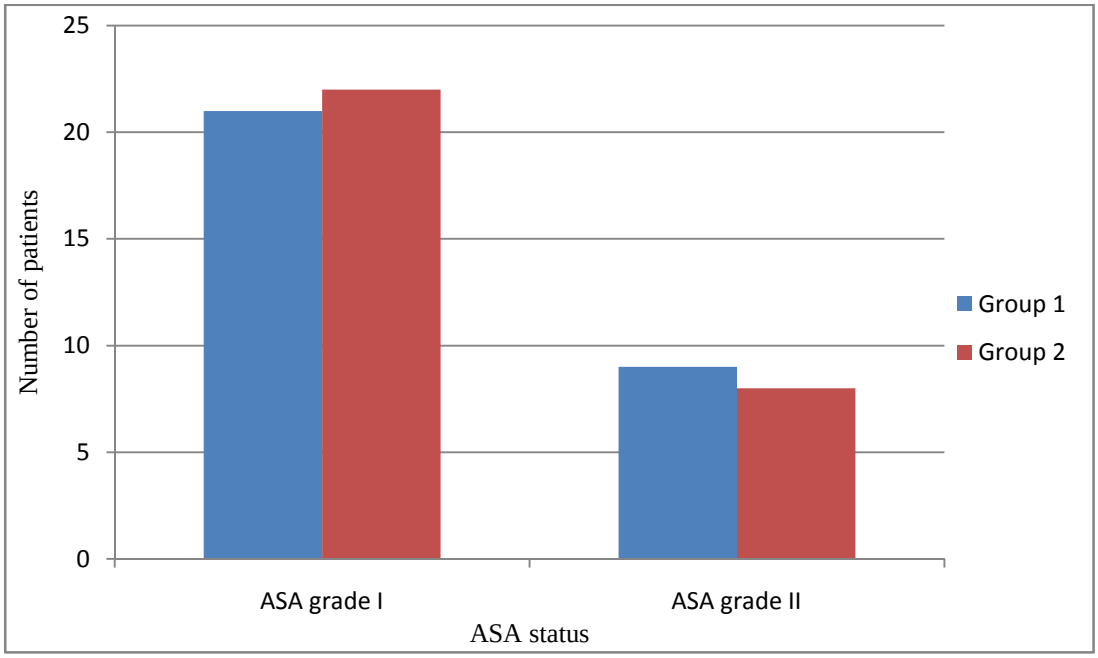
Of the total 30 patients in Group 1, 15 (50%) were female & 15 (50%) were male. Of the total 30 patients in Group 2, 16 (53%) were females and 14 (47%) were males. When compared the difference between the two groups was not found to be statistically significant (p=0.742).

Table 3: ASA physical status

	Group 1		Group 2	
	Number	Percent	Number	Percent
ASA Grade I	21	70	22	73.33
ASA Grade II	9	30	8	26.66
Total	30	100	30	100

p = 0.765

Graph 3: ASA physical status



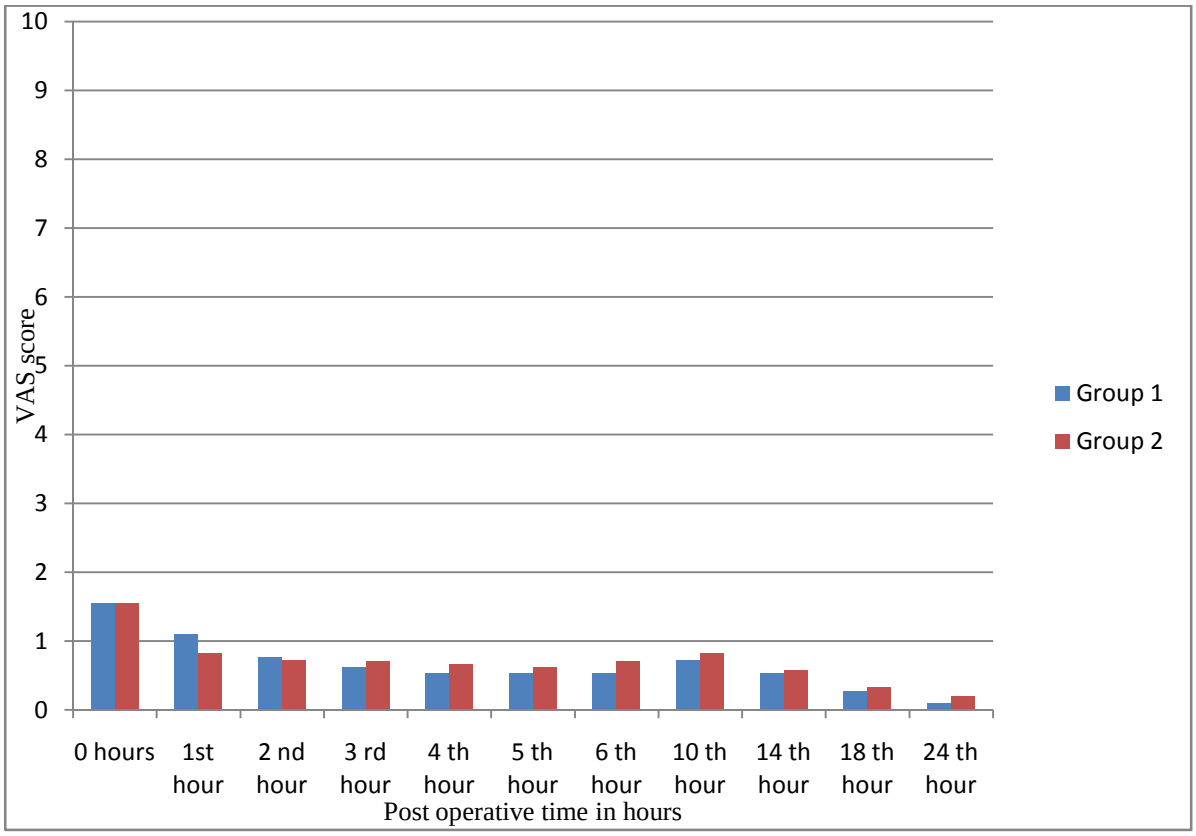
In group 1 70% patients were ASA grade I and 30 % were ASA grade II. In group 2 73.33 % patients were ASA grade I while 26.66 % were ASA grade II.

The data was comparable in both groups (p = 0.765)

Table 4 : Comparison of mean VAS score

Post operative time	Group 1		Group 2		p value
	Mean	SD	Mean	SD	
0 hours	1.56	1.91	1.56	2.07	0.837
1st hour	1.1	1.18	0.83	1.01	0.424
2nd hour	0.77	1.01	0.73	0.94	0.947
3rd hour	0.63	0.85	0.7	0.91	0.843
4th hour	0.53	0.73	0.67	0.84	0.604
5th hour	0.53	0.73	0.63	0.81	0.676
6th hour	0.53	0.73	0.7	0.95	0.661
10th hour	0.73	0.87	0.83	0.98	0.785
14th hour	0.53	0.73	0.57	0.73	0.827
18th hour	0.27	0.45	0.33	0.55	0.720
24th hour	0.1	0.31	0.2	0.41	0.282

Graph 4: Comparison of mean VAS score



In our study the mean VAS score at 0^{th} hour post operatively was 1.56 ± 1.91 in group 1 and 1.56 ± 2.07 in group 2 and was comparable (p=0.837).

The mean VAS score at 1^{st} hour post operatively decreased to 1.1± 1.18 in group 1 and 0.83 ± 1.01 in group 2 and was comparable (p=0.424). The mean VAS score further decreased and at 6^{th} hour post operatively was 0.53± 0.73 in group 1 and 0.7 ± 0.95 in group 2 and was comparable (p=0.661). Themean VAS score further decreased to 0.1± 0.31 in group 1 and 0.2 ± 0.41 in group 2 24^{th} hour post operatively and was comparable (p=0.282).

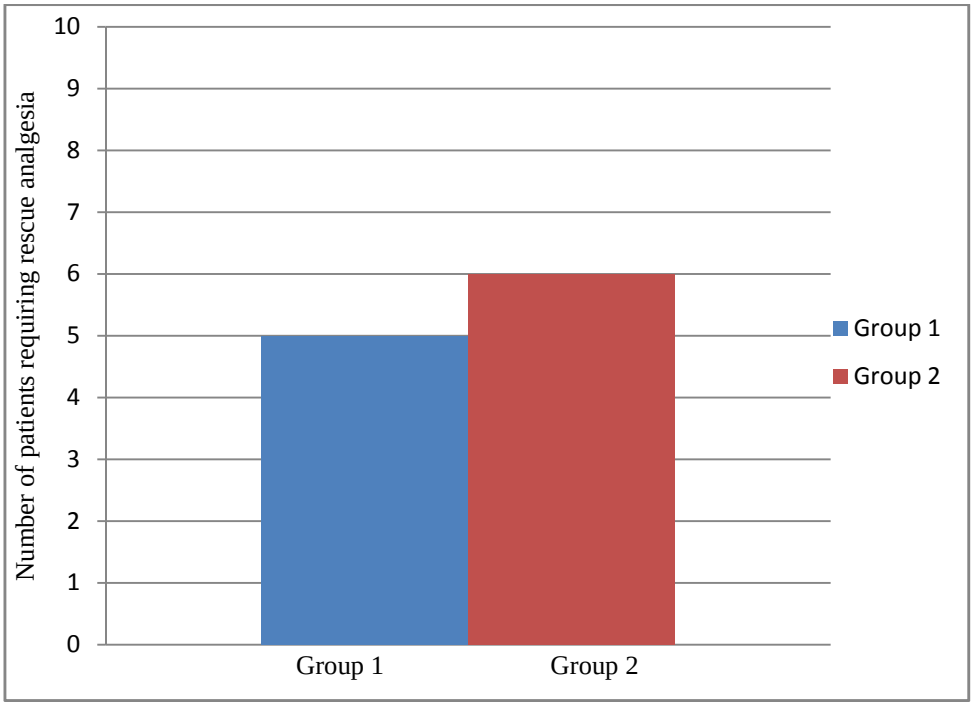
Hence the mean VAS scores were comparable in both the groups.

Table 5: Total number of patients requiring rescue analgesia

Rescue analgesia	Group 1		Group 2	
	Number	Percent	Number	Percent
Yes	5	16.66	6	20
No	25	83.33	24	80
Total	30	100	30	100

$x^2 = 0.156$ P = 0.874

Graph 5: Total number of patients requiring rescue analgesia

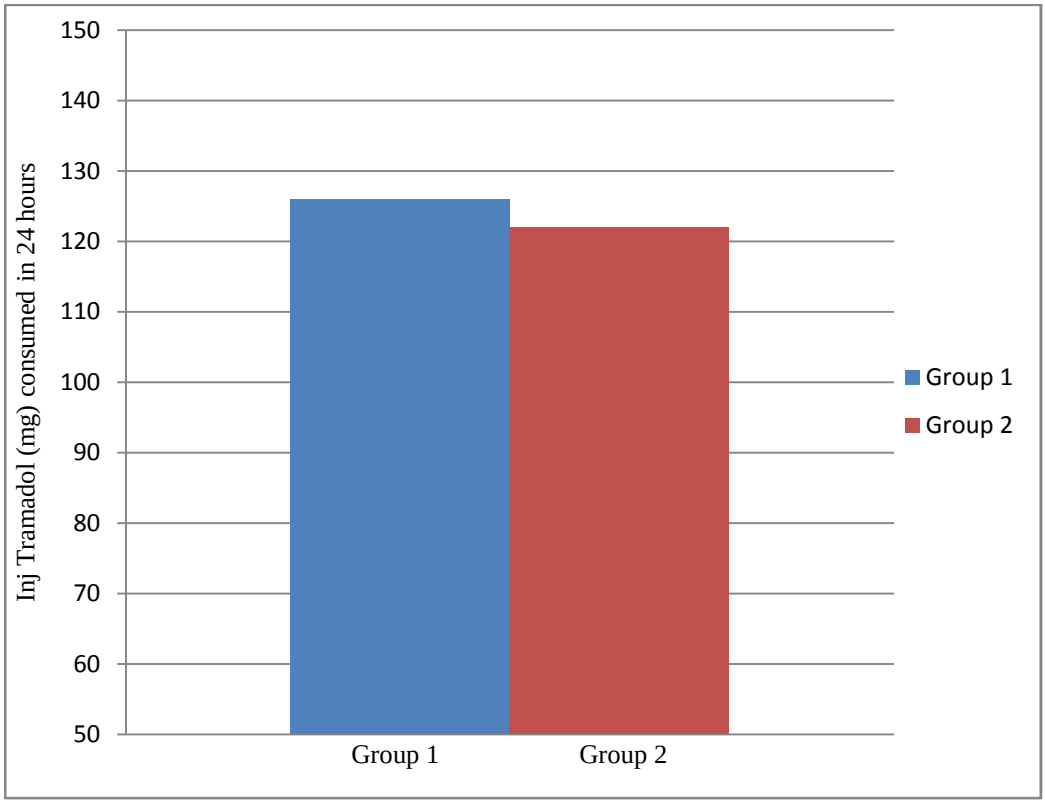


In our study 5 patients out of 30 in group 1and 6 patients out of 30 in group 2 required rescue analgesia. The number of patients who required rescue analgesia was comparable in both the groups (p = 0.843). The maximum VAS score recorded was 6 in both the groups and was identical.

Table 6: Total analgesic consumed in 24 hours

	Group 1		Group 2		
	Mean	Standard Deviation	Mean	Standard Deviation	P value
Inj. Tramadol 2mg/kg	126	14.76	122	12.77	0.641

Graph 6: Total analgesic consumed in 24 hours

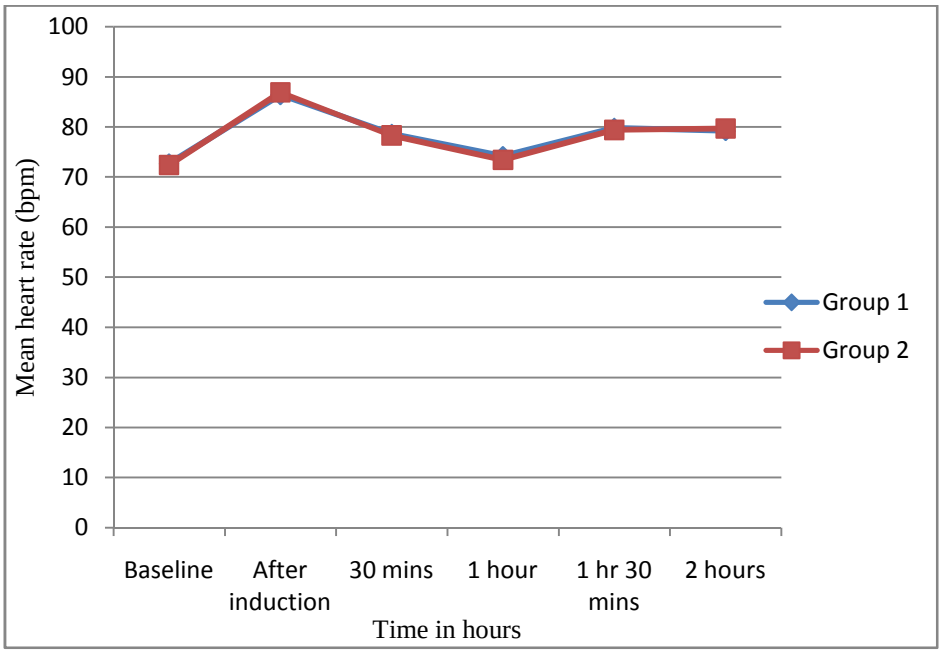


In our study the total amount of rescue analgesic consumed over 24 hours in the form of Inj. Tramadol IV was 126 ± 14.76 in group 1 and 122± 12.77 in group 2 and was comparable (p=0.641).

Table 7: Comparison of mean heart rate at different intervals (bpm)

Time	Group 1		Group 2		p value
	Mean	SD	Mean	SD	
Pre op	72.7	8.03	72.4	7.41	0.894
After induction	86.4	6.24	86.9	5.10	0.718
30 minutes	78.6	8.25	78.3	7.23	0.882
1 hours	74.2	8.49	73.4	6.88	0.727
1 hr 30 mins	79.8	6.38	79.4	5.67	0.840
2 hours	79.2	8.57	79.7	5.56	0.917

Graph 7: Comparison of mean heart rate at different intervals (bpm)



In our study the baseline mean heart rate was 72.7 ± 8.03 bpm in group 1 and 72.4 ± 7.14 bpm in group 2 and was comparable (p = 0.894).

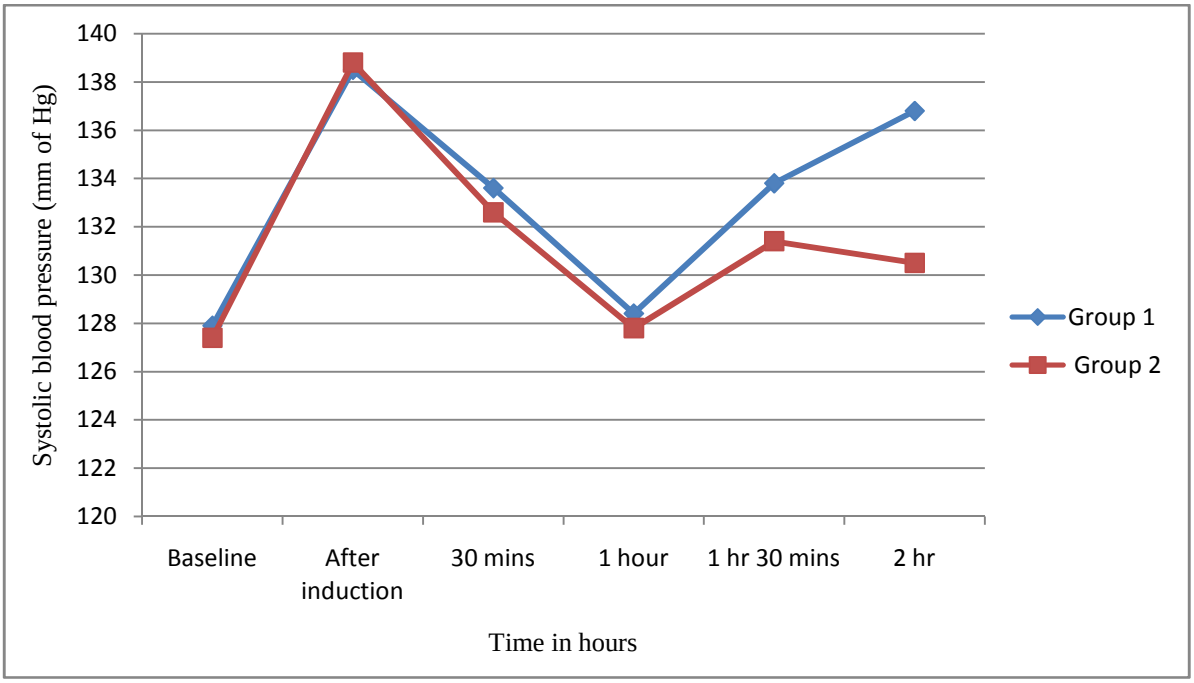
The intra operative mean heart rate after induction increased to 86.4 ± 6.24 bpm in group 1 and 86.9 ± 5.10 bpm in group 2 and was comparable (p= 0.718).

Mean heart rate after 30 mins, after 1 hour, after 1hour 30 mins, after 2 hours were comparable with p values 0.882, 0.727, 0.840, 0.917 respectively.

Table 8: Comparison of systolic blood pressure at different intervals (mm of Hg)

Time	Group 1		Group 2		p value
	Mean	SD	Mean	SD	
Pre op	127.9	12.03	127.4	9.88	0.852
After induction	138.5	11.02	138.8	10.08	0.951
30 minutes	133.6	10.55	132.6	9.47	0.710
1 hour	128.4	10.43	127.8	8.96	0.833
1 hr 30 mins	133.8	9.21	131.4	10.47	0.368
2 hours	136.8	8.07	130.5	1.91	0.175

Graph 8: Comparison of systolic blood pressure at different intervals (mm of Hg)



In our study the baseline mean systolic BP was 127.9 ± 12.03 mm of Hg in group 1 and 127.4 ± 9.88 in group B and was comparable (p = 0.852).

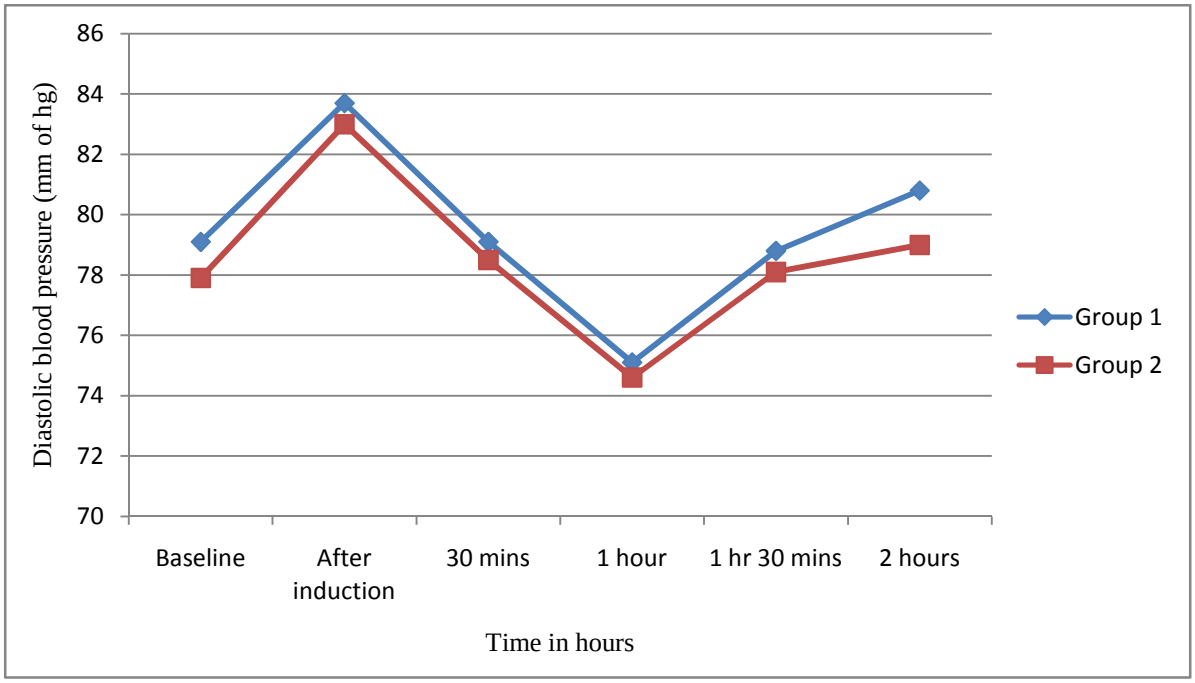
The intra operative mean systolic BP after induction increased to 138.5 ± 11.02 mm of Hg in group 1 and 138.8 ± 10.08 mm of Hg in group 2 and was comparable (p= 0.951).

The mean systolic BP after 30 mins, after 1 hour, after 1hour 30 mins, after 2 hours were comparable with p values 0.710, 0.833, 0.368, 0.175 respectively.

Table 9: Comparison of diastolic blood pressure at different time intervals (mm of Hg)

Time	Group 1		Group 2		p value
	Mean	SD	Mean	SD	
Pre op	79.1	6.35	77.9	6.42	0.495
After induction	83.7	4.65	83	5.58	0.566
30 minutes	79.1	4.83	78.5	5.16	0.626
1 hour	75.1	4.29	74.6	4.66	0.668
1 hr 30 mins	78.8	4.77	78.1	4.92	0.558
2 hours	80.8	1.78	79	3.40	0.343

Graph 9: Comparison of diastolic blood pressure at different time intervals (mm of Hg)



In our study the baseline mean diastolic BP was 79.1± 6.35 mm of Hg in group 1 and 77.9 ± 6.42 in group B and was comparable (p = 0.495).

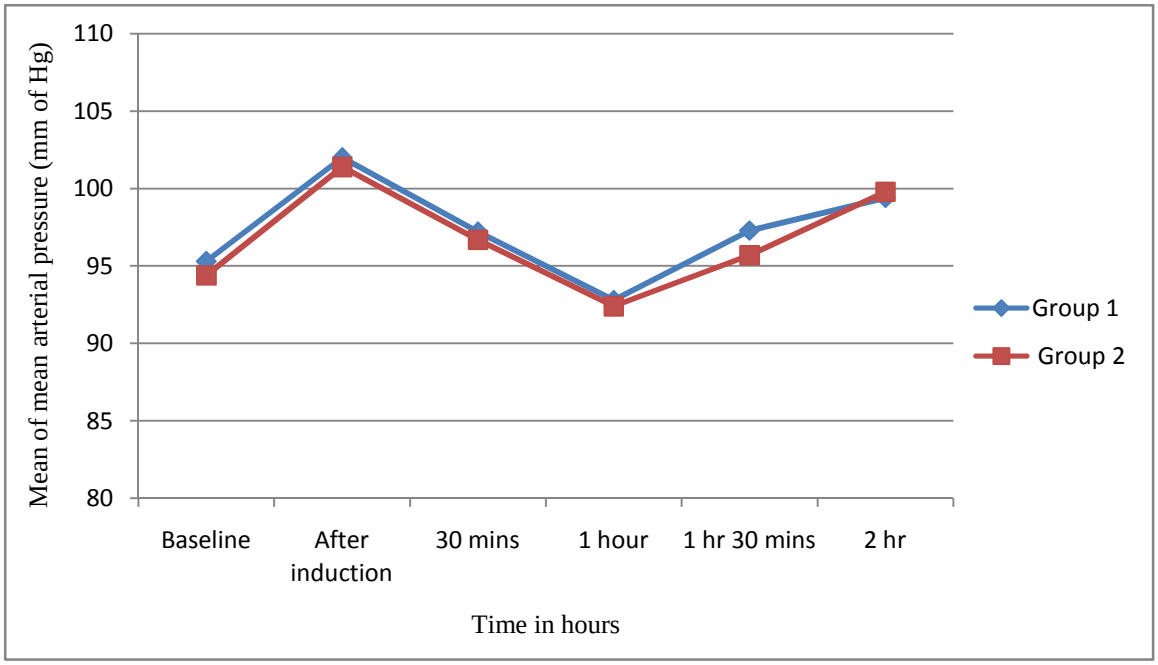
The intra operative mean diastolic BP after induction was 83.7 ± 4.65 mm of Hg in group 1 and 83 ± 5.58 mm of Hg in group 2 and was comparable (p= 0.566).

The mean diastolic BP after 30 mins, after 1 hour, after 1hour 30 mins and after 2 hours were comparable with p values 0.626, 0.668, 0.558, 0.343 respectively.

Table 10: Comparison of mean of mean arterial pressure at different time intervals (mm of Hg)

Time	Group 1		Group 2		p value
	Mean	SD	Mean	SD	
Pre op	95.3	7.07	94.4	7.03	0.626
After induction	102	6.45	101.4	6.65	0.724
30 minutes	97.2	6.28	96.7	6.12	0.740
1 hour	92.8	5.96	92.4	5.74	0.759
1 hr 30 mins	97.3	5.58	95.7	6.43	0.322
2 hours	99.4	3.05	99.8	2.94	0.510

Graph 10: Comparison of mean of mean arterial pressure at different time intervals (mm of Hg)



In our study the baseline mean of mean arterial BP was 95.3± 7.07 mm of Hg in group 1 and 94.4 ± 7.03 in group B and was comparable (p = 0.626).

The intra operative mean of mean arterial BP after induction was 102 ± 6.45 mm of Hg in group 1 and 101.4 ± 6.65 mm of Hg in group 2 and was comparable (p= 0.566).

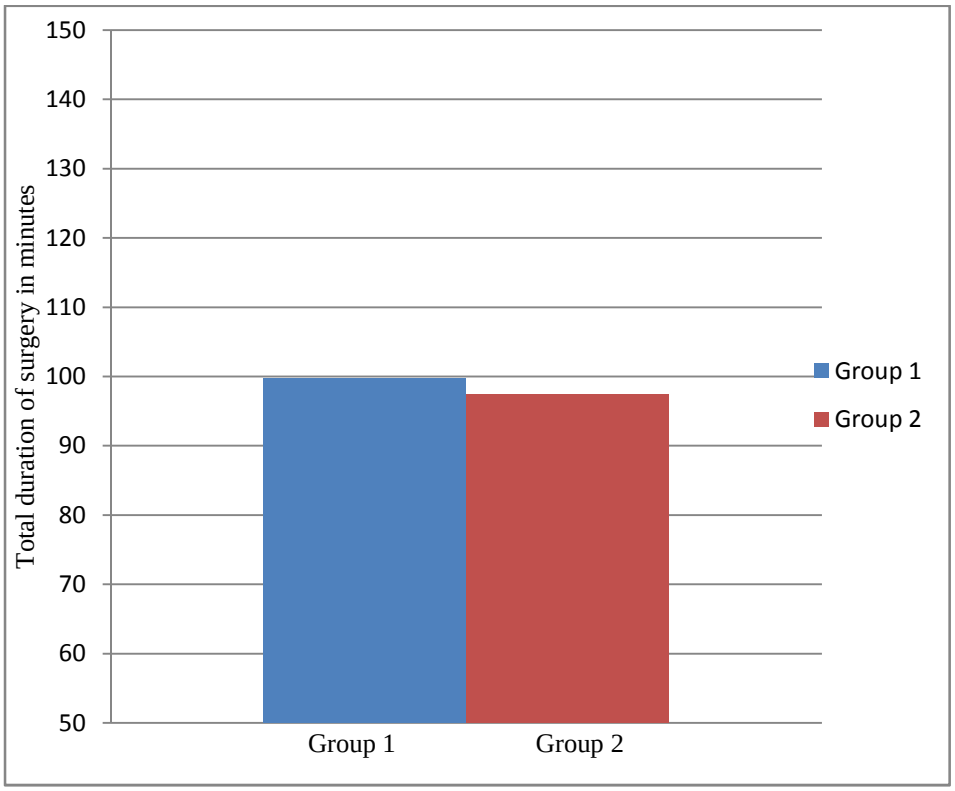
The mean diastolic BP after 30 mins, after 1 hour, after 1hour 30 mins and after 2 hours were comparable with p values 0.740, 0.759, 0.322, 0.510 respectively.

Table 11: Comparison of mean duration of surgery

	Group 1		Group 2	
	Mean	SD	Mean	SD
Mean duration of surgery	99.83	8.42	97.46	8.25

P = 0.276

Graph 11: Comparison of mean duration of surgery



In our study the total duration of surgery was 99.83 ± 8.42 in group 1 and 97.46 ± 8.25 in group 2 and was comparable in both the groups (p = 0.276).

DISCUSSION

Acute appendicitis is the common gastrointestinal emergency encountered in adults. As compared to open techniques, the emergence of laparoscopic surgeries involving multiple small incisions results in less postoperative pain, faster recovery and early discharge from the hospital which enables early resumption of routine actvities by the patient.[51-53]

However laparoscopic surgeries are not pain free.[96-98] The post operative pain remains a prevalent problem and may delay discharge from the hospital.[1] Pain intensity usually peaks during the first few postoperative hours and declines. Pain after laparoscopic surgeries results from port site incision, stretching of the parietal peritoneum, peritoneal inflammation, and phrenic nerve irritation caused by residual carbon dioxide in the peritoneal cavity.[54]

Incision for operative ports is the most common cause for post operative pain following laparoscopic surgery. Hence pre-emptive port site infiltration with local anaesthetic is an effective means of reducing post op pain following laparoscopic appendicectomy.[17]

Various modalities have been tried to achieve post operative pain relief following laparoscopic surgery. These include port site infiltration with local anaesthetics, intraperitoneal instillation of local anaesthetics, parenteral opioids, NSAID's etc.[4,16]

Concept of preemptive analgesia is based on the hypothesis that the most effective way to eliminate or reduce post operative pain is to prevent nociceptive input from afferent stimuli to the CNS hence, preventing CNS hyperexcitability.[17]

Port site infiltration has been found to be useful in reducing opioid requirement in the post operative period following laparoscopic surgery.[55] This modality of analgesia is cost effective, with least systemic side effects and convenient compared to other modalities.[56]

In a study Cervini et al, studied the effect of pre-emptive infiltration with 0.5% bupivacaine on parenteral narcotic requirement in the post op period following laparoscopic appendicectomy. They concluded that pre-emptive infiltration with bupivacaine decreased the need for post operative parenteral narcotics following laparoscopic appendicectomy.[57]

Various local anaesthetics have been used for port site infiltration in patients undergoing laparoscopic surgeries. Bupivacaine and Ropivacaine have been extensively used for port site infiltration to achieve post-op pain relief. Bupivacaine, the widely used local anesthetic agent is available in a commercial preparation as a racemic mixture (50:50) of its two enantiomers, Levobupivacaine, S(−) isomer and dextrobupivacaine, R(+) isomer. Central nervous system (CNS) and cardiovascular adverse reactions reported in the literature after inadvertent intravascular injection or intravenous regional anesthesia have been linked to the R(+) isomer of Bupivacaine. Levobupivacaine has emerged as more cardiostable including lesser incidence of neurotoxicity compared to bupivacaine. Hence these drugs are known to have a better safety profile with more specific action on pain relief and providing early ambulation.[49-52]

Cardiotoxicity was more with butyl derivatives of pipecoloxylidides like Bupivacaine than propyl derivatives. Ropivacaine a newer local anaesthetic is pure S – enantiomeric form of pipecoloxylidides. It has a lower systemic toxicity than

Bupivacaine and a better cardiostable profile, thus lower incidence of cardio and neuro toxicity are noted. Ropivacaine produces a more differential blockade allowing better separation between sensory and motor block and is therefore a better choice for use in post operative pain relief.[51,52]

In pre-emptive analgesia, treatment is initiated before the surgical procedure which prevents sensitization of nociceptors and can reduce pain postoperatively.[17]

The present one year randomized clinical study was conducted on 60 ASA grade I and II patients aged between 18 to 60 years of either gender who were divided into 2 groups by computer generated randomization table. Group 1 received preincisional port site infiltration of 14ml of 0.5% Levobupivacaine (6 ml at the umbilical port and 4 ml at each side port) Group 2 received preincisional port site infiltration of 14ml of 0.5% Ropivacaine(6 ml at the umbilical port and 4 ml at each side port) in patients undergoing laparoscopic appendicectomy under general anaesthesia at KLE'S Dr. Prabhakar Kore Hospital and Medical Research Centre, Nehru nagar, Belagavi. Post operatively pain was assessed using VAS score at 0,1,2,3,4,5,6,10,14,18 and 24 hours post operatively. Rescue analgesia was provided if VAS score recorded was > 3. Total rescue analgesia consumed over 24 hours was recorded.

Yu-Yin Liu et al, studied the effect of port site infiltration with local anaesthetics (ropivacaine vs placebo) on post operative pain following laparoscopic cholecystectomy. They used 6 ml of local anaesthetic at umbilical port and epigastric port and 4 ml at each working port. The study concluded that port site infiltration with local anaesthetic is an effective method of reducing post op pain. Several other studies have also used the same amount of LA for port site infiltration.[9]

Hence in our study we have used 6 ml and 4 ml of LA at umbilical and working port respectively.

In the present study no statistically significant difference was observed between group 1 and group 2 with regard to mean age i.e 38.1 $\pm$ 10.44 and 36.9 $\pm$ 11.54 years respectively; p = 0.650, mean weight 63.2 $\pm$ 7.70 and 61.7 $\pm$ 6.02 kgs respectively;p = 0.415 and mean height 163.1 $\pm$ 7.13 and 162.5 $\pm$ 7.81 cms respectively; p = 0.783. Of the total 30 patients in group 1, 15 (50%) were female & 15 (50%) were male. Of the total 30 patients in group 2, 16 (53%) were females and 14 (47%) were males. When compared the difference between the two groups was not found to be statistically significant (p=0.742). In group 1 70% patients were ASA grade I and 30 % were ASA grade II. In group 2 73.33 % patients were ASA grade I while 26.66 % were ASA grade II. The data was comparable in both groups (p = 0.765). Therefore both the groups had similar demographic characteristics.

In the present study, the preoperative hemodynamic parameters i.e, mean heart rate, mean systolic blood pressure, mean diastolic blood pressure and mean arterial pressure were comparable in group 1 and group 2 ($p > 0.05$). Intraoperative hemodynamic parameters i.e, mean heart rate, mean systolic blood pressure, mean diastolic blood pressure, mean arterial pressure, mean SpO2 were comparable in group 1 and group 2 after induction, after 30 mins , after 1 hour, after 1 hour 30 mins and after 2 hours ($p > 0.05$) i.e there was no significant difference in the hemodynamics in both the groups.

In the present study we found that the mean VAS score at 0^{th} hour post operatively was 1.56 $\pm$ 1.91 in group 1 and 1.56 $\pm$ 2.07 in group 2 and was comparable in both the groups (p=0.837).The mean VAS score decreased at 1^{st} hour

post operatively to 1.1± 1.18 in group 1 and 0.83 ± 1.01 in group 2.Though group 1 recorded higher mean VAS score compared to group 2 it was statistically insignificant (p=0.424). At 2nd hour post operatively the mean VAS score was 0.77± 1.01 in group 1 and 0.73 ± 0.94 in group 2 .Though group 1 recorded higher mean VAS score compared to group 2 it was statistically insignificant (p=0.947). At 3rd hour post operatively the mean VAS score decreased to 0.63± 0.85 in group 1 and 0.7 ± 0.91 in group 2 and was comparable in both the groups (p=0.843). Further at 4th hour post operatively the mean VAS scores were 0.53± 0.73 in group 1 and 0.67 ± 0.84 in group 2 and were comparable (p=0.604). The mean VAS score at 5th hour post operatively was 0.53± 0.73 in group 1 and 0.63 ± 0.81 in group 2 and was comparable (p=0.676). At 6th hour post operatively the mean VAS score remained 0.53± 0.73 in group 1 and 0.7 ± 0.95 in group 2 and was comparable (p=0.661). At 10th hour post operatively the mean VAS score decreased to 0.73± 0.87 in group 1 and 0.83 ± 0.98 in group 2 and was comparable in both the groups (p=0.785). The mean VAS score decreased at 14th hour post operatively to 0.53± 0.73 in group 1 and 0.57 ± 0.73 in group 2 and was comparable (p=0.827). At 18th hour post operatively the mean VAS score decreased to 0.27± 0.45 in group 1 and 0.33 ± 0.55 in group 2 and was comparable in both the groups (p=0.720). The mean VAS score decreased further at 24th hour post operatively to 0.1± 0.31 in group 1 and 0.2 ± 0.41 in group 2 and was comparable (p=0.282).

In both the groups, the mean VAS score was less than 3 and was comparable ($p > 0.05$) at all the recorded time intervals. Hence both levobupivacaine and ropivacaine were found to be equally effective in providing post op analgesia following laparoscopic appendicectomy.

Out of 30 patients in each group, 5 patients in group 1 and 6 patients in group 2 recorded VAS score > 3 and required rescue analgesic. Maximum VAS score recorded in group 1 was 6 and in group 2 was also 6. When compared statistically the difference was not found to be significant ($p = 0.843$). The maximum VAS score was recorded at 0 hour in both group1 and group 2. All patients who required rescue analgesia required it at 0 hour, i.e immediate post op. However in these patients second dose of rescue analgesia was not required. Hence in our study pre-emptive port site infiltration with both levobupivacaine and ropivacaine was found to be effective in preventing post operative pain following laparoscopic appendicectomy. Between the two drugs there was no distinct advantage of either.

Ingelmo et al performed a prospective, randomized, double-blind study to determine the minimum local analgesic concentrations of a caudal single shot of ropivacaine and levobupivacaine in children and to describe the upper dose-response curve. In phase 1, 80 boys were randomized to receive either ropivacaine or levobupivacaine. In the second phase a further 32 patients were randomly allocated to receive caudal anesthesia with doses designed to delineate the upper dose-response range (the 50% effective dose [ED50]-ED95 range).[24]

They found that there was no significant differences in ED50 values for caudal ropivacaine and levobupivacaine. The ED50 for levobupivacaine estimated from the Dixon Massey method was 0.069% (95% CI 0.056%-0.082%) and for ropivacaine was 0.075% (95% CI 0.058%-0.092%). Estimated by isotonic regression the ED50 and ED95 respectively of levobupivacaine were 0.068 (0.04-0.09) and 0.20% (95% CI 0.16%-0.24%). For ropivacaine ED 50 and ED95 were 0.066 (0.033-0.098) and 0.225% (95% CI 0.21%-0.24%). Therefore in children receiving one minimum

alveolar anesthetic concentration of sevoflurane, there were no significant differences in the ED50 for caudal levobupivacaine and ropivacaine. They concluded by saying that that caudal levobupivacaine and ropivacaine have a similar potency.[24] Hence we compared 0.5% levobupivacaine and 0.5% ropivacaine which have been found to be equipotent.

In a study done by Cihangir Bicer et al. on 60 ASA I and II patients aged 18-55 years undergoing septorhinoplasty under general anaesthesia were divided into two groups 30 in each. Group L received preincisional surgical field infiltration with 5ml of 0.5% levobupivacaine plus 5 ml of 0.9 % saline. Group R received preincisional surgical field infiltration with 5ml of 07.5% ropivacaine plus 5 ml of 0.9 % saline. The degree of pain as assessed by mean VAS score postoperatively were as follows – at 0^{th} min it was 5.32 in group L and 5.75 in group R($p = 0.313$), at 10^{th} min it was 6.48 in group L and 5.82 in group R($p = 0.780$), at 20^{th} min it was 6.57 in group L and 6.48 in group R($p = 0.729$), at 30^{th} min it was 6.68 in group L and 6.32 in group R($p = 0.595$), at 1^{st} hr it was 6.15 in group L and 6.28 in group R($p = 0.943$), at 2^{nd} hr it was 5.58 in group L and 5.77 in group R($p = 0.852$), at 4^{th} hr it was 4.95 in group L and 5.37 in group R($p = 0.440$), at 8^{th} hr it was 4.73 in group L and 4.73 in group R($p = 0.508$), at 12^{th} hr it was 4.48 in group L and 4.37 in group R($p = 0.553$), at 24^{th} hr it was 4.05 in group L and 4.12 in group R($p = 0.530$).There was no statistically significant difference in mean VAS scores between both the groups. Hence they concluded that local tissue infiltration with 0.25% levobupivacaine or 0.375% ropivacaine appears similarly effective in reducing the postoperative pain associated with septorhinoplasty. They concluded that levobupivacaine and ropivacaine were equipotent in providing post operative pain relief. The results from this study are similar to the results of our study.[58]

In our study 5 out of 30 patients in group 1 required rescue analgesia and in group 2 out of 30 patients only 6 of them required rescue analgesia. In our study the total amount of rescue analgesic consumed over 24 hours in the form of Inj. Tramadol IV was 126 + 14.76 in group 1 and 122+ 12.77 in group 2 and was comparable (p = 0.641). These findings are similar to the findings of the previously mentioned study done by Cihangir Bicer et al. Five patients (16.6%) in PACU (initial 2 hours) and 3 patients (10%) in the first 24 hours who received levobupivacaine required rescue morphine postoperatively, compared with 6 patients(20%) in PACU (initial 2 hours) and 3 patients (10%) in the first 24 hours in the ropivacaine group. No difference were reported between the 2 groups for the proportion of patients requiring rescue morphine in PACU (P = 0.739) and first 24 hours (p = 1.000) postoperatively and the total morphine consumption in the first 24 hours (p = 0.498). Thus they concluded that both levobupivacaine and ropivacaine were equally effective in reducing postoperative pain.[58]

In another study done by Goldstein et al. in 2000 for prevention of postoperative pain in patients undergoing laparoscopic gynecologic surgeries, a total of 180 patients were randomly assigned into three groups to receive an intraperitoneal instillation of 20 mL of either bupivacaine 0.5% (Group B), ropivacaine 0.75% (Group R) or saline (Group S) at the end of surgery. Pain was assessed by using a 0–10 graded numerical scale (NS) every 5 min in the postanesthesia care unit and IV morphine was administered if NS was >4. Assessment of pain was continued every 4 hr in the ward, and subcutaneous morphine was injected if needed to keep the NS score < 4. They found that the morphine dose required to obtain a NS score <4 at wake-up was significantly smaller in Groups B 0.92 $\pm$ 2.27 and R 0.25 $\pm$ 1.89 than in Group S 4.18 $\pm$ 3.98. The morphine consumption in Group R was also significantly

less than in Group B and Group S. Thus they concluded that ropivacaine is the best choice because of its higher efficacy and larger safety margin for treatment of postoperative pain .These findings do not correlate with our study. However the concentration of ropivacaine used was higher than the concentration of bupivacaine hence might have shown better outcomes in ropivacaine group compared to bupivacaine group.[18]

0.5% Ropivacaine showed similar characteristics as 0.5% Levobupivacaine when used in axillary, interscalene, sciatic or combined femoral and sciatic nerve block.[59]

In another study done by Marcel A. De Leeuw et al. to study the efficacy of Levobupivacaine 3 mg/mL, Ropivacaine 4.5 mg/mL, and Bupivacaine 3 mg/mL for combined psoas compartment–sciatic nerve block in patients undergoing total hip arthroplasty. Forty-five patients undergoing total hip arthroplasty under general anesthesia combined with PCSNB, were randomly assigned to receive either 50 mL levobupivacaine 3 mg/mL, 50 mL ropivacaine 4.5 mg/mL or 50 mL bupivacaine 3 mg/mL with epinephrine. Postoperative, the pain intensity at rest were recorded at 4, 8, 12, 24, and 48 hours following initial injection in a double blind fashion. They found that postoperative pain intensity was low and did not differ between groups, except for a significantly lower pain intensity in group ropivacaine compared with group levobupivacaine at 4 hours. Five patients (11%), equally divided over three groups, needed parenteral rescue opioids postoperatively. They concluded that levobupivacaine, bupivacaine and ropivacaine are equally effective for PCSNB in patients undergoing total hip arthroplasty These results were similar to our study.[23]

Findings of our study are similar to a study conducted by So Ra Aha et al, who studied the effect of pre-emptive port site infiltration with 0.5% bupivacaine in single incision laparoscopic surgery for appendicectomy. So Ra Ahn et al, concluded that pre-emptive infiltration with 0.5% Bupivacaine is a technically simple and effective method of post operative pain relief following laparoscopic appendicectomy.[16]

Duration of surgery is an important factor which can affect postoperative pain. In our study all the surgeries were performed by an experienced group of surgeons and the duration of the surgery was comparable in both the groups (< 2 hours). This eliminated bias which may result from any surgical factors.

With the expanding role of ambulatory and minimally invasive surgery, the need to facilitate an earlier discharge, improving post operative discomfort related to pain due to surgery and repeated intramuscular/intravenous analgesia has become an increasingly important issue. The present study showed that, single time preincisional postsite infiltration with both 0.5% levobupivacaine or 0.5% ropivacaine in patients undergoing laparoscopic appendicectomy are equally effective in terms of postoperative pain relief and decreases the need of analgesics such as opioids or NSAIDs with minimal discomfort and adverse effects. Thus reduces need for hospital stay just for analgesia postoperatively, while patient resumes daily routine activities early. However, large multicentric studies are required to confirm these findings. Further research with lower concentrations of local anaesthetics can be undertaken to decrease the dose of local anaesthetic used.

CONCLUSION

Preincisional port site infiltration with both 0.5% levobupivacaine or 0.5% ropivacaine are equally effective in providing postoperative pain relief in patients undergoing elective laparoscopic appendicectomy .

SUMMARY

The present study was conducted in the Department of Anaesthesiology, KLES Dr.Prabhakar Kore Hospital and MRC, Nehru nagar, Belagavi after obtaining an approval from institutional ethics committee and written informed consent.

The study was conducted on 60 ASA grade I and II patients aged between 18 to 60 years of either gender, undergoing elective laparoscopic appendicectomy under general anaesthesia. Thorough Pre Anaesthetic Evaluation was done. Computer generated randomization table was used to allocate the patients into 2 groups, Group 1 (preincisional port site infiltration with 0.5% Levobupivacaine) and Group 2 (preincisional port site infiltration with 0.5% Ropivacaine). After induction of general anaesthesia, group 1 received preincisional port site infiltration of 14ml of 0.5% Levobupivacaine and group 2 received preincisional port site infiltration of 14ml of 0.5% Ropivacaine (6 ml at the umbilical port and 4 ml at each side port). Laparoscopic appendicectomy was done according to standard protocol.

Post operatively pain was assessed using VAS score at 0,1,2,3,4,5,6,10,14,18 and 24 hours post operatively. Rescue analgesia was provided if VAS score recorded was > 3. Total rescue analgesia consumed over 24 hours was recorded.

The mean VAS score was less than 3and was comparable in both the groups at different time intervals post operatively ($p > 0.05$). In our study the total amount of rescue analgesic consumed over 24 hours in the form of Inj. Tramadol IV was 126 + 14.76 in group 1 and 122+ 12.77 in group 2 and was comparable ($p = 0.641$).

Thus based on the results we conclude that both 0.5% Levobupivacaine and 0.5% Ropivacaine were equally effective in preventing postoperative pain in patients undergoing laparoscopic appendicectomy.

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ANNEXURE – I – ETHICAL CLEARANCE LETTER

K.L.E.UNIVERSITY'S
JAWAHARLAL NEHRU MEDICAL COLLEGE,
NEHRU NAGAR, BELAGAVI-590010 (KARNATAKA-INDIA)
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Ref: MDC/DOME/ 213 **Date: 20/11/2014**

To,

PG student in Anaesthesilogy,
J.N.Medical College,
BELAGAVI.

Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"COMPARISON OF PREINCISIONAL PORT SITE INFILTRATION OF 0.5% LEVOBUPIVACAINE V/S 0.5% ROPIVACAINE FOR POST OPERATIVE PAIN RELIEF IN PATIENTS UNDERGOING LAPAROSCOPIC APPENDICECTOMY – A ONE YEAR HOSPITAL BASED DOUBLE BLIND RANDOMIZED CONTROLLED TRIAL ",** is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

(Dr.Hema Dhumale)
Member Secretary
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

(Dr.Ganga Pilli)
Chairman,
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

ANNEXURE – II - CONSENT FORM

Mr/Mrs/Miss. _____ we are requesting you to enroll yourself in study titled **"COMPARISON OF PREINCISIONAL PORT SITE INFILTRATION OF 0.5% LEVOBUPIVACAINE V/S 0.5% ROPIVACAINE FOR POST OPERATIVE PAIN RELIEF IN PATIENTS UNDERGOING LAPAROSCOPIC APPENDICECTOMY" A ONE YEAR HOSPITAL BASED DOUBLE BLIND RANDOMISED CONTROLLED TRIAL.** conducted by Dr. _____, Post Graduate Student in M.D. Anaesthesiology under the guidance of Dr. _____ Professor, Department of Anaesthesiology, J.N. Medical College, Belagavi under KLE university, Belagavi.

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

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

Purpose of the study:

The purpose of research is to compare the efficasy of preincisional port site infiltrationof 0.5%Levobupivacaine v/s 0.5%Ropivacaine for post operative pain relief in patients undergoing laparoscopic appendicectomy.

Procedure Involved:

If you agree to enroll yourself in my study, you will be interviewed regarding your present, past and family history, then you will be clinically examined in detail and investigated accordingly. You will be randomly allocated in either of the two study groups by computer generated randomisation table. You will receive preincisional port site infiltration of 14ml solutiuon of Levobupivacaine 0.5% or Ropivacaine 0.5% and under general anaesthesia you will undergo laparoscopic appendicectomy as per standard guidelines,there is no change in the anaesthesia or surgical procedure.

Benefits and Risks

The benefits of taking part in this research are that we can avoid adverse effects of opoids, NSAIDS and prolonged hospitalization with good quality of analgesia and early ambulation. There are no observable risks associated with the study.

Voluntary participation / Withdrawal

Taking part in the study is voluntary; you may choose not to enroll in this study. Your decision will not change present or future health care services offered to you at Dr. Prabhakar Kore Hospital.

Alternatives

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

Confidentiality

All information collected about you during the course of the study will be kept Confidential. The code numbers will identify you in this Study records and the information from this study may be published but your identity will be confidential in any publication. The only people to know that you are a research subject are members of the research team. No information about you or information provided by you during the research will be disclosed to other without your written permission except:

- In emergency to protect your rights and welfare.
- If required by law.

Authorization to Publish Results:

When the results of the research are published or discussed, in a conference, no information will be displayed that would disclose your identity. Any information that is obtained in connection with this study and that can be identified with you will remain confidential.

Financial Incentives for participation

No financial incentives are being offered to enrolled patients. It is purely being done with the idea of research and all the cost of the study will be borne by the investigator.

Compensation

In the event of injury, related to the study, treatment will be made available at Dr. Prabhakar Kore Hospital and MRC, Belagavi. No reimbursement, compensation or free medical care will be given by law.

Queries/ Contact details

In case you have any questions related to the study, in future or in case of study related injury or illness, you can contact Dr. _____, Post Graduate student, Department of Anaesthesiology, JNMCollege, KLES Hospital and MRC, Dept Ph. No. 0831-2551292 or phone number: 8762465089or Dr. _____ ,Professor, Dept. Of Anaesthesiology, JNMCollege, KLES Hospital and MRC, Belagavi .

If you have any queries about your rights as a study subject, you may call Dr. Ganga Pilli, Prof. & Head of Pathology as Chairman of J. N. Medical College Institutional Ethics Committee on Human Subjects Research, Phone No.9480275601or Extension-4052 at J. N. Medical College, Belagavi.

Consent for participation in research trial

I, _____ voluntarily agree for the participation as a subject of study. By signing this consent form I am not giving up any of my legal rights, I may withdraw from the study anytime. I am signing the consent form after having read or been read form in my own vernacular language, including the risks and the benefits and having all my questions answered.

Subject Name : _____

Signature or the Left Thumb Print of Subject :_____

Date: _____

Place : _____

Witness Name : _____Signature: _____

Investigators Name: _____Signature: _____

Date:

Place : _____

ANNEXURE - III – PROFORMA

"COMPARISON OF PREINCISIONAL PORT SITE INFILTRATION OF 0.5% LEVOBUPIVACAINE V/S 0.5% ROPIVACAINE FOR POST OPERATIVE PAIN RELIEF IN PATIENTS UNDERGOING LAPAROSCOPIC APPENDICECTOMY" A ONE YEAR HOSPITAL BASED DOUBLE BLIND RANDOMISED CONTROLLED TRIAL.

Patient Name:

IP No.:

Age:

Gender:

Occupation:

Education:

Address:

Date of operation:

Anaesthesiologist: : _____ Surgeon: _____

Preanesthetic Evaluation:

Chief Complaints:

History of presenting illness:

Past History:

Family history:

Personal history: Diet:

Appetite:

Sleep:

Bowel& bladder:

Habits:

General physical examination

Pallor / Icterus / Clubbing / Cyanosis / Lymphadenopathy / Edema

Height: Weight:

Vitals:

PR : BP :

RR : Temp :

Airway Assessment:

Mouth opening: Teeth :

Jaw movements : MP Grading:

Trachea:

Systemic Examination:

Respiratory System : CardioVascularSystem :

Per abdomen : Central nervous system:

Investigations

Hb% : Total Leukocyte Count :

Differential Leukocyte Count :N: L: E: M: B:

Platelet Count:

RBS:

Blood urea :

Serum creatinine:

ECG : Chest X-Ray:

Preoperative physical status: ASA Grade I, II, III, IV, V

Diagnosis:

Proposed Surgery:

Patient explained about the VAS scoring of pain in the pre operative period.

Selection criteria:

Inclusion criteria:

1) ASA grade I and II.

2) Age between 18 to 60 years.

3) Patients undergoing laparoscopic appendicectomy under General Anaesthesia.

Exclusion criteria:

1) Patients not willing to give consent

2) Patients with known allergic reactions to local anaesthetics.

3) Patients in whom time from port site infiltration to endotracheal extubation is more than 2 hours.

Methodology

After obtaining approval from ethical committee and written informed consent from patients satisfying inclusion and exclusion criteria, 60 adult patients undergoing elective laparoscopic appendicectomy will be included in the study.

A thorough Pre-Anaesthetic Evaluation will be done. Investigations such as Complete blood count, Random Blood Sugar, Blood Urea, Serum Creatinine will be advised. Chest-radiography and Electrocardiography will be advised, if the patient is aged more than 40 years . Patients will be advised for overnight fasting and procedure will be explained.

Patients will be divided into 2 groups by computer generated randomisation table. Group 1 patients will receive 14ml of 0.5% Levobupivacaine preincisional port site infiltration and Group 2 patients will receive 14ml of 0.5% Ropivacaine preincisional port site infiltration.

On the day of surgery base line vitals will be recorded, under sterile aseptic precaution 18 or 20 gauge IV cannula will be secured. Patient will be shifted into the OT and standard monitors like pulseoxymeter, NIBP, ECG, will be connected.

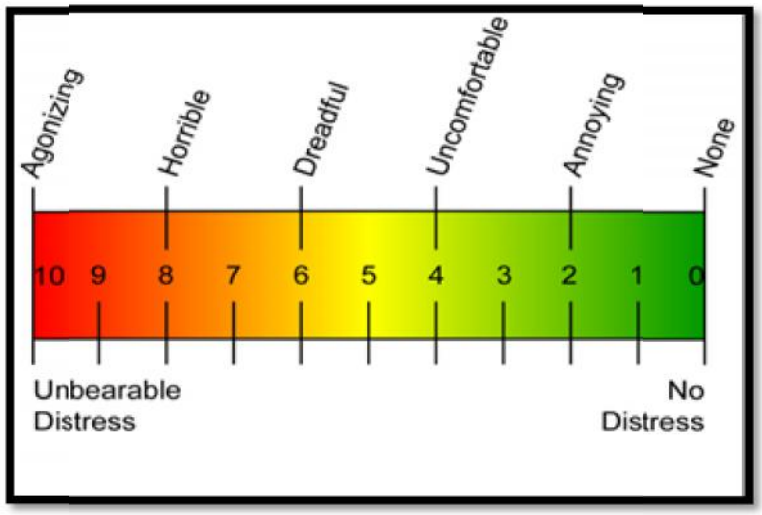
Following preoxygenation, patient will be premedicated with Inj.glycopyrrolate 0.005mg/kg iv, Inj.midazolam 0.05mg/kg iv and Inj Pentazocine 0.5mg/kg. Induction of anaesthesia will be done with Inj.thiopentone sodium 5mg/kg iv sufficient to obtund the eye-lash reflex, followed by Inj.vecuronium 0.1 mg/kg iv. Patient will be manually ventilated for five minutes with 100% oxygen. The endotracheal tube will be lubricated with 2% lignocaine jelly. Tracheal intubation will be performed by an experienced anaesthesiologist with an appropriate sized endotracheal tube. Immediately after intubation, cuff of the endotracheal tube will be filled with a volume of room air required to prevent a palpable air leak. Anaesthesia will be maintained with 0.5MAC Halothane+ Vecuronium and supplemented with oxygen 33% in nitrous oxide. Intracuff pressure will be maintained throughout the procedure to prevent palpable air leak.

Patient will be painted with povidone iodine and surgical spirit sequencially, parts draped.Study drug will be prepared in identical 20ml syringes by an anaesthesia resident containing 14ml of the study drug. An anaesthesiologist who is blinded to the study drug will infiltrate the drug at the port site before the ports are inserted, 6ml at the umbilical port and 4 mL at each working port under sterile aseptic precautions.

Laparoscopic appendicectomy will be done according to standard protocol,by a well trained surgical team. Intra op vitals will be recorded.

Residual neuromuscular relaxation with vecuronium will be antagonized with Inj. Neostigmine iv (0.05mg/kg body weight) and Inj. Glycopyrrolate iv (0.01mg/kg body weight) on completion of surgery.

In the post operative period anaesthesia resident blinded to the drug used will asses for post operative pain at 0, 1,2,3,4,5,6,10,14,18,24 hours using VAS pain scale.



If VAS>3 rescue analgesia in the form of Inj Tramadol 2mg/kg will be given. Total Opioid consumption at the end of 24hrs will be noted. Adverse effects if any of local anaesthetics as well opioids will be noted.

Intra operative vitals

TIME	**HEART RATE**	**BLOOD PRESSURE**	**RESP RATE**	**SpO_2**	**$EtCO_2$**

Patient will be shifted to PACU and monitoring of the patient done.

Asessment of post operative pain will be done using VAS scoring by anaesthesia resident at 0,1,2,3,4,5,6,10,14,18,24 hours post op, who will be sensitized about VAS and will be blinded about the group to which the patient belongs.

POST OPERATIVE TIME	**VAS SCORE**
0th hour	
1st hour	
2nd hour	
3rd hour	
4th hour	
5th hour	
6th hour	
10th hour	
14th hour	
18th hour	
24th hour	

Post Operative Analgesia :

- Time for first rescue analgesia in minutes. :
- Total analgesic consumption in 24 hrs Inj Tramadol iv in mg:

Adverse effects (if any**)**:

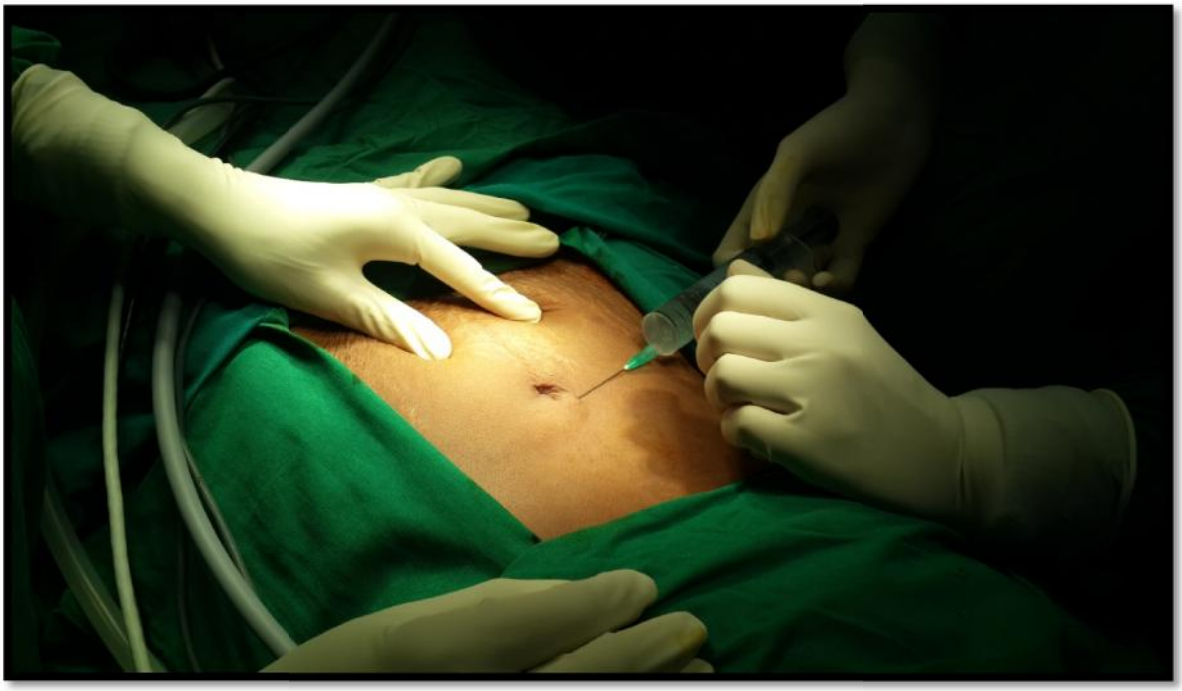
ANNEXURE III – PHOTOGRAPHS

DRUGS USED FOR PORT SITE INFILTRATION

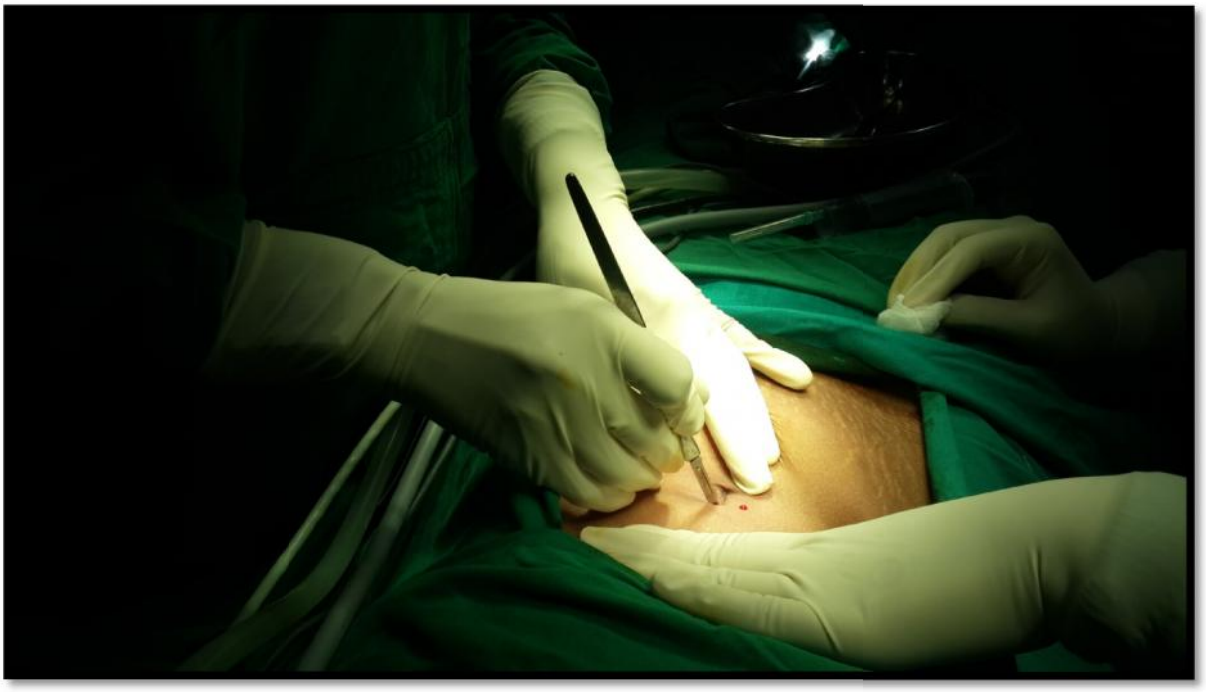
PHOTOGRAPH 1 –- showing 0.5% Levobupivacaine

PHOTOGRAPH 2 –- showing 0.5% Ropivacaine

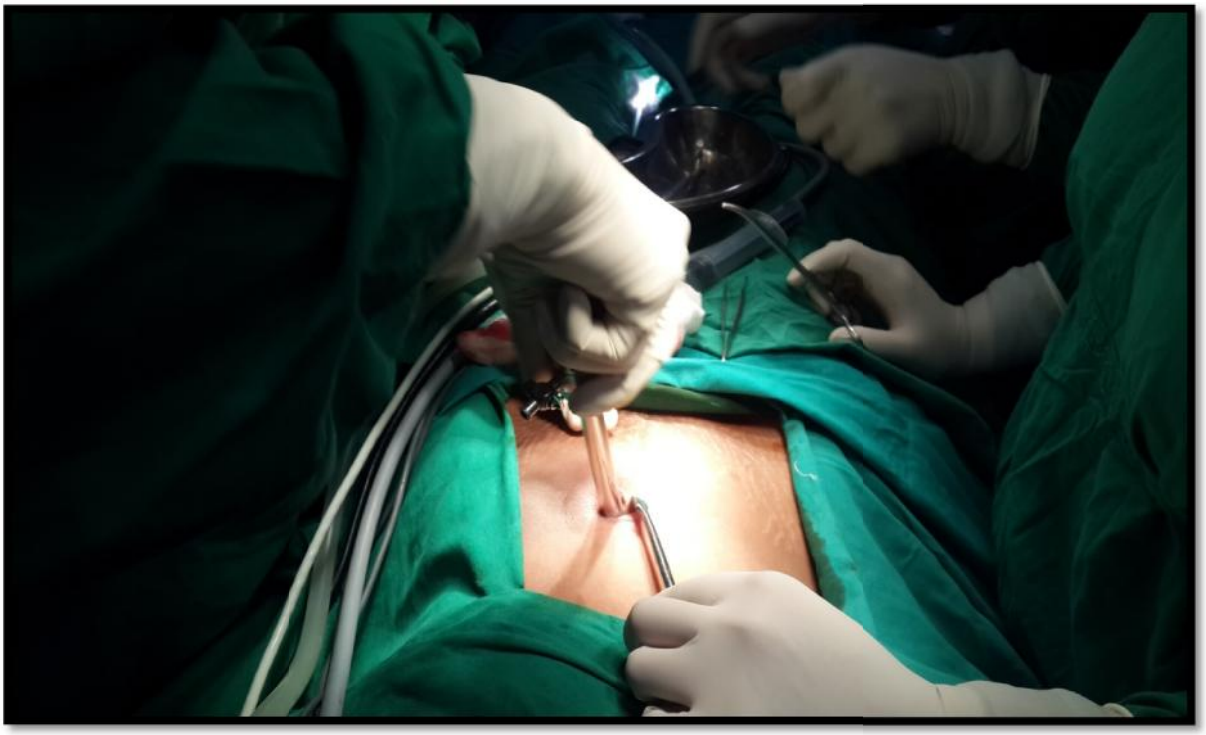
PHOTOGRAPH 3 –- showing 20 ml syringe loaded with the study drug



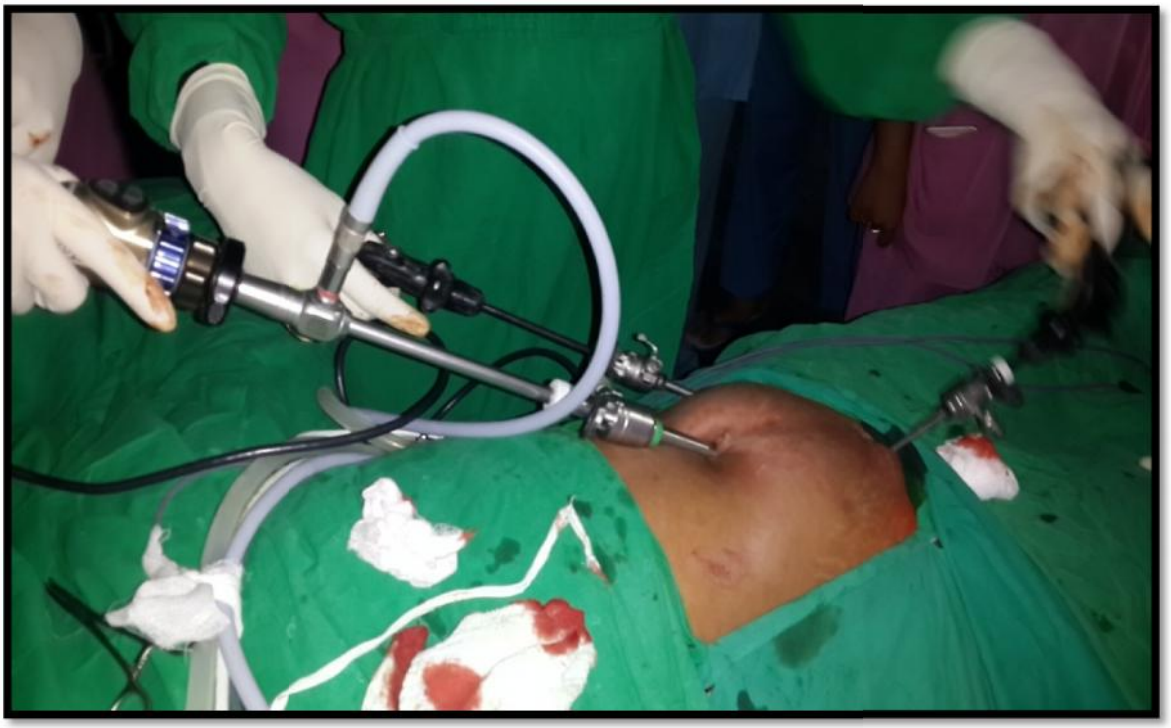
PHOTOGRAPH 4 –- showing preincisional umbilical port site infiltration with the study drug



PHOTOGRAPH 5 -- showing umbilical port site incision



PHOTOGRAPH 6 -- showing umbilical port trocar insertion



PHOTOGRAPH 7 -- showing all the ports

ANNEXURE IV – MASTER CHART

ASA	-	American Society of Anaesthesiologist
BPM	-	Breaths per minute
Cm	-	Centimeter
DBP	-	Diastolic Blood Pressure
EtCO2	-	End tidal carbon dioxide
F	-	Female
Kgs	-	Kilograms
L	-	Levobupivacaine
M	-	Male
MAP	-	Mean Arterial Pressure
R	-	Ropivacaine
SBP	-	Systolic Blood Pressure
SPO_2	-	Saturation percentage of oxygen
VAS	-	Visual analogue scale