"A PROSPECTIVE STUDY OF PRE-EMPTIVE ANALGESIA WITH LORNOXICAM IN LAPAROSCOPIC APPENDICECTOMY UNDER GENERAL ANESTHESIA- A RANDOMIZED CONTROLLED TRIAL"

By

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ENDORSEMENT

This is to certify that the dissertation entitled **"A PROSPECTIVE STUDY OF PRE-EMPTIVE ANALGESIA WITH LORNOXICAM IN LAPAROSCOPIC APPENDICECTOMY UNDER GENERAL ANESTHESIA- A RANDOMIZED CONTROLLED TRIAL"** is a bonafide research work done by **REG NO. BH0110008.**

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LIST OF ABBREVIATIONS USED

Cms	- Centimeters
DVT	- Deep Vein Thrombosis
COX-2	- Cyclooxygenase 2
NSAID's	- Non Steroidal Anti-Inflammatory Drugs
U.S	- United States of America
CO_2	- Carbon Dioxide
GIT	- Gastro-intestinal Tract
NO- cGMP	- Nitrous Oxide- cyclic Guanine Monophosphate
IL- 6	- Interleukin 6
VAS	- Visual Analogue Scale
I.V.	- Intra- Venous
PONV	- Post operative Nausea and Vomiting

ABSTRACT

Background and objectives

The post- operative period is an important part of the surgical experience and affects the recovery. Patients experience moderate to severe pain post-operatively. The most commonly used agents for the control of postoperative pain are parenteral NSAID's and opioid analgesics. . The concept of pre-emptive analgesia suggests that the best post-operative pain management begins pre-operatively. Laparoscopic appendicectomy is a standard procedure that is routinely being performed for appendicitis. However most patients undergoing laparoscopic appendicectomy complain of pain at the port site preventing ambulation and delaying recovery. Lornoxicam is a newer NSAID belonging to the oxicam class. It has a strong analgesic and anti-inflammatory activity. The present study was conducted to study the pre-emptive analgesic efficacy of Lornoxicam in patients undergoing laparoscopic appendicectomy

Methodology

The present study was conducted in the Department of General Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum between January 2011 to December 2011. A total of 66 patients undergoing laparoscopic appendicectomy were included in the study. These patients were randomized into two groups based on computer generated blocked random numbers into Group A (Pre-emptive) and Group B (Placebo). .

Results

In the present study, comparison of the pain scores at 3 hours post-operatively between the pre-emptive group (Group A) and placebo group (Group B) did not show any statistically significant reduction in the pain. p=0.5261. However there was statistically significant difference in the analgesic requirements between the two groups. The analgesic requirement for patients in Group B (39.39%) was significantly higher as compared to patients in Group A (6.06%). $p < 0.001$. Assessment at post-operative 6 hours shows there was no statistically significant difference in the pain scores between Group A and Group B. p= 0.586 and also the analgesic requirement between the two groups were comparable. p= 0.056

At post-operative 10 hours there was no statistically significant difference in the pain scores between Group A and Group B. p= 0.555 Further there was no statistically significant reduction in the analgesic requirement between the patients in Group A and Group B at Post-operative 10 Hours. p= 0.573 Similarly, there was no statistically significant difference in the pain scores between Group A and Group B at post-operative 24 hours, p= 0.641; however, the analgesic requirement in Group A at 24 hours post-operatively was significantly lower than the analgesic requirement by patients in Group B. p< 0.001

Conclusion and interpretation

The present study concludes that pre-emptive administration of Lornoxicam in patients undergoing laparoscopic appendicectomy is associated with better pain management and patient satisfaction. The intensity of pain and thereby the total dosage of analgesic consumption in the post-operative period is significantly lesser in the Lornoxicam group as compared to the placebo group.

Keywords

Post-operative pain, Post Laparoscopic appendicectomy pain, Pre-emptive analgesia, Lornoxicam.

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Chapter 1

Introduction

INTRODUCTION

Pain is one of the most common symptoms that brings the patient to the doctor. A significant number of patients suffer from severe post-operative. This is in-spite of great advances in the field of pain management including advances in techniques and analgesic agents.[1]

Post-operative pain causes considerable distress to the patient. It prolongs the recovery time and adversely affects the patient outcome.[2]

A recent survey shows that most adults still expect to have significant post-operative pain after surgery and that this is their primary concern before surgery. This fear may be justified because the traditional modalities of post-operative pain management using intra-muscular administration of NSAID's and opioids given on demand often fails to provide adequate analgesia.[3] The adequate control of post-operative pain is very important because it has been proved as one of the most important factors affecting recovery and outcome.[2]

Pre-emptive analgesia involves the introduction of an analgesic regimen before the onset of the noxious stimulus. This has been postulated to prevent the sensitization of the nervous system to subsequent stimulus that could amplify pain. Although some studies have failed to demonstrate the efficacy of pre-emptive analgesia in humans, other studies have reported a significant reduction in post-operative analgesic requirement in patients receiving pre-emptive analgesia.[1]

Lornoxicam is a newer NSAID belonging to the oxicam class. It has analgesic, anti-inflammatory and anti-pyrogenic properties. It has a very short elimination half-life of 3- 5 hours & hence is better tolerated than other NSAID's. Clinical trials suggest that Lornoxicam is as effective as the opioid analgesic morphine, pethidine and tramadol in relieving post-operative pain in orthopedic and gynecological surgery.[4]

Laparoscopic appendicectomy is a standard procedure that is routinely being performed for appendicitis. However most patients undergoing laparoscopic appendicectomy complain of pain at the port site preventing ambulation and thus delaying recovery.

There are no studies regarding the use of lornoxicam as a pre-emptive analgesic agent in laparoscopic appendicectomy. Hence the present study has been undertaken to assess the pre-emptive analgesic effect of lornoxicam in reducing the intensity of pain and requirement for analgesics in the post-operative period in patients undergoing laparoscopic appendicectomy under general anesthesia.

Chapter 2

Objectives

OBJECTIVES

Objectives of the present study was to determine-

Effect of pre-emptive administration of Lornoxicam on post-operative pain and thus on the post-operative analgesic requirement in patients undergoing laparoscopic appendicectomy.

Chapter 3

Review of Literature

REVIEW OF LITERATURE

Pain is defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage".[5] Pain is a subjective experience and is hence is rather difficult to describe. There are two features that are universal to pain:

1. It is an unpleasant experience.

2. It is evoked by a stimulus which is potentially damaging to living tissues.

Like all sensory responses, pain too has two components:

1. Awareness of a painful stimulus

2. And emotional impact evoked by the experience.

The awareness to pain is localized to the area stimulated, whereas the emotional experience involves the whole being.[6]

The post- operative period is an important part of the surgical experience and affects the recovery. Many advances have been made in the field of pain management with the advent of newer analgesic agents and techniques. However patients continue to experience moderate to severe pain post- operatively.

The reasons for the poor control of post-operative pain are:

1. The responsibility of pain management is given to the nursing staff who, usually err on the side of caution in administration of analgesics.

2. Because the measurement of pain is difficult, it is very difficult to adjust the dosage and frequency of administration of analgesic to match the extent of the pain.[7]

Post- operative pain is one of the most common types of acute pain. There are also a lot of variations in the extent of analgesic requirement depending on the type of surgery, pharmacokinetic variability, etc.[8] It differs from other types of pain in that it is usually transitory with progressive improvement over a relatively short time course. In a study conducted by Pakize Kirdemir and Anil Marsan on patients undergoing laparoscopic cholecystectomy, 59% of the subjects were concerned about the post-operative pain.[2] The provision of adequate analgesia post-operatively is not only important from a humanitarian perspective but it also has been shown to improve postoperative recovery and outcome. The most commonly used agents for the control of postoperative pain are parenteral NSAID's and opioid analgesics. However, almost 25% of these patients experience side effects secondary to the use of opioid's and NSAID's.[5]

Despite an increased focus on pain management and the development of new standards for pain management, many patients continue to have intense pain after surgery.[9] In addition to immediate unpleasantness, painful experiences can imprint themselves on the nervous system, amplifying the response to subsequent noxious stimuli (hyperalgesia) and causing typically painless sensations to be experienced as painful (allodynia). This results in the development of a chronic condition that produces continuous pain long after surgery. Prior painful experiences have been identified as predictors of increased pain and analgesic use in subsequent surgery.[9]

Surgery produces tissue injury resulting in release of histamine and inflammatory mediators such as peptides e.g. bradykinin, lipids e.g. prostaglandin, neurotransmitters e.g. serotonin and neurotrophins e.g. nerve growth factor. These inflammatory mediators result in activation of peripheral nociceptors. The activated peripheral nociceptors then initiate the transduction and transmission of the nociceptive information. The transmission of this information to the central nervous system results in the initiation of neurogenic inflammation. It results in release of neurotransmitters such as substance P and calcitonin gene related peptide in the periphery, both of which are responsible for vasodilatation and plasma extravasation.

Noxious stimulus are transduced by the peripheral nociceptors and transmitted by Aδ and C nerve fibres. These stimuli are transduced from the peripheral viscera and somatic sites to the dorsal horn of the spinal cord. The integration of peripheral nociceptive inputs and descending modulatory input i.e. serotonin, noradrenaline and encephalin occurs in the dorsal horn of the spinal cord. Further transmission of nociceptive information is determined by complex modulating influences in the spinal cord. Some impulses pass to the anterior and anterolateral horns to initiate segmental i.e. spinal reflex responses. The spinal reflex responses account for increased skeletal muscle tone, inhibition of phrenic nerve function and decreased gastro-intestinal motility. Spinothalamic tract and spinoreticular tracts transmit the other signals to the higher centers where they produce supra-segmental and cortical responses to ultimately produce the sensation of pain.[10]

The central pain pathway includes spinothalamic, spinoreticular and spinomesencephalic tracts. The spinothalamic tract is the most important among the sensory pathway for the conduction of somatic pain and thermal sensation from the body. It also contributes to tactile sensation. The spinothalamic tract originates from the second order neurons located in the spinal cord (primarily laminae 1 & IV to VI). The axons of these cells cross to the opposite side of the cord at or near their level of origin. The fibres then ascend to the brain in the ventral part of the lateral funiculus and subsequently through the brain stem to the thalamus. The spinothalamic tract terminates on the 3rd order neurons, i.e. the spinothalamic cells conveying pain and temperature. The fibres of the spinothalamic tract target the VP1 portion of the ventral posterior complex, the posterior nucleus and the intra-laminar nuclei of the thalamus. Nocicepetive signals are then forwarded to both the somatosensory cortex and cortical areas.

Continuous release of inflammatory mediators in the periphery sensitizes the functional nociceptors and relative dominant ones. Sensitization of peripheral nociceptors results in decreased threshold for activation, increased discharge rate with activation, and increased rate of basal (spontaneous) discharge after a noxious stimulus. Intense noxious input from the periphery results in central sensitization and hyper-excitability. Such noxious input may lead to functional changes in the dorsal horn of the spinal cord. All these factors contribute to cause post-operative pain to be perceived as more painful than it would normally have been. N-methyl-D-aspartate receptor has been identified as the most important receptor for the development of chronic pain after an acute injury. Others e.g.

substance P, protein kinase C- gamma, may also play important role in the sensitization of the spinal cord with resultant development of chronic pain.[10]

Experimental studies show that a noxious stimulus can produce expression of new genes in the dorsal horn of the spinal cord within one hour of the stimulus. Results of studies show that these changes in the dorsal horn are sufficient to alter behavior within the same time frame.[8] Clinical studies also suggest that the intensity of acute post-operative pain is a significant predictor for the development of chronic post-operative pain. The factors which have been identified to play a role in facilitating short and long term patient convalescence after surgery include: control of acute post-operative pain and the timing, duration e.g. pre-emptive analgesia and the fashion in which it is implemented e.g. multi-modal perioperative management.[10] Reduction of nociceptive input into the CNS in the peri-operative period and optimization of analgesia may decrease complications and facilitate faster patient recovery during the immediate post-operative period and after discharge from the hospital. [11]

Evidence suggests that surgery suppresses the immune system and that this suppression is proportionate to the invasiveness of the surgery. Good analgesia can help reduce this deleterious effect.[12]

Adverse Effects of Post-operative Pain[13,14]

Cardiovascular System:

- ✓ Tachycardia, Hypertension.
- ✓ Myocardial Infarction, Arrhythmia

Pulmonary System:

- ✓ Ventilation- Perfusion mismatch
- ✓ Pneumonia
- ✓ Atelectasis
- ✓ Arterial Hypoxemia.

Coagulation System:

- ✓ Increased Platelet adhesiveness→ Hypercoagulability, DVT.

Gastrointestinal System: Ileus.

Genitourinary System: Urinary Retention.

Measurement of Pain:

Patient care is improved by monitoring the severity and duration of pain. Pain is a complex experience involving sensory, emotional, psychological and social factors. The subjective nature of pain explains the difficulty with its measurement. Pain could be measured using single dimensional or multi-dimensional assessment tools.[15]

The most commonly used pain evaluation tools are single dimensional and includes: Verbal description scale, Visual analogue scale, Numerical rating scale and Pain relief scale. [16]

Verbal Description Scale: This a simple five-point scale, wherein words are used to assess the degree of pain.

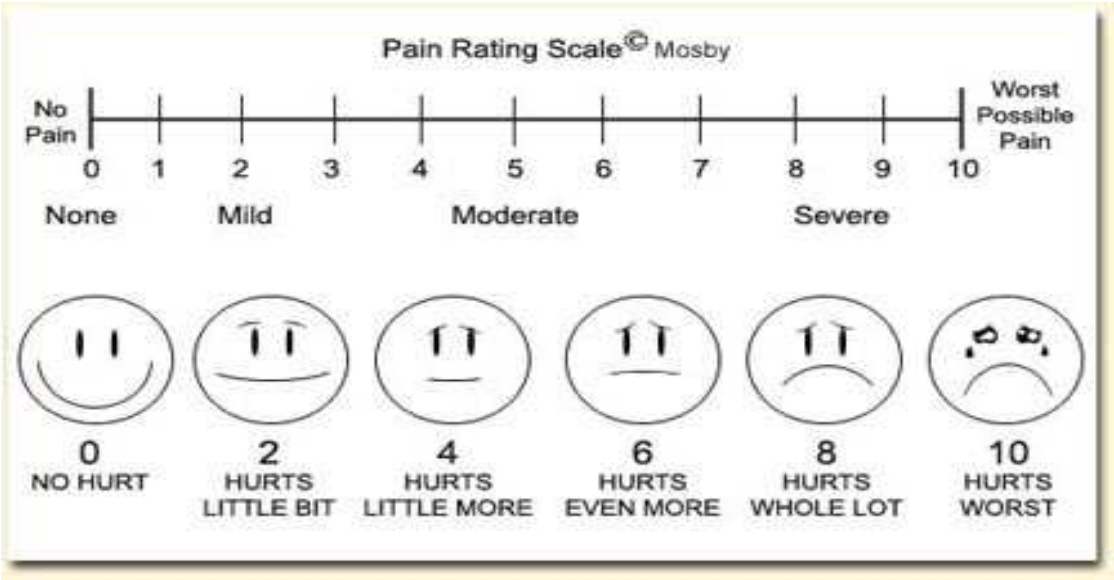
No pain	Mild	Moderate	Severe	Excruciating

Visual Analogue Scale: In this method of assessment, on a 10 cm line the patient is asked to mark a vertical mark to signify the intensity of their pain.

No Pain _____ Severe Pain

The distance from the left end of the line towards the side of severe pain is measured and is used as a measure of the severity of the pain. The distance measured is used to score a visual analogue. These readings are used to compare the changes in the pain level.

Pain Faces Scale:



Numerical: In the visual analogue scale, numbers are assigned at regular intervals and the patient is required to choose a number between 0 and 10 to represent their pain. Zero indicates patient has no pain and 10 refers to maximum pain.

0	1	2	3	4	5	6	7	8	9	10

Multi-dimensional methods:

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

Assessment of post-operative pain should be made at regular intervals. The analgesic agent administration should be guided as per the need which can be assessed by the assessment on the scale.

Management of Post-Operative Pain:

The choice of analgesic techniques for post-operative pain management depends on: the site of surgery, availability of the drug and familiarity with different methods of analgesia. For example, although patient-controlled analgesia (PCA) has often been shown to be better than the intermittent delivery of intramuscular opioids, the pain relief with epidural analgesic administration has been proved to be superior. Similarly a local anesthetic block can effectively relieve pain only for the duration of the particular agent used.

The various modalities available for management of post-operative pain include-

Pharmacological Agents:

Opioids: It is a commonly used medication for postoperative pain (usually morphine).[17] Opioids act as agonists on central and peripheral opioid receptors. They provide very effective analgesia, however they are associated with an array of side-effects.

Side effects: Sedation,

Respiratory depression,

Nausea and vomiting,

Hypotension and Bradycardia,

Pruritus,

Ileus.

For the treatment of these complications antihistamines are used, which further increases sedation and respiratory depression.

Non-steroidal anti-inflammatory drugs:

These agents are used widely to treat pain and inflammation. They act by inhibiting the enzyme cyclooxygenase (COX), which is responsible for the synthesis of prostaglandins. Prostaglandins are responsible for pain, fever, and vasodilatation in response to trauma.

NSAID's do not carry the same side effects of the opiates; hence although they are less potent than the narcotics, they are used as opiate-sparing agents.

Side effects: Peptic ulcer disease,

Gastrointestinal hemorrhage,

Renal dysfunction,

Altered liver function and platelet dysfunction.

<u>Regional techniques</u>

Neuraxial anesthesia

- Spinal Anesthesia
- Epidural Aesthesia

Regional/ Local Anesthesia

Intravenous Regional Anesthesia

Epidural and spinal analgesia improve surgical outcomes by decreasing intraoperative blood loss, postoperative catabolism, and the incidence of thromboembolic events. They also help in improving vascular graft blood flow and postoperative pulmonary function. Epidural and spinal analgesia provide better analgesia than systemic opioids.

Complications: Risk of Spinal hematoma.

Non-pharmacologic techniques:

Electrical stimulation of peripheral nerves may influence pain inhibitory pathways, inhibit substance-P release, and enhance the release of endogenous opiate substances. However the efficacy of these modalities in reducing the requirement for conventional pain medications is still controversial.

Pre- Emptive analgesia

Pre-emptive analgesia has been defined as "administration of an analgesic agent before surgical incision, which prevents establishment of central sensitization resulting from incision injury only i.e. intra-operative period, or which prevents central sensitization resulting from incisional and inflammatory injuries i.e. intra-operative and post-operative period.[10]The importance of peripheral and central sensitization in amplifying pain perception has directed research towards preventing these processes and fortified the concept of "pre-emptive analgesia" in patients undergoing surgery. Experimentally, it has been shown that functional changes in the spinal cord occur secondary to nociceptive stimulation from the periphery which leads to enhancement and prolongation of

the sensation of pain. It has also shown that prior administration of analgesics may inhibit the development of hyper-excitability within the spinal cord.[18]

The concept of pre-emptive analgesia suggests that the best post-operative pain management begins pre-operatively. Some studies suggest that this anesthetic technique can also reduce the neuroendocrine stress response to surgery and pain. This type of management induces an effective analgesic state prior to the surgical trauma.[1]

Owing to the protective effect on the nociceptive system, pre-emptive analgesia has the potential to be more effective than a similar analgesic treatment initiated after surgery.[8]

Studies have proved that an adequate level of general anesthesia with a volatile drug such as isoflurane does not prevent central sensitization. Thus the potential for central sensitization exists even in an unconscious patient who appears to be clinically unresponsive to a surgical stimulus.[8] Injection of an opioid such as fentanyl before painful surgical stimulation occurs may decrease the subsequent amount of opioid requirement in the post-operative period to provide analgesia. [19]

Pre-emptive analgesia has been studied using a variety of agents and techniques. The combination of positive clinical trials and experimental data suggests that pre-emptive analgesia is a clinically relevant phenomenon.[10]The various methods used are infiltration of the wound with local anesthetic agents, central neural blockade or the administration of effective doses of opioids, NSAIDS or ketamine. Experimental evidence suggests that pre-emptive analgesia

can effectively attenuate peripheral and central sensitization to pain.[1] Unfortunately in clinical practice, prior administration of analgesics (pre-emptive analgesia) has not consistently been shown to have an important effect on post-operative pain.[10] Although some studies have failed to demonstrate pre-emptive analgesia in humans, other studies have reported significant reduction in post-operative analgesic requirements in patients receiving pre-emptive analgesia.[1]

Surgery offers the most promising setting for preemptive analgesia because the timing of noxious stimuli is known. When adequate drug doses are administered to appropriately selected patients before surgery, intravenous opiates, local anesthetic infiltration, nerve block, subarachnoid block and epidural block offer benefits that can be observed as long as one year after surgery.[20] The most effective preemptive analgesic regimens are those that are capable of limiting sensitization of the nervous system throughout the entire perioperative period.

Appendicitis and Laparoscopic Appendicectomy:

Appendicectomy for appendicitis is the most commonly performed emergency operation in the world.[21]The incidence of acute appendicitis in the US is approximated to be around 11 cases per 10,000 population annually. The life time risk of acute appendicitis is about 8.6% in males and 6.7% in females.[22] The first documented appendicectomy was performed in 1736 by Amyand, when he operated on a boy with an entero-cutaneous fistula within an inguinal hernia. The hernial sac was seen to contain a perforated appendix. Laparoscopic appendicectomy was first reported by the gynecologist Kurt Semm in 1982 but

has only gained widespread acceptance in recent years. Laparoscopic appendicectomy offers the advantage of diagnostic laparoscopy combined with the potential for shorter recovery and incisions that are less conspicuous.[23]

Advantages of laparoscopic appendicectomy over open appendectomy include:

- smaller wounds,
- lesser risk of wound infection since the appendix is removed without contaminating the surgical incision,
- better pain management and hence faster recovery to normal.[24]

Pain that is related to laparoscopic surgery is of variable duration, character and severity. Patients tend to be discharged earlier after laparoscopic surgeries and results in failure of diagnosis and treatment of post-operative pain which arises after the first few hours after the surgery.[16]

Pain in laparoscopic surgery:

It presents as parietal pain in the insertion sites, visceral pain from the intra-abdominal wound and the irritated peritoneum, and pain referred to the shoulder tip.

Mechanism of pain in laparoscopy

Rapid distension of the peritoneum without adequate relaxation results in tearing of blood vessels, traumatic traction of the nerves and release of inflammatory mediators. Therefore, abdominal distention should be slow with adequate muscle relaxation to ensure suitable abdominal compliance.[17]

a. Factors associated with gaseous pneumoperitoneum

1. Neuropraxia of the phrenic nerve

Stretching of the phrenic nerve secondary to distention of the diaphragm during gas insufflation with the resultant neuropraxia possibly contributes to postoperative pain. This pain is characteristically seen to involve the C4 dermatome.[25]

2. Residual intra-abdominal gas

Carbon dioxide left in the peritoneal cavity after laparoscopy gets dissolved resulting in intra-abdominal acidosis. Intra- abdominal acidosis later on causes peritoneal irritation which persists for a long period.[26]

3. The type of insufflated gas and intra-abdominal pH

The phrenic nerves may be damaged by the acid milieu created by the dissolution of CO2. Cases where argon has been used as a substitute, similar results were obtained.[27]

4. Temperature of gas

Studies have demonstrated that there is significant reduction in post laparoscopy pain when warmed gas is used, especially with respect to diaphragmatic and shoulder tip pain.[28]

5. Humidity of gas

Experimental data has shown that use of humidified gas results in significantly reduced postoperative pain. There is evidence to suggest that use of

humidified gas is associated with lesser post- operative analgesic consumption, along with shorter hospital stay and earlier return to work.[29]

b. Operational factors

1. Wound pain

Post- laparoscopy pain is significant at the port site and is one of the major limiting factors preventing early mobilization and thus delaying recovery.

2. Wound drainage

Drains placed after laparoscopic surgery are usually situated in the region of the lateral port sites, traversing muscle layers. There is an increased incidence of pain, infection, and potential incisional herniation at umblical port site and hence it is rarely used for placing drains.

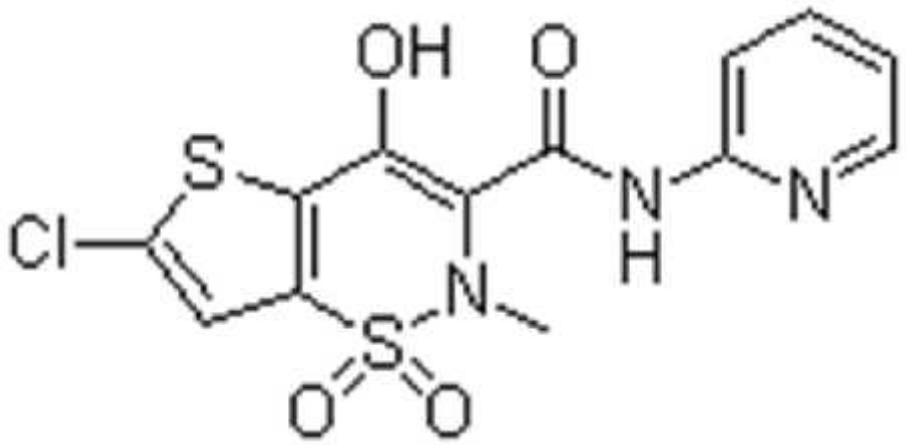
c. Socio-cultural and individual factors

The socio-cultural environment affects hospital stay and recovery time. [30]

Lornoxicam:

Lornoxicam is a newer NSAID belonging to the oxicam class. It has a strong analgesic and anti-inflammatory activity. Its analgesic activity is comparable to that of opioids. It has a short half life and has a better gastro-intestinal toxicity profile. It has an elimination half-life of 3 to 5 hours. Lornoxicam has been established as a potent analgesic with excellent anti-inflammatory properties in a variety of inflammatory and painful conditions.[4]

Chemistry:The active drug substance is 6-chloro-4-hydroxy-2-methyl-N-2H-thieno-(2,3-e)-1,2-thiazine-3-carboxamide-1,1-diaoxide. It has relatively low lipophilicity because it is highly ionized at physiological pH. Hence lornoxicam has decreased distribution to fattytissues.[4]



Lornoxicam

Figure 1: Chemical Structure of Lornoxicam

Molecular Formula C13H10ClN3O4S2

It is the only oxicam with a 15 times shorter half-life than piroxicam and tenoxicam. In addition, lornoxicam can be given by intra-venous route. Lornoxicam has a better safety profile than diclofenac and naproxen with regards to renal and hepatic function tests. In addition to better GIT tolerability compared to selective COX2 inhibitors; it is completely metabolized to inactive metabolites.[31]

Mechanism of action: Lornoxicam acts on the arachidonic acid pathway by inhibiting both the COX isoforms in the same concentration. It produces the analgesic effect by inhibiting NO-cGMP pathway and opening of potassium

channels. It inhibits the spinal nociceptive processing and causes increased levels of β-endorphins and dysnorphin. Experimental evidence has also shown that it inhibits formation of nitric oxide, and has inhibitory activity on the endotoxins induced IL-6 formation.[4]

In the treatment of post-operative pain following orthopedic and gynecological surgery, lornoxicam is as effective as opioid analgesics.[31] It is also as effective as other NSAIDs after oral surgery. It has been proved effective in relieving symptoms of osteoarthritis, ankylosing spondylitis, low back pain and acute sciatica. Lornoxicam provides a better-tolerated alternative or adjuvant to opioid analgesics for the management of moderate to severe pain. It can also be used as an alternative to other NSAIDs for the management of inflammatory and painful conditions such as arthritis.[4]

In a randomized controlled study done by Pakize Kirdemir and Anil Marsan comparing the efficacy of preemptively used lornoxicam and tramadol for postoperative pain in patients undergoing laparoscopic cholecystectomy showed that both improved postoperative analgesia, while statistically significant lower VAS values were seen in the lornoxicam group than the other groups. The study showed that preemptive administration of lornoxicam improved postoperative analgesia, resulting in reduced analgesic consumption with highest patients' satisfaction.[2]

In a study conducted by Arslan and colleagues, use of lornoxicam i.v. in thyroidectomy was associated with decreased opioid need, PONV and postoperative pain. [32]

In a study done by Xuerong and colleagues, comparing the efficacy of lornoxicam and ketamine in post-operative pain management concluded that the use of lornoxicam or ketamine could reduce postoperative morphine requirements induced by intra-operative administration of fentanyl.[33]

When preemptive analgesia was studied by comparing pre-incisional versus post-incisional treatment groups, many authors found no difference in the pain outcome, while some reported statistically significant but clinically modest benefits with pre-incisional analgesia.[34]

Chapter 4

Methodology

METHODOLOGY

The present study was conducted in the Department of General Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum.

Study design

A one year randomized controlled trial.

Study period and duration

The present one year study was conducted during January 2011 to December 2011.

Source of data

Patients with Appendicitis undergoing Elective Laparoscopic Appendicectomy at KLE Dr. Prabhakar Kore Hospital, Belgaum.

Sample size

Total Number of Cases: 66

Group A (Study Group): 33

Group B (Control Group): 33

Inclusion Criteria:- Patients undergoing elective Laparoscopic Appendicectomy.

Exclusion Criteria:-

1. Patients with Diabetis Mellitus, Renal Insufficiency, Bronchial Asthma and Peptic Ulcer Disease.
2. Patients with bleeding disorders.
3. Patients on Warfarin, Digoxin, Furosemide, Sulfonylureas.
4. Pregnancy and Lactation.
5. Patients who required placement of intra-peritoneal drains.

Method of Randomization:-

The qualifying persons were informed of the risks and benefits of the intervention and are then asked to sign a detailed informed consent in their native language.

Computer generated Random number table was used to assign the patient in either the pre-emptive group i.e. the study group or the saline group i.e. control group.

Group A (Study group): Lornoxicam 8 mg/ 2 ml was given i.v. 20 minutes before induction of anesthesia.

Group B (Control group): Normal Saline 2ml was given i.v. 20 minutes before induction of anesthesia.

Blinding:

The patient is unaware about the pre-operative medication being given to him/ her. The pain grading was done by using the Visual Analogue scale. Pain was assessed at 3, 6, 10 and 24 hours post-surgery. The pain grading charts obtained from the patient was received and analyzed by another post-graduate from the Department of General Surgery who was unaware of the protocol followed in each patient.

Protocol:

Each patient enrolled in the study was administered a standard anesthetic protocol. Post-operatively patients of both the groups were given Inj. Diclofenac 1ml. aqueous (75mg/ ml) as the rescue analgesia as and when demanded by the patient.

Procedure of Laparoscopic Appendicectomy:

After induction of General Anesthesia with the patient in supine position entry into the peritoneal cavity is made through the umbilical region. A 10mm cannula is inserted and carbon dioxide is insufflated to achieve pneumo-peritoneum. A 10-mm diameter laparoscope is inserted through the umbilical port. Two 5-mm ports, 1st in the supra-pubic region and the 2nd in the left iliac fossa are inserted under vision. Atraumatic bowel grasping forceps is used to hold the appendix and dissection is done using dissecting forceps. The appendix is raised to the anterior abdominal wall to apply traction. Dissection is carried to the base of the appendix. Window is created in the mesoappendix to skeletonize the

appendicular artery. Appendicular artery is then either ligated or cauterized using bipolar cautery. Next the base of the appendix is ligated and cut. A 5mm camera is then introduced through one of the 5 mm ports. The specimen is placed in an indigenous sterile bag and removed from the umbilical port. Rest of the abdomen is inspected for evidence of any other pathology. Pneumo-peritoneum is deflated slowly and the ports are removed under vision. The umbilical wound is closed with Vicryl Portt suture and the skin is closed with Ethilon sutures.

Statistical Analysis:

Data obtained was tabulated and expressed as rates, ratios and percentages. Comparison was done by applying Mann Whitney U test and Fisher's exact test. A probability value ('p' value) of less than or equal to 0.05 was considered as statistically significant.

Chapter 5

Results

RESULTS

The present one year Randomized Placebo Controlled trial was conducted in the Department of General Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period from January 2011-December 2011.

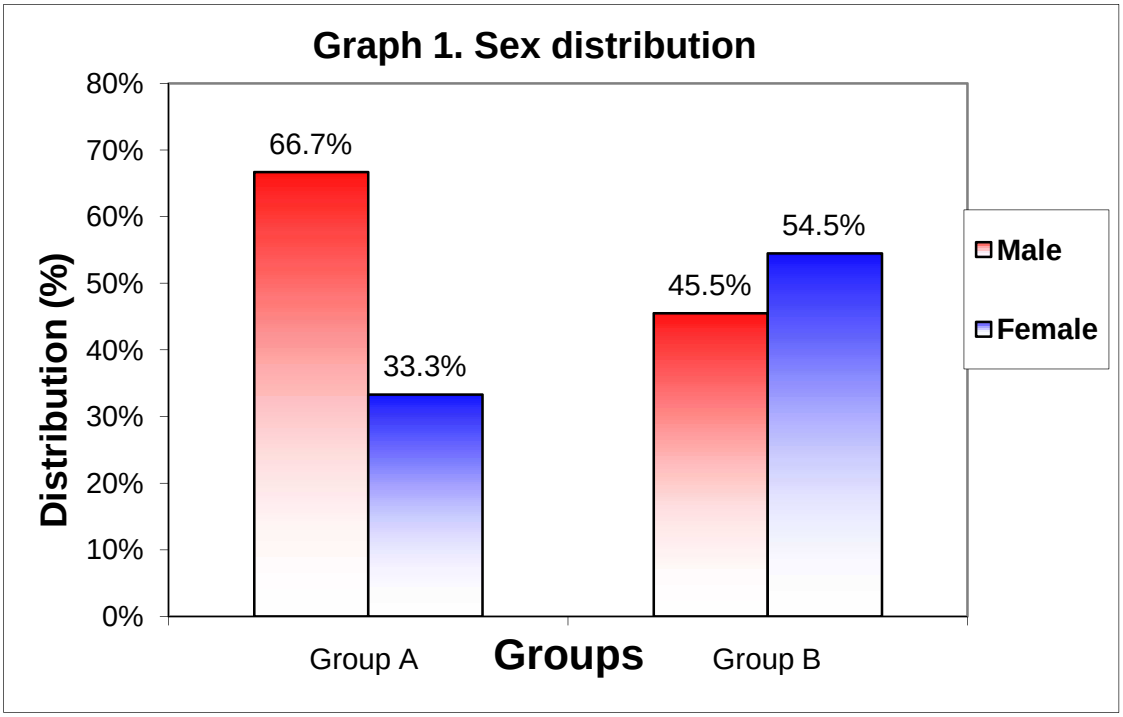
Based on computer generated randomization, patients were allocated into 2 groups

- Group A (n=33) – Patients received Inj. Lornoxicam (8mg/ 2ml) i.v. 20 min. prior to induction of anesthesia.
- Group B (n=33) – Patients received 2 ml. normal saline i.v. 20 min. prior to induction of anesthesia as a placebo agent.

Table 1. Sex distribution

Sex	Group A (n=33)		Group B (n=33)	
	Number	**Percentage**	**Number**	**Percentage**
Male	22	66.7	15	45.5
Female	11	33.3	18	54.5
Total	**33**	**100**	**33**	**100**

p=0.787

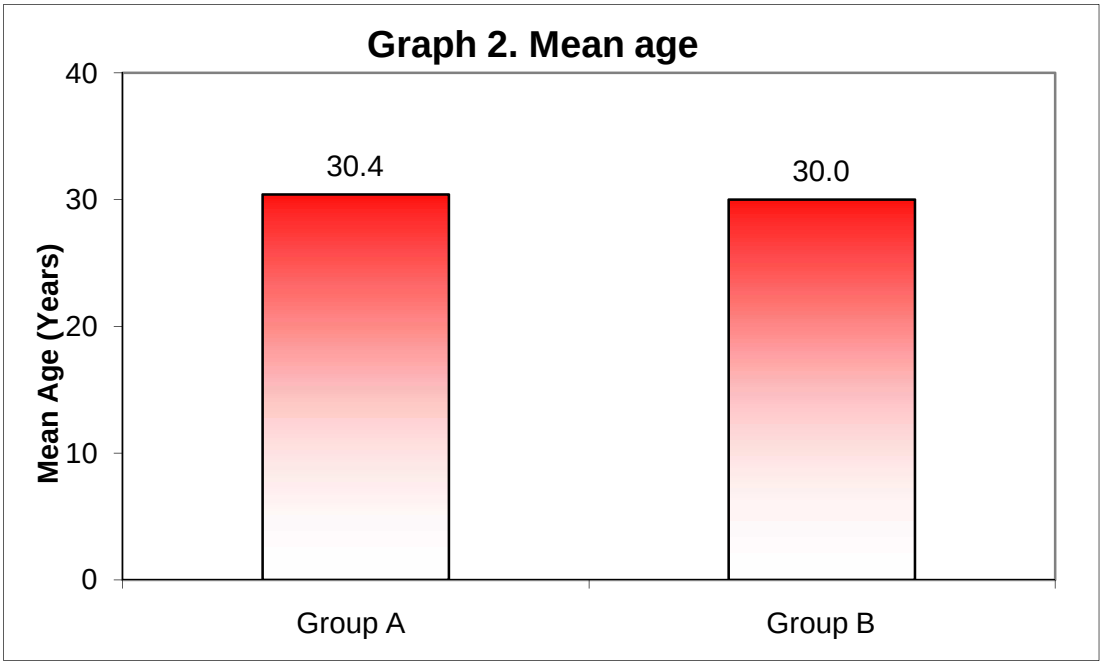


In Group A there were 66.7% males and 33.3% females with a male to female ratio of 2.01:1. In group B there were 45.5% males and 54.5% females with male to female ratio of 0.83:1.

Table 2. Mean Age

	Mean Age	
	Mean	**SD**
Group A	30.39	13.63
Group B	30.12	10.12

p=0.978



The mean age in Group A was 30.4±13.63years and in Group B was 30.12 ± 10.12 years suggesting both groups had similar age.

Table 3: Diagnosis

	Diagnosis			
	Acute Appendicitis	**Recurrent Appendicitis**	**Chronic Appendicitis**	**Perforated Appendicitis**
Group A	**20**	**9**	**4**	**0**
Group B	**16**	**6**	**10**	**1**
Total	**36**	**15**	**14**	**1**

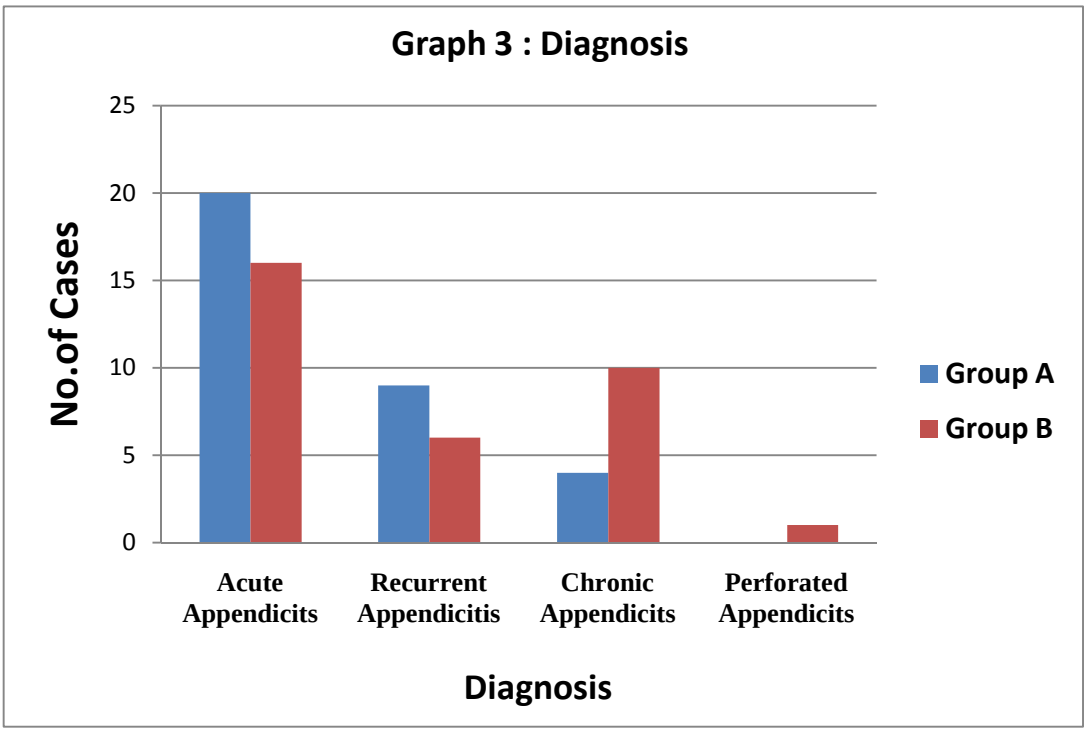


Table 4.Pain Score at Post-Operative 3 hours.

Pain Score	Group A		Group B	
	Number	**Percentage**	**Number**	**Percentage**
0	0	-	0	-
1	0	-	0	-
2	0	-	0	-
3	10	30.30	4	12.12
4	17	51.52	12	36.36
5	4	12.12	10	30.30
6	1	3.03	5	15.16
7	1	3.03	1	3.03
8	0	-	1	3.03
9	0	-	0	-
10	0	-	0	-
Total	**33**	**100**	**33**	**100**

p=0.5261

Comparison between the pain scores at 3 hours does not show ant statistically significant reduction in the pain scores between Group A and group B. p=0.5261.

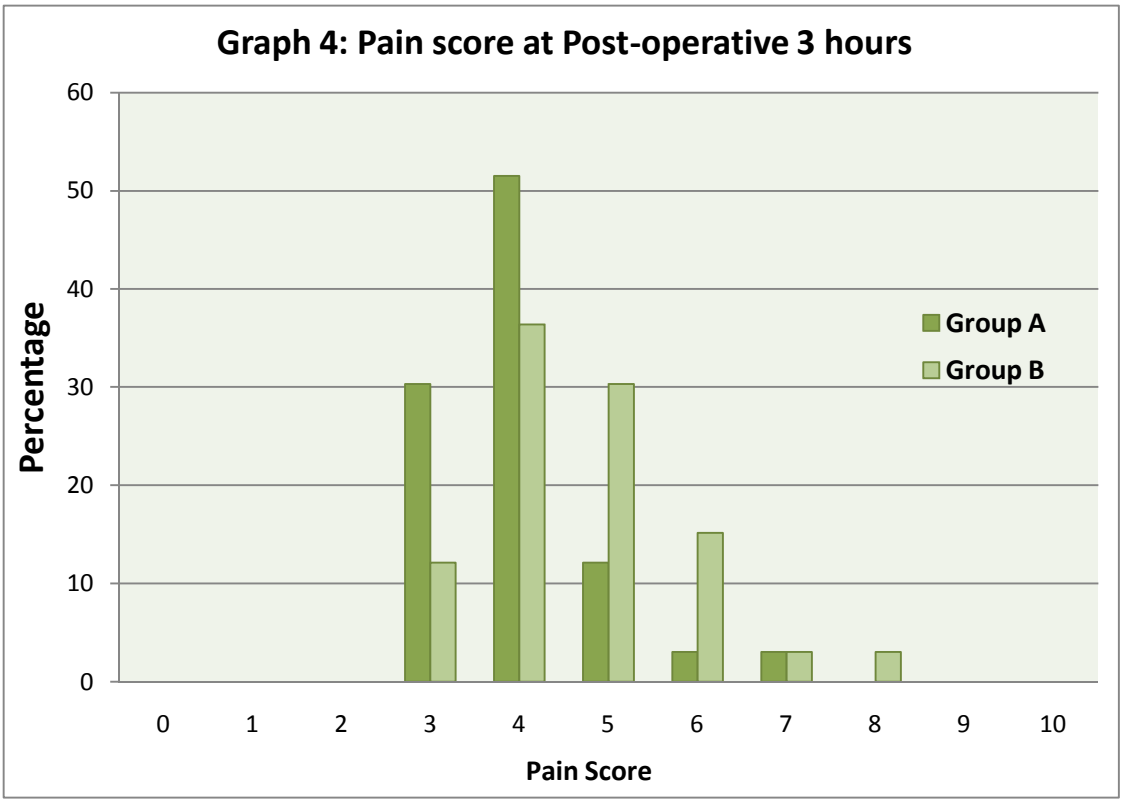
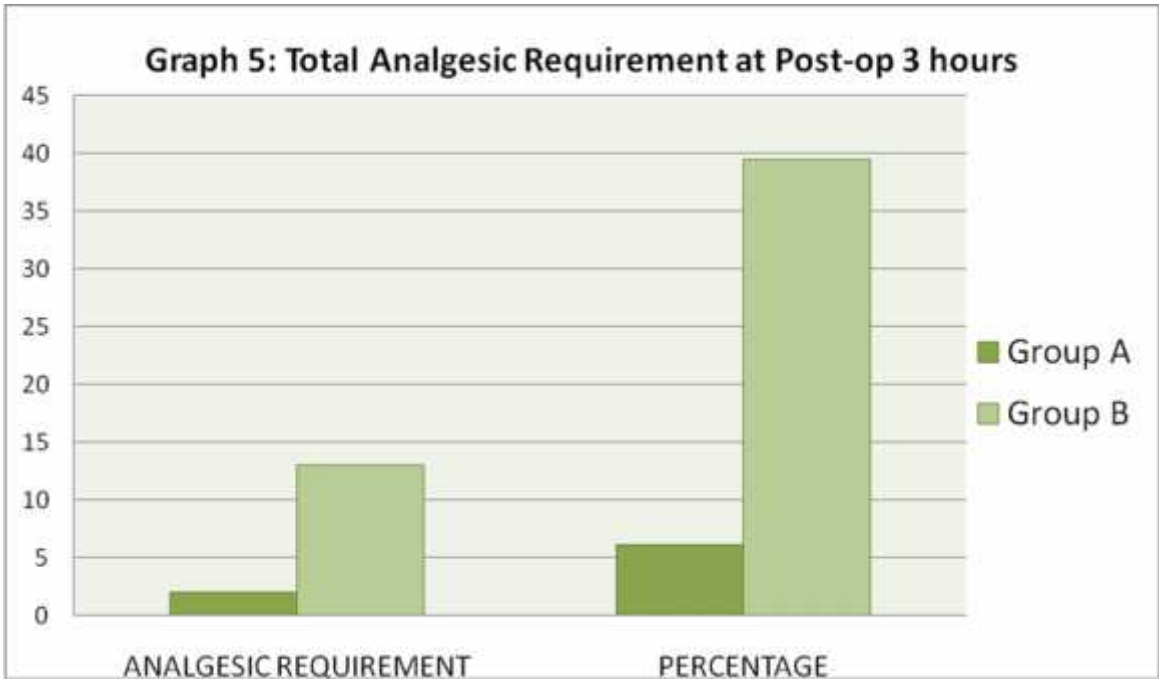

Graph 4: Pain score at Post-operative 3 hours
Percentage
60
50
40
30
20
10
0
0
1
2
3
4
5
6
7
8
9
10
Pain Score
Group A
Group B

Table 5: Total Analgesic Requirement at Post-Op 3 hours.

	Patients requiring Rescue Analgesia	Percentage
Group A	**2 out of 33**	**6.06**
Group B	**13 out of 33**	**39.39**



The analgesic requirement for patients in Group B (39.39%) was significantly higher as compared to patients in Group A (6.06%) at Post- op 3 hours. $p < 0.001$.

Table 6. Pain Score at Post-Operative 6 hours.

Pain Score	Group A		Group B	
	Number	**Percentage**	**Number**	**Percentage**
0	0	-	0	-
1	0	-	0	-
2	3	9.09	0	-
3	11	33.33	5	15.15
4	6	18.18	13	39.39
5	4	12.12	10	30.30
6	7	21.21	6	18.18
7	0	-	1	3.03
8	0	-	0	-
9	0	-	0	-
10	0	-	0	-
Total	**33**	**100**	**33**	**100**

p= 0.586

At post-operative 6 hours there was no statistically significant difference in the pain scores between Group A and Group B. p= 0.586

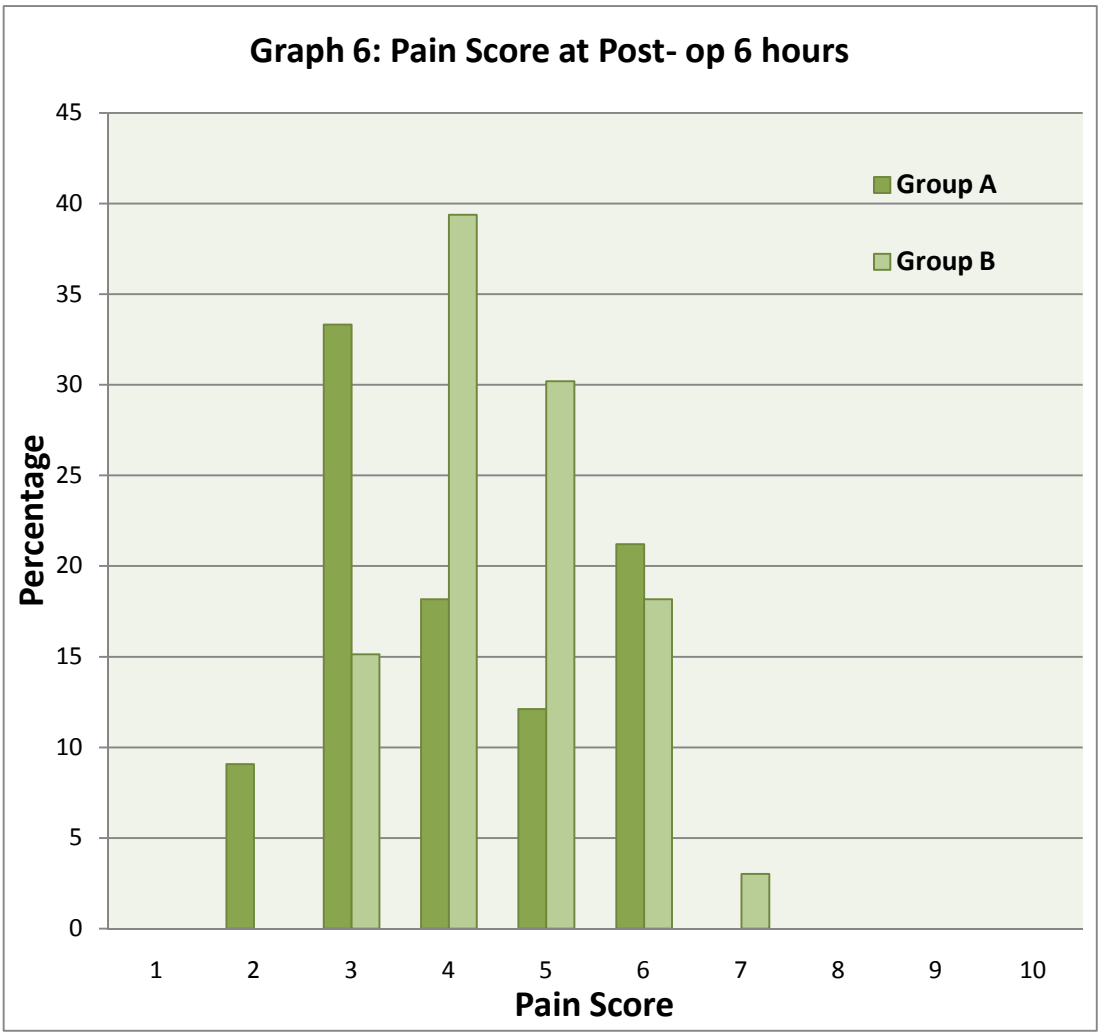

Graph 6: Pain Score at Post- op 6 hours
45
40
35
30
25
20
15
10
5
0
Percentage
Group A
Group B
1
2
3
4
5
6
7
8
9
10
Pain Score

Table 7: Total Analgesic Requirement at Post- Op 6 hours.

	Patients requiring analgesia	Percentage
Group A	**8 out of 33**	**24.24**
Group B	**10 out of 33**	**30.30**

p= 0.056

There was no statistically significant difference in the analgesic requirement between Group A and Group B at post-operative 6 hours. p= 0.056

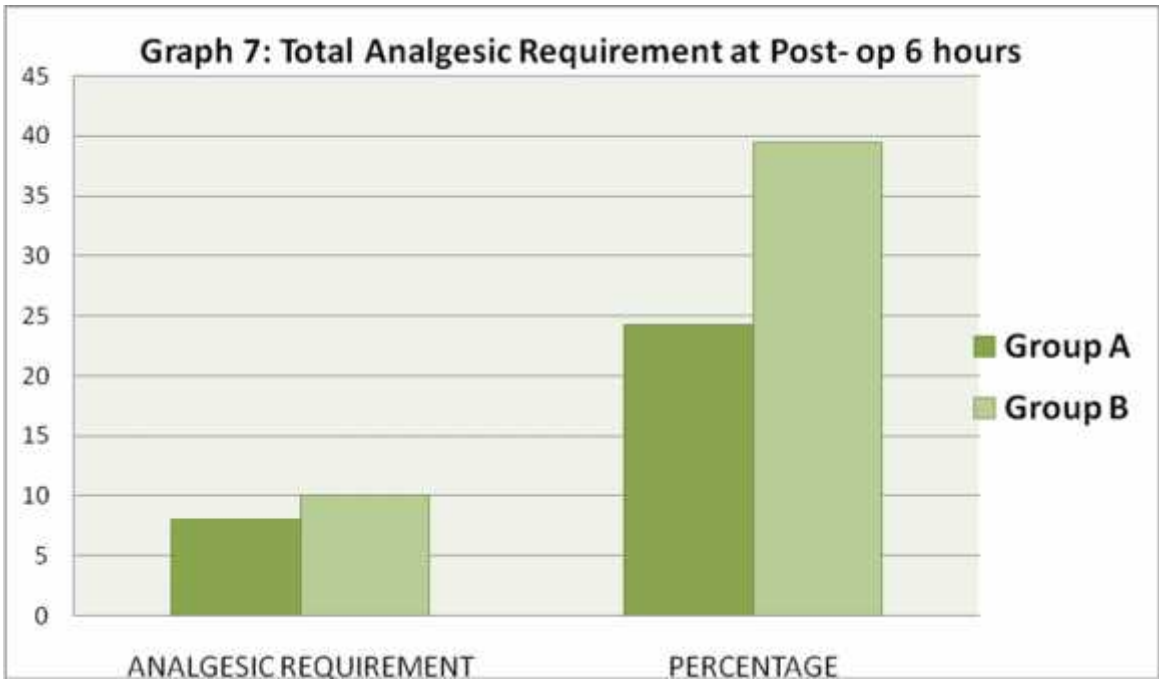


Table 8. Pain Score at Post-Operative 10 hours.

Pain Score	Group A		Group B	
	Number	**Percentage**	**Number**	**Percentage**
0	0	-	0	-
1	0	-	0	-
2	2	6.06	2	6.06
3	17	51.51	9	27.27
4	7	21.21	7	21.21
5	5	15.15	2	6.06
6	2	6.06	13	39.39
7	0	-	0	
8	0	-	0	-
9	0	-	0	-
10	0	-	0	-
Total	**33**	**100**	**33**	**100**

p=0.555

Table 8 shows there is no statistically significant difference in the pain scores between Group A and Group B at post-operative 10 hours. p= 0.555

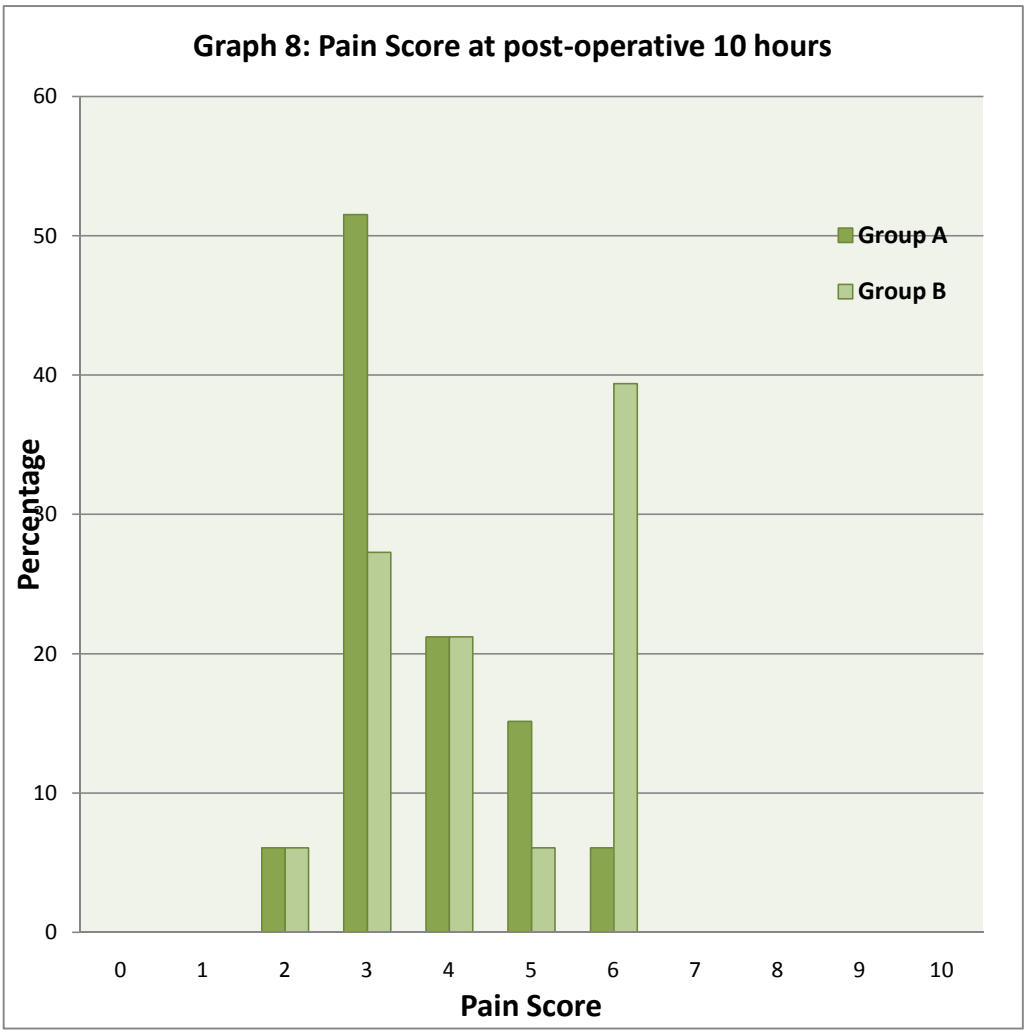

Graph 8: Pain Score at post-operative 10 hours
60
50
40
30
20
10
0
Percentage
Group A
Group B
0
1
2
3
4
5
6
7
8
9
10
Pain Score

Table 9: Total Analgesic Requirement at Post- Op 10 hours.

	Patients requiring analgesia	Percentage
Group A	**7 out of 33**	**21.21**
Group B	**13 out of 33**	**39.39**

p= 0.573

Table 9 shows that there was no statistically significant reduction in the analgesic requirement between the patients in Group A and Group B at Post-operative 10 Hours. p= 0.573

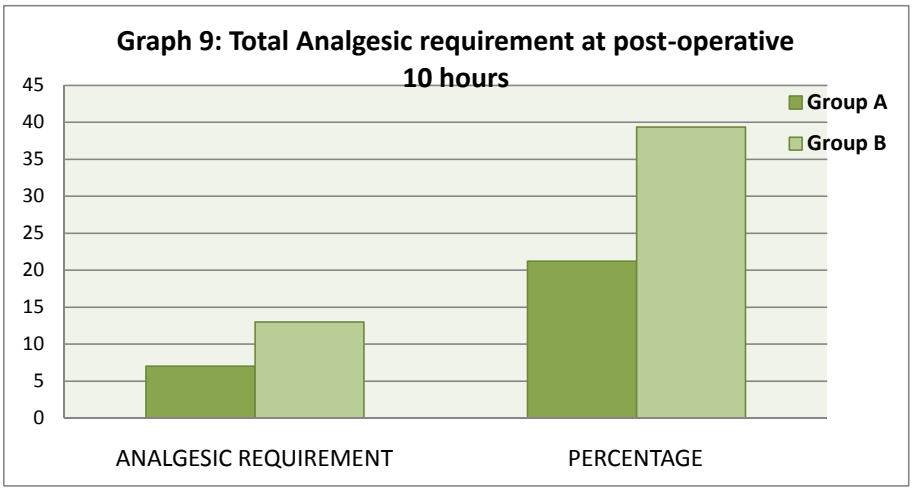


Table 10. Pain Score at post-operative 24 hours.

Pain Score	Group A		Group B	
	Number	**Percentage**	**Number**	**Percentage**
0	0	-	0	-
1	0	-	0	-
2	8	24.24	8	24.24
3	18	54.54	10	30.30
4	5	15.15	2	6.06
5	1	3.03	10	30.30
6	1	3.03	3	9.09
7	0	-	0	
8	0	-	0	-
9	0	-	0	-
10	0	-	0	-
Total	**33**	**100**	**33**	**100**

p=0.641

Table 10 shows that there is no statistically significant difference in the pain scores between Group A and Group B 24 hours post-operatively. p= 0.641

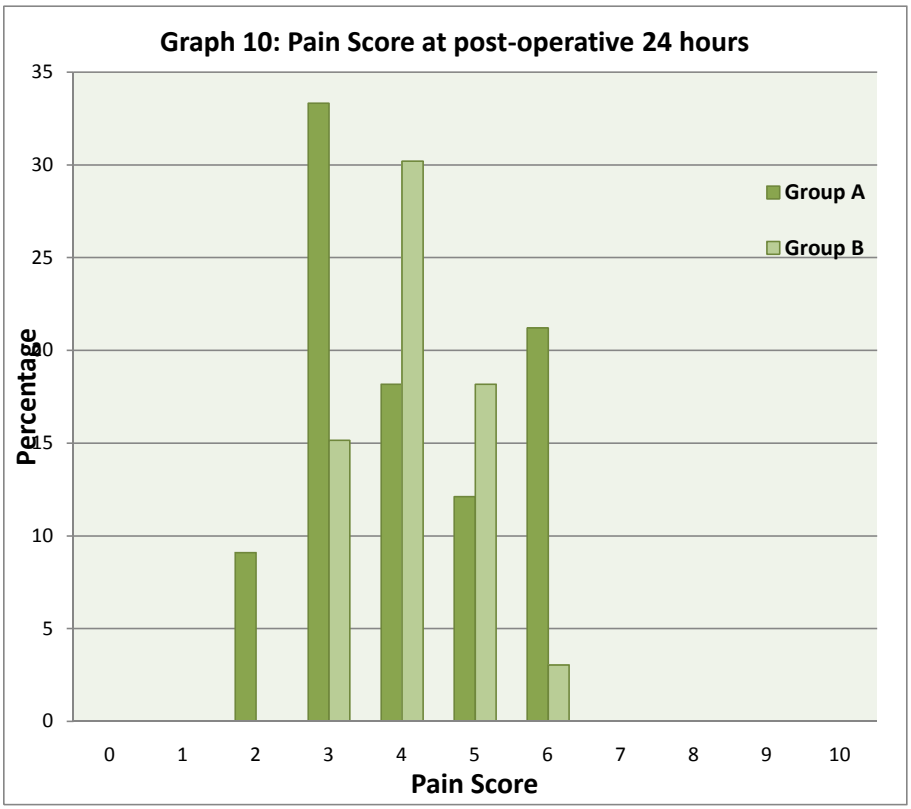
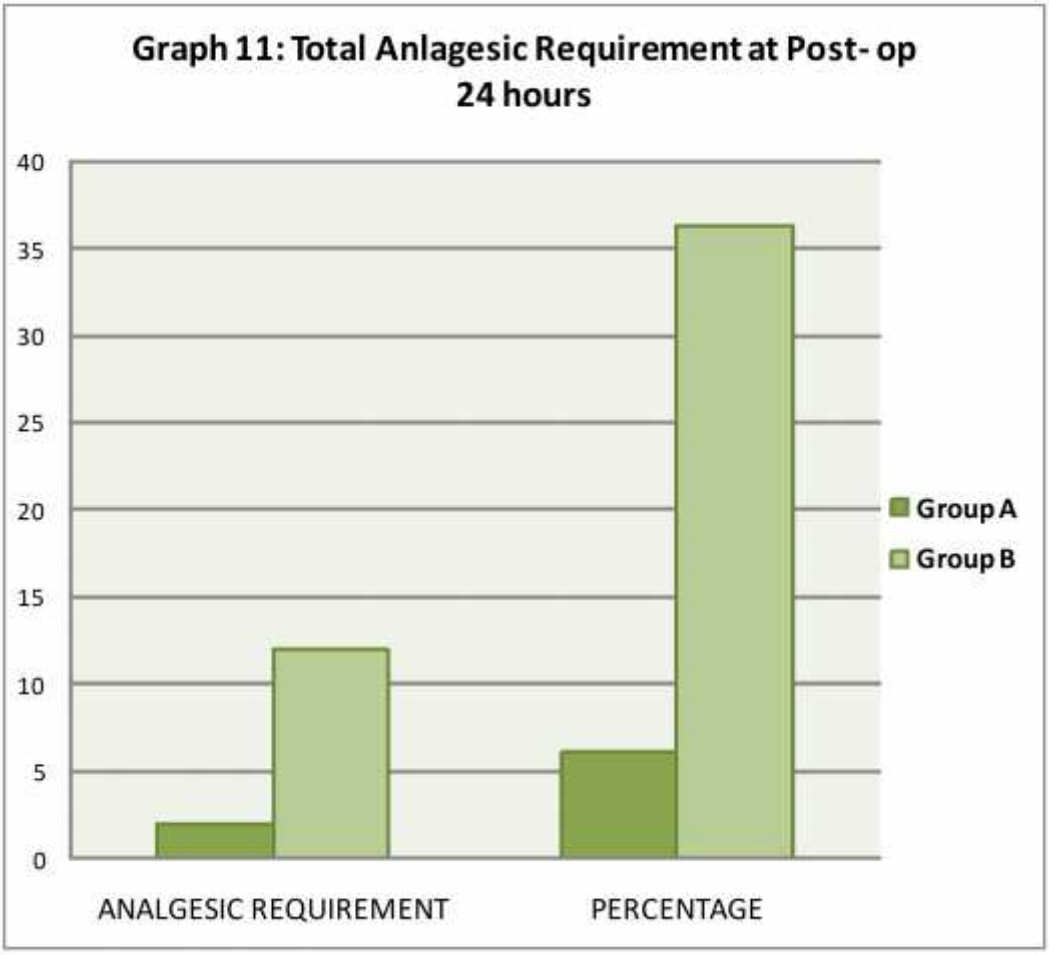

Graph 10: Pain Score at post-operative 24 hours
35
30
25
20
15
10
5
0
Percentage
Group A
Group B
0
1
2
3
4
5
6
7
8
9
10
Pain Score

Table 11: Total Analgesic Requirement at Post- Op 24 hours.

	Patients requiring analgesia	Percentage
Group A	**2 out of 33**	**6.06**
Group B	**12 out of 33**	**36.36**



$p < 0.001$

The analgesic requirement in Group A at 24 hours post-operatively was significantly lower than the analgesic requirement by patients in Group B.

$p < 0.001$

Chapter 6

Discussion

DISCUSSION

Laparoscopic appendicectomy is a standard procedure being performed for appendicitis. Patients who undergo laparoscopic appendicectomy are likely to have less post-operative pain and be discharged from the hospital and return to activities of daily living sooner than those who have undergone open appendisectomy.[36] However most patients undergoing laparoscopic appendicectomy complain of pain at the port site preventing ambulation and thus delaying the recovery.

Pre-emptive analgesia refers to analgesic intervention initiated prior to the onset of noxious stimuli and is designed to limit sensitization of the nervous system in response to these stimuli, with the goal of reducing subsequent pain. It prevents central sensitization, and hence along with intensive multi-modal analgesic intervention, reduces postoperative pain and chronic pain after surgery.[37]

Controversy exists in the efficacy and benefits of pre-emptive analgesia because not all clinical trials for pre-emptive analgesia have resulted in clear demonstration of its efficacy. Although some studies have failed to show a beneficial effect of pre-emptive analgesia in the control of post-operative pain, others have demonstrated that pre-emptive analgesia offers improved pain control and a reduced consumption of analgesics. Hence the present study was conducted as a one year prospective randomized controlled trial studying the pre-emptive analgesic efficacy of Lornoxicam in patients undergoing laparoscopic appendicectomy.

In the present study, comparison of the pain scores at 3 hours post-operatively between the pre-emptive group (Group A) and placebo group (Group B) does not show any statistically significant reduction in the pain. p=0.5261. However there was statistically significant difference in the analgesic requirements between the two groups. The analgesic requirement for patients in Group B (39.39%) was significantly higher as compared to patients in Group A (6.06%). $p < 0.001$.

Assessment at post-operative 6 hours shows there was no statistically significant difference in the pain scores between Group A and Group B. p= 0.586 and also the analgesic requirement between the two groups were comparable. p= 0.056

At post-operative 10 hours there was no statistically significant difference in the pain scores between Group A and Group B. p= 0.555 Further there was no statistically significant reduction in the analgesic requirement between the patients in Group A and Group B at Post-operative 10 Hours. p= 0.573

Similarly, there was no statistically significant difference in the pain scores between Group A and Group B at post-operative 24 hours, p= 0.641; however, the analgesic requirement in Group A at 24 hours post-operatively was significantly lower than the analgesic requirement by patients in Group B. p< 0.001

Farnad Imani et al studied the efficacy of Morphine and Lornoxicam following use of patient controlled intra-venous analgesia on pain after Laparoscopic Gastric Bypass Surgery. The results of the study suggest that administration of lornoxicam through PCIA is as effective as administration of

morphine through PCIA for the management of post-operative pain in patients undergoing laparoscopic surgery. In addition, lornoxicam has less side-effect such as sedation, nausea and vomiting than morphine.[38]

Girish Babu Narasimha Murthy et al (2012) conducted a study comparing ketorolac with lornoxicam as pre-emptive analgesic in patients undergoing elective abdominal surgeries. The results showed that the pain scores were significantly lower in the lornoxicam group as compared to those in the placebo group ($p=0.0001$). The pain scores were also significantly lower in the ketorolac group as compared to those in the placebo group. However there was no difference in the pain score between the ketorolac and the lornoxicam groups ($p>0.05$). Also noted was that there was a significant difference with respect to the first analgesic requirement time between the three groups. The time for the first analgesic requirement was longer in the lornoxicam (302.75 ± 92.57 min) and the ketorolac groups (291.25 ± 100.34 min) as compared to that in the placebo group (107.50 ± 50.71 min) ($p=0.0001$). Significant difference was seen in the analgesic consumption between the groups and it was less in the ketorolac (47%) and the lornoxicam (54%) groups as compared to that in the placebo group ($p=0.0001$). The analgesic consumption between the lornoxicam and the ketorolac groups was comparable. However, the degree of satisfaction with the post-operative pain management was better in the lornoxicam group (40%) as compared to the ketorolac group (15%).[39]

In a study conducted by Guzel AI, Kuyumcuoglu U and Celik Y comparing effect of lornoxicam and paracetamol in pain relief in patients

undergoing endometrial sampling for benign conditions under general anesthesia showed that the patients in lornoxicam group had lower VAS pain score than the paracetamol group ($p < 0.05$). According to the study, oral lornoxicam is more effective in pain relief than oral paracetamol in patients undergoing endometrial sampling.[40]

Qi-Feng Tang and others, studied the effects of pre-emptive intravenous lornoxicam on reducing the need of epidural morphine and also the effects of lornoxicam on the expression of chemokines in women undergoing hysterectomy. Preemptive i.v. lornoxicam treatment was associated with attenuation of the plasma concentrations of MCP-1 and SDF-1α immediately after and 24 hours after hysterectomy. Use of lornoxicam was associated with more rapid resolution of both the above mentioned cytokines to near-baseline compared with controls thus reducing the degree of inflammation. However there was no significant reduction in the requirement of epidural morphine.[41]

Trampitsch E and others , in a study to compare the efficacy of lornoxicam as a pre-emptive analgesic in gynecological surgeries showed that lornoxicam as a pre-emptive analgesic agent improves the quality of postoperative analgesia and leads to reduced consumption of opioid analgesics postoperatively in patients undergoing gynecological operations.[42]

Mowafi HA et al, conducted a study comparing the post-operative analgesic effects of lornoxicam and paracetamol after lower abdominal surgeries. The study concluded that Lornoxicam is superior to paracetamol for postoperative analgesia after lower abdominal surgeries.[43]

Karaman Y and others in a study done to assess the preemptive analgesic effect of lornoxicam in patients undergoing major abdominal surgeries concluded that Lornoxicam administered preemptively appears to improve the quality of postoperative analgesia and leads to reduced consumption of tramadol postoperatively in this category of patients.[44]

A study conducted by Lustenberger FD and others studying efficacy of ibuprofen versus lornoxicam after third molar surgery demonstrated that ibuprofen 400 mg and lornoxicam 8 mg are comparable and are effective pain treatment medication after wisdom tooth surgery.[45]

Petrova VV et al (2005) studied Lornoxicam as an agent for the prevention and treatment of postoperative pain after extensive cancer surgery. The studies performed proved that lornoxicam used in therapeutic doses shows a 50% reduction (versus 30% when ketorolac or ketoprofen is used) in a need for the potent opioid bepronorfine after extensive operations for cancer. [46]

Arslan M and others (2011) compared the analgesic effects of intravenous paracetamol and lornoxicam in postoperative pain following thyroidectomies. Administration of i.v. lornoxicam and i.v. paracetamol following thyroid surgery decreased the postoperative opioid requirement and pain scores. There was a significant reduction in the incidence of nausea and vomiting, and also significantly prolonged the time to the first rescue analgesic requirement.[47]

Cevik E et al (2012), comparing the efficacy of intravenous tenoxicam, lornoxicam, dexketoprofen and tramadol for the treatment of renal colic concluded in their study that all the above mentioned drugs are effective in the

treatment of renal colic, although lornoxicam appeared to reduce VAS pain scores with the fastest rate in comparison to the others.[48]

In a study conducted by Inanoglu K and colleagues, intravenous lornoxicam given preemptively had a better pain relieving effect for varicocelectomy than when administered postoperatively.[49]

Mowafi HA and others (2011) studies the preoperative use of lornoxicam for pain prevention after tonsillectomy in adults. The study concluded that preoperative 16 mg lornoxicam was effective for immediate postoperative pain relief after tonsillectomy in adults.[50]

All the above mentioned studies demonstrate the efficacy of Lornoxicam as a pre-emptive analgesic agent in a variety of surgical procedures. Our study was aimed at analyzing the efficacy of lornoxicam as a pre-emptive analgesic agent in reducing post-operative pain and delaying the requirement for the first analgesic dose. Our study has demonstrated that lornoxicam is a very useful agent in reducing post-operative analgesic requirement in laparoscopic appendicectomy. It was also effective in reducing the total number of analgesics consumed post-operatively. The study reaffirms the findings of the previous studies mentioned and shows that Lornoxicam can be used as a suitable alternative to other NSAID's because of its better GI tolerability and shorter duration of action. However there is a need to confirm the above results with larger randomized controlled trials.

Chapter 7

Conclusion

CONCLUSION

Pre-emptive administration of Lornoxicam in patients undergoing laparoscopic appendicectomy is associated with better pain management and patient satisfaction. The intensity of pain and thereby the total dosage of analgesic consumption in the post-operative period is significantly lesser in the Lornoxicam group as compared to the placebo group.

Chapter 8

Summary

SUMMARY

The post- operative period is an important part of the surgical experience and affects the recovery. Many advances have been made in the field of pain management with the advent of newer analgesic agents and techniques. However patients continue to experience moderate to severe pain post- operatively. The concept of pre-emptive analgesia suggests that the best post-operative pain management begins pre-operatively. Laparoscopic appendicectomy is a standard procedure being performed for appendicitis. Patients who undergo laparoscopic appendicectomy are likely to have less post-operative pain and be discharged from the hospital and return to activities of daily living sooner than those who have undergone open appendicectomy. Lornoxicam is a newer NSAID belonging to the oxicam class. It has a strong analgesic and anti-inflammatory activity.

The present study was conducted as a one year prospective randomized controlled trial studying the pre-emptive analgesic efficacy of Lornoxicam in patients undergoing laparoscopic appendicectomy. The study was conducted in Department of Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum between January 2011 to December 2011. A total of 66 patients undergoing laparoscopic appendicectomy were included in the study. These patients were randomized into two groups based on computer generated blocked random numbers that is Group A (Pre-emptive) and Group B (Placebo).

In the present study, comparison of the pain scores at 3 hours post-operatively between the pre-emptive group (Group A) and placebo group (Group B) did not show any statistically significant reduction in the pain. p=0.5261.

However there was statistically significant difference in the analgesic requirements between the two groups. The analgesic requirement for patients in Group B (39.39%) was significantly higher as compared to patients in Group A (6.06%). $p < 0.001$. Assessment at post-operative 6 hours shows there was no statistically significant difference in the pain scores between Group A and Group B. $p= 0.586$ and also the analgesic requirement between the two groups were comparable. $p= 0.056$

At post-operative 10 hours there was no statistically significant difference in the pain scores between Group A and Group B. $p= 0.555$ Further there was no statistically significant reduction in the analgesic requirement between the patients in Group A and Group B at Post-operative 10 Hours. $p= 0.573$ Similarly, there was no statistically significant difference in the pain scores between Group A and Group B at post-operative 24 hours, $p= 0.641$; however, the analgesic requirement in Group A at 24 hours post-operatively was significantly lower than the analgesic requirement by patients in Group B. $p< 0.001$ The present study leads to the conclusion that pre-emptive administration of Lornoxicam in patients undergoing laparoscopic appendicectomy is associated with better pain management and patient satisfaction. The intensity of pain and thereby the total dosage of analgesic consumption in the post-operative period is significantly lesser in the Lornoxicam group as compared to the placebo group.

Chapter 9

Bibliography

BIBLIOGRAPHY

1. G. Edward Morgan, Jr., Maged S. Mikhail, Michael J. Murray. Clinical Anesthesiology. 4th Ed. TATA McGraw-Hill.

2. Kirdemir Pakize, Marsan Anil. Comparing efficacy of pre-emptively used Lornoxicam and Tramadol for post-operative pain in patients undergoing laparoscopic cholecystectomy. Journal of Clinical and experimental investigation. Vol. 1, Nos. 1-6.

3. Alan K Aitkenhead, David V. Rowbotham, Graham Smith, Textbook of Anesthesia, 4th Ed., Churchill Livingstone, Elsevier.

4. Balfour JA, Fitton A, Barradell LB. Adis International Limited, Auckland, New Zealand. Lornoxicam: A review of its pharmacology and therapeutic potential in the management of painful and inflammatory condition. Drugs 1996, April 51(4), 639-57,

5. Kim E. Barret, Susan M. Barman, Scott Bortan, Heddwen L. Ganong Review of Medical Physiology.22nd Edition, Lange

6. GI Bijlani& S. Manjunatha , Understanding Medical Physiology. 4th Edition. Jaypee

7. Alan K. Aitkenhead, David V.,Graham Smith, Textbook of Anesthesia, 4th Edition,

8. Allan Gottschalk, David S. Smith, New Concepts in Acute Pain Therapy: Preemptive Analgesia, Am Fam Physician. 2001 May 15;63(10):1979-1985.

9. Apfelbaum JL, Chris C, Mehta SS, Gan TJ, AnesthAnalo 2003,Aug; 97(2): 534- 40.

10. Ronald Miller, Ule A. Fleisher, Roger A. Johns, John J. Savarese, Jaamine P. Wiener, Kronish, William L. Young. Miller's Anesthesia, 6th Edition,

11. Kehlet H, Holte K: Effect of post- operative analgesia on surgical outcome. British journal Of Anesthesia 87: 62; 2001.

12. Michael A.E. Ramsay, Acute postoperative pain management.

13. Taylor MS, Managing post-operative pain. Hosp. Med. 2001: 62: 560- 563.

14. Craw CJ. Multimodal Pain Management. JAMA 2002: 28: 629- 632.

15. Eulchene Alanmanou. Measurement of post-operative Pain. Pain measurement.

16. S. Ramamurhty, James N. Rogers, E. Alanmanou. Decision Making in Pain Management. 2nd edition. Elsevier.

17. Dr Ed Charlton, The Management of Postoperative Pain, Issue 7 (1997) Article 2.

18. JI. Alexander. Management of Post-operative Pain, British Journal of Anesthesia1997, 79, 369-378.

19. Robert K. Stoelting, Ronald D. Miller. Basics of Anesthesia- 4th Edition.

20. Jorgen B. Dahl, Steen Morniche. Oxford Journals Medicine British Medical Bulletin Vol. 71, Issue 1 Pp, 13- 27

21. Brunicardi CF, Andersen DK. Schwartz's manual of surgery. 9th ed. New York, NY:McGraw-Hill;2010.

22. Michael J. Zinner, Stanley W. Ashley. Maingot's Abdominal Operations. 11th Edition. Mc Graw Hill.

23. Beauchamp, Evers, Mattox, Sabiston Textbook of Surgery, 18th Edition. Elsevier.

24. Garbutt JM, Soper NJ, Shannon WD, Botero A, Littenberg. Meta- analysis of Randomized controlled trials comparing Laparoscopic and open appendectomy. SurgLaparosc 1999; 9: 17- 26.

25. Korell M, Schmaus F. Pain intensity following laparoscopy. Surg Lapar Endos 1996; 6: 375-9.

26. Alexander JI, Hull MGR. Abdominal pain after laproscopy: the value of a gas drain. Br J Obstet Gynaecol 1987; 94: 267-9.

27. Sharp JR, Pierson WP. Comparison of CO2 and N2O induced discomfort during peritoneoscopy under local anaesthesia. Gastroenterology 1982; 82: 453-6.

28. Mounton WG, Bessel JR. A randomized controlled trial assessing the benefit of humidified insufflation gas during laparoscopic surgery. Surg Endos 1999; 13: 106-8.

29. Vitale GC, Collet D, Miller FB. Interruption of professional and home activity after laparoscopic cholecystectomy among French and American patients. Am J Surg 1991; 161: 396-8.

30. Inanoglu K, Gorur S, Akkurt CO, Guven OE, Kararamaz A. The analgesic efficacy of pre-operative versus post-operative Lornoxicam in varicocele repair. J ClinAnesth 2007. Dec; 19(8): 587-90.

31. Mohamed Daabiss ,Medhat Al-Sherbiny , Rashed Al-Otaibi and Rima Al-Nimar. Analgesia in day-case ENT surgery: The efficacy of lornoxicam BJMP Sept 2009 Volume 2 Number 3

32. Arsalan M, Cicele R, Celep B. Yilmaz H. Comparison of the analgesic effect of Intravenous Paracetamol and Lornoxicam in post-operative pain following thyroidectomy.

33. Xuerong Y, Yugang H, Xia J, Harlan W. Ketamine and Lornoxicam for preventing fentanyl induced increase in post-operative Morphine requirement.AnesthAnalog 2008. Dec 107 (6), 2032- 7.

34. Ong CK, Lirk P, Seymour RA, Jenkins BJ. The efficacy of pre-emptive analgesia for acute post-operative pain management: a meta analysis. AnesthAnalg 2005 Mar; 100(3): 757- 73.

35. Farnad Imani, Mahzad Alimian, Mohammad Radmehr, Atousa Deljou, Nazanin Mirabi. Comparison of Morphine and Lornoxicam following PCIA on Pain after Laparoscopic Gastric Bypass Surgery,

36. Girish Babu Narasimha Murthy, Girish M. Bengalorkar, Ravi Madhusudhan. A Comparative Study of Ketorolac with Lornoxicam as Pre-emptive Analgesics in Patients Who were Undergoing Elective Abdominal Surgery under General Anaesthesia. Journal of Clinical and Diagnostic Resaerch. 2012 | Month : May, Volume : 6, Issue : 3

37. Guzel AI, Kuyumcuoglu U, Celik Y. Comparative effect of lornoxicam and paracetamol in pain relief in endometrial sampling. J Exp Ther Oncol. 2012;9(4):317-20.

38. Qi-Feng Tang, Yan-Ning Qian, Yu-Hua Qiu, Jian-Jun Yang, Zhong-Yun Wang. Effects of preemptive intravenous lornoxicam on the analgesic efficacy of epidural morphine and expression of chemokines in women undergoing hysterectomy. Current Therapeutic Research, Volume 70, Issue 1 , Pages 1-9, February 2009,

39. Trampitsch E, Pipam W, Moertl M, et al. Preemptive randomized, double-blind study with lornoxicam in gynecological surgery.. Schmerz 2003 Jan; 17(1) :4-10.

40. Mowafi HA, Elmakarim EA, Ismail S, Al-Mahdy M, El-Saflan AE, Elsaid AS. Intravenous Lornoxicam Is More Effective than Paracetamol as a Supplemental Analgesic After Lower Abdominal Surgery: A Randomized Controlled Trial. World J Surg. 2012 May 15.

41. Karaman Y, Kebapci E, Gurkan A. The Preemptive Analgesic Effect of Lornoxicam in Patients undergoing Major Abdominal Surgery: A Randomised Controlled Study. Int J Surg. 2008 Jun;6(3):193-6. Mar 10.

42. Lustenberger FD, Grätz KW, Mutzbauer TS. Oral Maxillofac Surg. 2011 Mar;15(1):57-62. Epub 2010 Dec 1. Efficacy of ibuprofen versus lornoxicam after third molar surgery: A Randomized, double-blind, crossover pilot study.

43. Petrova VV, Osipova NA, Beresnev VA, Dolgopolova TV, Biriukov VI, Torchinskaia EV, Ivanova LM Lornoxicam (xefocam) as an agent for the prevention and treatment of postoperative pain among other nonsteroidal anti-inflammatory drugs. Anesteziol Reanimatol. 2005 Sep-Oct;(5):39-43.

44. Arslan M, Ciçek R, Celep B, Yılmaz H, Ustün Kalender H. Comparison of the analgesic effects of intravenous paracetamol and lornoxicam in postoperative pain following thyroidectomies. Agri. 2011 Oct;23(4):160-6.

45. Cevik E, Cinar O, Salman N, Bayir A, Arziman I, Ardic S, Youngquist ST. Comparing the efficacy of intravenous tenoxicam, lornoxicam, and dexketoprofen, tramdomol for the treatment of renal colic. Am J Emerg Med. 2012 Feb 3.

46. Mowafi HA, Telmessani L, Ismail SA, Naguib MB. Preoperative lornoxicam for pain prevention after tonsillectomy in adults. J Clin Anesth. 2011 Mar; 23(2):97-101.

Annexures

Annexure I

ANNEXURE I – CONSENT FORM

Mr / Mrs / Miss _____ we are requesting you to enroll yourself in a study entitled, "**A PROSPECTIVE STUDY OF PRE-EMPTIVE ANALGESIA WITH LORNOXICAM IN LAPAROSCOPIC APPENDICECTOMY- A RANDOMIZED CONTROLLED TRIAL"** being conducted by **REG No. BH0110008**, Post Graduate student in MS General Surgery at Jawaharlal Nehru Medical College Belgaum, Karnataka under the guidance of Dr. _____, Department of Surgery, Jawaharlal Nehru Medical College, Belgaum, under KLE University, Belgaum.

Objective/ Purpose of this study

You have been requested to participate in this research because we find your profile matching with our study group. During the study you will be asked some questions regarding your present complaints and you are supposed to answer to the best of your knowledge.

Your participation in research is absolutely voluntary. If you decide to participate you are free to withdraw at any time.

The purpose of research is to evaluate the efficacy of Lornoxicam as a pre-emptive analgesic agent in Laparoscopic Appendicectomy under General Anesthesia.

Procedure

Depending on the Group you will be administered either Inj. Lornoxicam or Placebo 20 minutes before induction of General Anesthesia.

Benefits and Risks

There is no increased risk involved in becoming a part of this study and the complications are those which are normally anticipated. The study will help us estimate the efficacy of Lornoxicam as a pre-emptive analgesic agent in patients undergoing laparoscopic appendicectomy under general anesthesia. The results derived at the end of the study will benefit all similar patients admitted in this hospital.

Withdrawal/ Removal from the study

The participant has full freedom to withdraw from the study whenever he/ she wishes and without prior notice. Even if you decline to participate, there will not be any change in the line of your management or the relationship with your doctor. You will be told about all the new information that may affect your decision to participate in the study. The Investigator may also exclude a participant from the study at anytime.

Privacy and confidentiality

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:

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

Institutional/ Sponsors policy:

If any unforeseen complications or injury occurs during the period of the study, the participants will be given treatment within the limitations of KLE's Dr. Prabhakar Kore Hospital general ward.

Financial Incentives for participation:

The participants will neither get any financial incentives during the period of the study nor will be asked to pay for the purpose of this study.

AUTHORIZATION TO PUBLISH RESULTS:

When the results of the research are published or discussed in any 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.

CONSENT TO PARTICIPATE IN A RESEARCH STUDY:

I, the undersigned have been explained in my own vernacular language about the study. I am aware that my participation in this study is voluntary and I could withdraw at any time. Also I have been given enough time to comprehend and clarify my doubts about the study and my rights as a study participant.

Signature or the left thumb impression of the participant or legally authorized representative.

Participant Name: _____Signature_____

Witness name: _____

Signature: _____

Investigator's name: _____ Signature: _____

Place:_____

Date _____

Annexure II

ANNEXURE II – PROFORMA

STUDY: A PROSPECTIVE STUDY OF PRE-EMPTIVE ANALGESIA WITH LORNOXICAM IN LAPAROSCOPIC APPENDICECTOMY UNDER GENERAL ANESTHESIA- A RANDOMIZED CONTROLLED TRIAL.

PATIENT DETAILS

Patient No.

Research No.

Name of the Patient : Date of Admission:

Address: Date of Discharge:

Age/ Sex :

Occupation :

I.P. No :

Chief Complaints

1.

2.

3.

General Physical Examination:

Vital Signs: PR

BP

RR

Any Other:

Systemic Examination:

1. Per Abdomen:
2. Respiratory System:
3. C. V. S.:
4. C.N. S:
5. Any Other findings:

Provisional Diagnosis:

Final Diagnosis:

Operative Procedure:

Anesthesia:

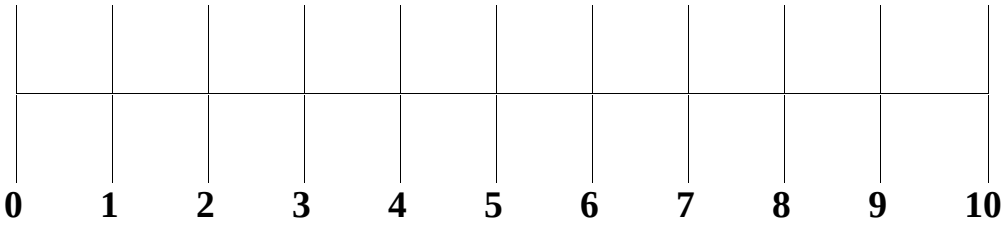
Drugs used Intra-operatively:

Intra- operative Findings:

Evaluation of Pain:

At post-operative 3 Hours:

No Pain **Max.**

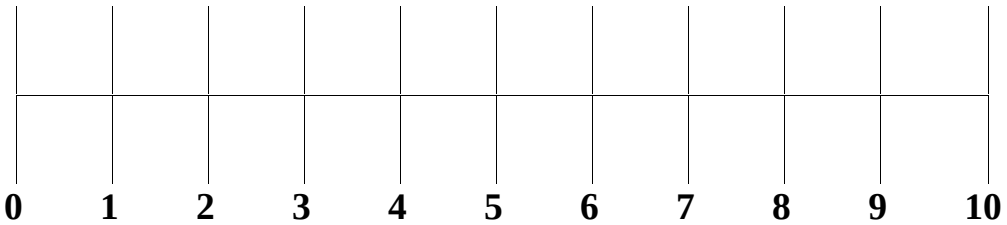


Dosage of Analgesic given:

Vitals:

At Post- operative 6 hours

No Pain **Max.**

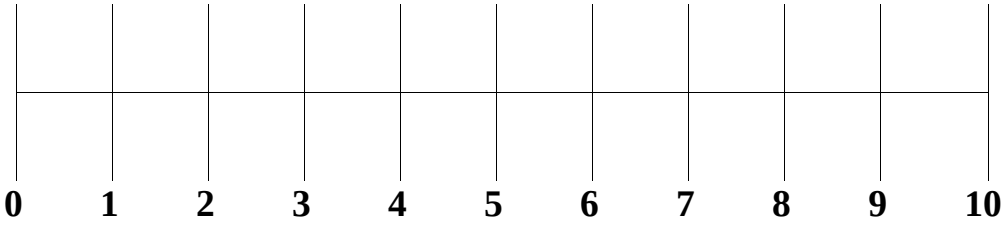


Dosage of Analgesic given:

Vitals:

At Post- operative 10 hours

No Pain **Max.**

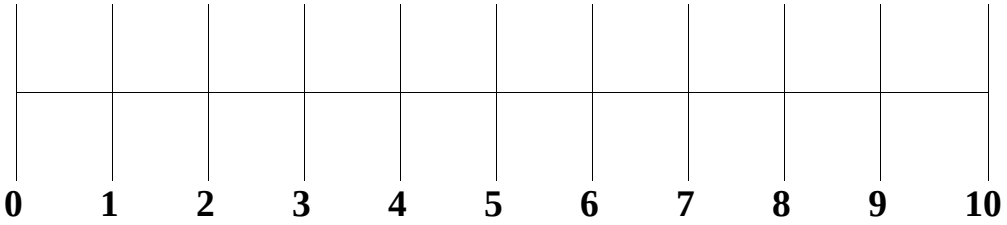


Dosage of Analgesic given:

Vitals:

At Post- operative 24 hours

No Pain **Max.**



Dosage of Analgesic given:

Vitals:

Signs of Hypersensitivity:

Toxicity:

Wound Infection:

ANNEXURE - IV-MASTER CHART

Sr. No.	I.P. No	Age/ Sex	Diagnosis	Pain Evaluation at different intervals				Analgesic Requirement				Complications
				3 hrs.	6 hrs.	10 Hrs.	24 Hrs.	3 hrs.	6 hrs.	10 Hrs.	24 Hrs.	
Pre-Emptive												
1	428892	24/ M	Recurrent Appendicitis	4	6	3	2	-	✓	-	-	-
2	422806	22/ M	Acute Appendicitis	4	4	3	3	-	-	-	-	-
3	446165	32/ M	Acute Appendicitis	3	3	6	2	-	-	✓	-	-
4	442352	30/ F	Recurrent Appendicitis	5	4	6	3	-	-	✓	-	-
5	424342	33/ M	Acute Appendicitis	3	5	3	3	-	✓	-	-	-
6	422708	45/ M	Chronic Appendicitis	5	4	5	4	✓	-	✓	-	-
7	407370	40/ M	Acute Appendicitis	4	3	5	2	-	-	✓	-	-
8	402825	24/ F	Chronic Appendicitis	4	3	3	3	-	-	-	-	-
9	406933	18/ F	Chronic Appendicitis	4	3	3	3	-	-	-	-	-
10	392974	34/M	Acute Appendicitis	4	4	5	3	-	-	✓	-	-
11	410166	69/ F	Chronic Appendicitis	4	3	5	3	-	-	✓	-	-
12	430689	19/ F	Recurrent Appendicitis	3	4	3	4	-	-	-	-	-
13	439035	39/ F	Recurrent Appendicitis	4	4	4	3	-	-	-	-	-
14	436110	29/M	Acute Appendicitis	4	4	3	3	-	-	-	-	-
15	432385	31/ F	Recurrent Appendicitis	4	4	3	4	-	-	-	-	-
16	419969	21/ F	Acute Appendicitis	5	6	3	3	-	✓	-	-	-
17	428758	22/ M	Acute Appendicitis	5	4	5	3	-	-	✓	-	-
18	431231	18/ M	Acute Appendicitis	3	3	4	4	-	-	-	-	-
19	447618	20/ M	Recurrent Appendicitis	7	4	2	2	✓	-	-	-	-
20	436060	25/ M	Acute Appendicitis	4	4	3	3	-	-	-	-	-

Master Chart

Sr. No.	I.P. No	Age/ Sex	Diagnosis	Pain Evaluation at different intervals				Analgesic Requirement				Complications
				3 hrs.	6 hrs.	10 Hrs.	24 Hrs.	3 hrs.	6 hrs.	10 Hrs.	24 Hrs.	
Pre-Emptive												
21	429937	18/ F	Acute Appendicitis	4	4	4	3	-	-	-	-	-
22	435654	28/ M	Acute Appendicitis	3	2	3	2	-	-	-	-	-
23	446384	28/ M	Acute Appendicitis	4	6	3	3	-	✓	-	-	-
24	443641	70/ M	Acute Appendicitis	3	2	2	2	-	-	-	-	-
25	447618	20/ M	Recurrent Appendicitis	3	3	3	2	-	-	-	-	-
26	443179	19/ M	Acute Appendicitis	3	6	3	3	-	✓	-	-	-
27	439379	31/ M	Acute Appendicitis	4	5	3	3	-	✓	-	-	-
28	445197	26/ M	Acute Appendicitis	3	3	3	2	-	-	-	-	-
29	446190	60/ M	Recurrent Appendicitis	4	5	4	5	-	✓	-	✓	-
30	430367	18/ F	Acute Appendicitis	6	6	3	4	-	✓	-	-	-
31	438689	21/ F	Acute Appendicitis	4	4	4	3	-	-	-	-	-
32	431108	31/ M	Acute Appendicitis	4	3	4	6	-	-	-	✓	-
33	443613	38/ M	Recurrent Appendicitis	3	3	4	3	-	-	-	-	-

Master Chart

Sr. No.	I.P. No	Age/ Sex	Diagnosis	Pain Evaluation at different intervals				Analgesic Requirement				Complications
				3 hrs.	6 hrs.	10 Hrs.	24 Hrs.	3 hrs.	6 hrs.	10 Hrs.	24 Hrs.	
Placebo												
34	443647	37/ M	Acute Appendicitis	6	3	6	2	✔	-	✔	-	-
35	423719	33/ F	Acute Appendicitis	4	5	4	5	-	✔	-	✔	-
36	419091	19/ M	Acute Appendicitis	4	6	4	5	-	✔	-	✔	-
37	403077	35/ F	Acute Appendicitis	5	5	6	5	✔	-	-	✔	-
38	394346	29/ M	Perforated Appendix	6	5	6	6	✔	-	✔	✔	-
39	408324	33/ M	Acute Appendicitis	5	4	6	5	✔	-	✔	✔	-
40	403081	25/ F	Chronic Appendicitis	4	4	3	2	-	-	-	-	-
41	403437	21/ F	Acute Appendicitis	5	4	5	5	✔	-	✔	✔	-
42	447427	21/ F	Acute Appendicitis	5	4	5	3	✔	-	✔	-	-
43	446165	32/ M	Chronic Appendicitis	4	4	6	4	-	-	✔	-	-
44	446233	24/ M	Recurrent Appendicitis	4	3	3	3	-	-	-	-	-
45	448151	19/ M	Recurrent Appendicitis	3	3	2	2	-	-	-	-	-
46	431460	20/ F	Chronic Appendicitis	4	6	4	6	-	✔	-	✔	-
47	419897	40/ M	Chronic Appendicitis	4	5	3	3	-	✔	-	-	-
48	429405	26/ M	Acute Appendicitis	3	4	6	4	-	-	✔	-	-
49	430735	58/ F	Recurrent Appendicitis	5	6	4	5	-	✔	-	-	-
50	398018	45/ F	Chronic Appendicitis	6	4	6	5	✔	-	✔	✔	-
51	399358	35/ F	Acute Appendicitis	6	5	6	5	✔	-	✔	✔	-
52	404053	30/ F	Chronic Appendicitis	5	4	6	5	✔	-	✔	✔	-
53	395508	32/ F	Acute Appendicitis	7	5	6	6	✔	-	✔	✔	-
54	401455	18/ F	Acute Appendicitis	8	5	6	5	✔	-	✔	✔	-

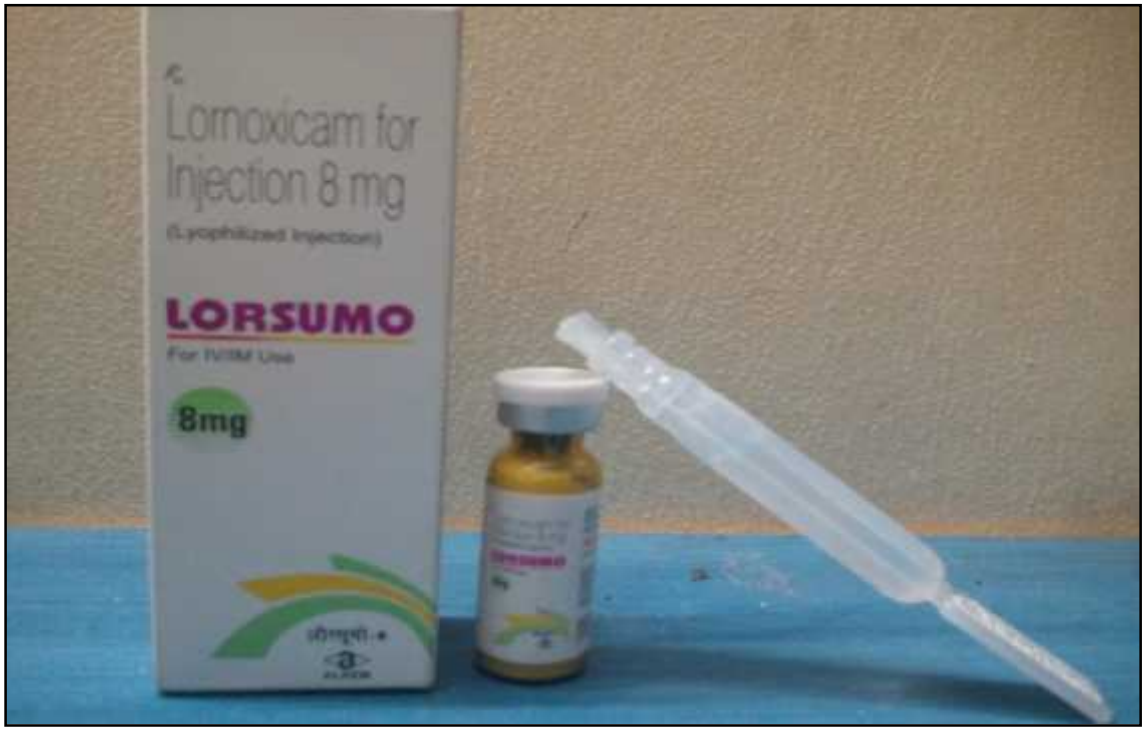
Master Chart

Sr. No.	I.P. No	Age/ Sex	Diagnosis	Pain Evaluation at different intervals				Analgesic Requirement				Complications
				3 hrs.	6 hrs.	10 Hrs.	24 Hrs.	3 hrs.	6 hrs.	10 Hrs.	24 Hrs.	
Placebo												
55	438893	35/ F	Acute Appendicitis	4	4	4	3	-	-	-	-	-
56	443997	27/ M	Recurrent Appendicitis	3	4	4	3	-	-	-	-	-
57	444988	23/ M	Acute Appendicitis	5	4	6	2	-	-	-	-	-
58	433750	27/ M	Chronic Appendicitis	3	4	4	3	-	-	-	-	-
59	441222	47/ F	Acute Appendicitis	4	6	3	3	-	✓	-	-	-
60	437167	29/ F	Acute Appendicitis	5	6	3	3	-	✓	-	-	-
61	446384	28/ M	Recurrent Appendicitis	4	5	3	2	-	✓	-	-	-
62	449174	55/ M	Recurrent Appendicitis	4	5	2	2	-	✓	-	-	-
63	433745	21/ F	Chronic Appendicitis	5	7	3	3	-	✓	-	-	-
64	447427	21/ F	Chronic Appendicitis	5	3	3	2	✓	-	-	-	-
65	449570	18/ F	Acute Appendicitis	4	4	3	2	-	-	-	-	-
66	428508	31/ M	Chronic Appendicitis	6	3	6	3	✓	-	✓	-	-

Annexure III

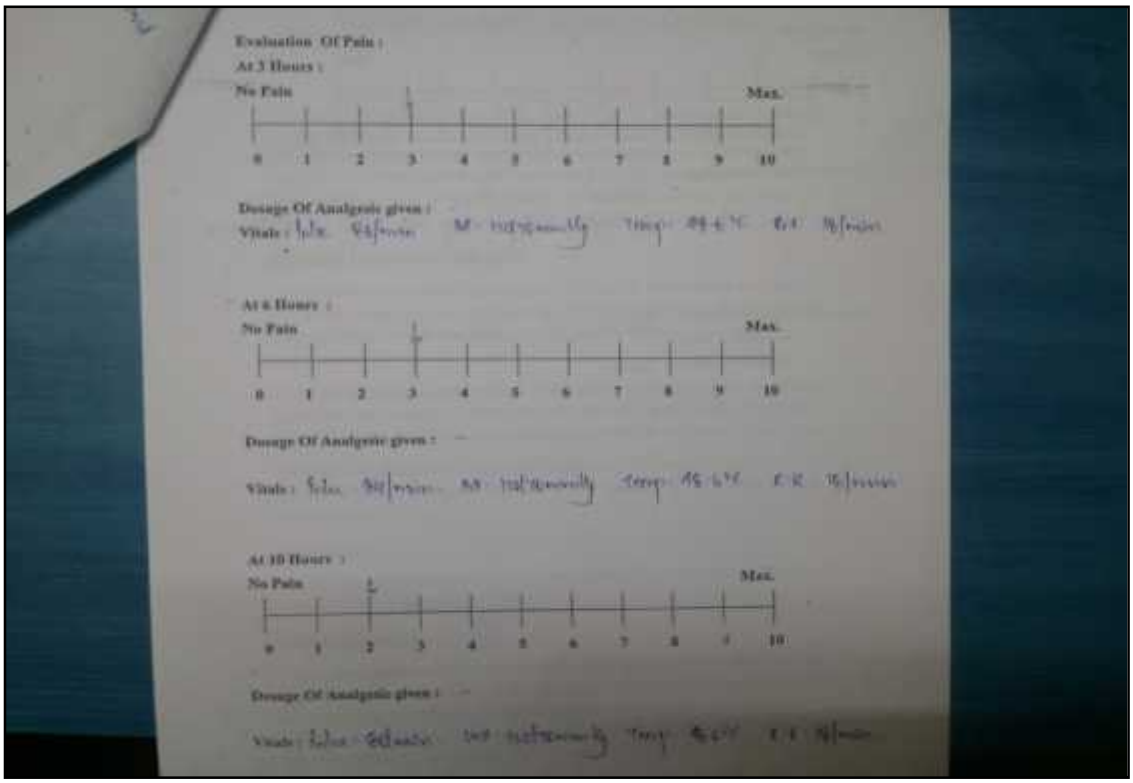
ANNEXURE III – PHOTOGRAPHS

Lornoxicam Ampoule



Patient marking VAS

VAS at 3, 6 and 10 Hours post-op



VAS at 24 Hours post-op