A COMPARATIVE STUDY OF INTRAVENOUS LORNOXICAM AND PARACETAMOL FOR POST-OPERATIVE ANALGESIA IN PATIENTS UNDERGOING ELECTIVE LAPAROTOMY UNDER GENERAL ANESTHESIA

BY

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Dissertation submitted to the

Sri Devaraj Urs Academy of Higher Education and Research,

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In partial fulfillment of the requirements for the degree of

DOCTOR OF MEDICINE
IN
PHARMACOLOGY

Under the guidance of

Dr. BHUVANA K, MD

DEPARTMENT OF PHARMACOLOGY
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April 2015

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I hereby declare that this dissertation entitled **"A COMPARATIVE STUDY OF INTRAVENOUS LORNOXICAM AND PARACETAMOL FOR POST-OPERATIVE ANALGESIA IN PATIENTS UNDERGOING ELECTIVE LAPAROTOMY UNDER GENERAL ANESTHESIA"** is a bonafide and genuine research work carried out by me under the direct guidance of **Dr. BHUVANA K, MD** Associate professor, Department of Pharmacology, Sri Devaraj Urs Medical College, Tamaka, Kolar.

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This is to certify that, the ethics committee of Sri Devaraj Urs Medical College, Tamaka, Kolar has unanimously approved the dissertation work of **Dr. DHEEPAN NAYAGAM B**, a postgraduate student in the Department of Pharmacology of Sri Devaraj Urs Medical College entitled **"A COMPARATIVE STUDY OF INTRAVENOUS LORNOXICAM AND PARACETAMOL FOR POST-OPERATIVE ANALGESIA IN PATIENTS UNDERGOING ELECTIVE LAPAROTOMY UNDER GENERAL ANESTHESIA"** to be submitted to the Sri Devaraj Urs Academy of Higher Education and Research, Tamaka, Kolar.

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In the end I thank **The Almighty** for blessing me and giving me the strength and courage to complete this task.

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Dr. DHEEPAN NAYAGAM B

DEDICATED WITH

REVERENCE

TO

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LIST OF ABBREVIATIONS

NSAIDs - Non-steroidal anti-inflammatory drugs

COX – Cyclooxygenase

VAS – Visual analog scale

APS – Acute pain service

PCA – Patient-controlled analgesia

IDET – Intra Discal Electrothermic Therapy

IASP – International association for the study of pain

DPQ – Dartmouth pain questionnaire

HYPQ – Haven-Yale pain questionnaire

CHEOPS – Children's Hospital of Eastern Ontario Pain Scale

NMDA – N-methyl-D-aspartate

TENS – Transcutaneous electrical nerve stimulation

PG – Prostaglandin

PDGF – Platelet derived growth factor

TNF – Tumor necrosis factor

PGHS – Prostaglandin H2 synthase

POX – Peroxidase

IL – Interleukin

AUC – Area under curve

CB – Cannabinoid

NAPQI – N-acetyl-p-benzoquinoneimine

GSH – Glutathione

FDA – Food and drug administration

NAC – N-acetyl cysteine

IV – Intravenous

ABSTRACT

Background: Non-steroidal anti-inflammatory drugs (NSAIDs) and opioids are the most commonly used analgesics for post-operative pain management. To minimize the unwanted effects of opioids, NSAIDs lornoxicam and paracetamol are compared for efficacy and safety in patients undergoing elective abdominal surgery under general anesthesia.

Objectives of this study:

1. To assess the analgesic effect of lornoxicam and paracetamol in post-operative pain following laparotomy by using Visual Analogue Scale (VAS) score
2. To assess the time for first rescue analgesic and total amount required in the first 24hrs after surgery
3. To assess the patient's satisfaction score with lornoxicam and paracetamol
4. To monitor the adverse effects of above drugs

Materials and methods: The study was conducted by departments of Pharmacology and Anesthesiology on patients admitted for elective laparotomy under general anesthesia in R. L. Jalappa Hospital and Research Centre attached to Sri Devaraj Urs Medical College, Kolar. The study was done from January 2013 to June 2014. Among 69 patients who were recruited were randomly divided into two groups i.e., 35 patients in group P (Gp P) and 34 patients in group L (Gp L). Patients in Gp P received a single dose of injection paracetamol 1gm 100 ml infusion and Gp L received injection lornoxicam 8mg in 100 ml normal saline. Both the drugs were administered as intra-venous infusion over 20 minutes half an hour before skin closure. Pain was assessed using Visual Analogue Scale (VAS) score, Rescue analgesic tramadol 100mg intravenously was administered to the patients if VAS score was more than three during post-operative period. The time required for first rescue analgesic and total amount required in the first 24hrs after surgery were assessed. Patient's satisfaction was assessed at the end of 8 hours and adverse effects were monitored.

Results: Study involved 69 patients, 45 males and 24 females. Mean age of 41.60 ± 12.71 and 37.41 ± 12.18 in Gp P and Gp L respectively. The baseline demographic variables were comparable between two groups. Mean VAS scores in patients who received paracetamol was more than lornoxicam but it was significant at 12^{th} hour (p=0.04). Time to first rescue analgesic was less in patients who received paracetamol compared to lornoxicam but it was not significant. Lornoxicam group required significantly lesser amount of rescue analgesic (p=0.018).

At the end of 8 hours, 37.1 % of patients graded their satisfaction score as good in paracetamol group and 44.1% in lornoxicam group. The common adverse effect in both the groups was nausea but both the drugs were well tolerated.

Conclusion: Intra-operative administration of 1 gm intravenous paracetamol is non-inferior to 8 mg lornoxicam for post-operative analgesia following elective laparotomy under general anesthesia.

Key words: Laparotomy, lornoxicam, paracetamol.

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Introduction

INTRODUCTION:

Pain is an unpleasant sensory and emotional experience associated with tissue damage, due to generation of noxious stimuli that are transduced by nociceptors with the release of algesic substances. The nociceptive sensation is transmitted by A delta and C nerve fibers to the neuraxis. Few impulses reach the anterior and anterolateral horns to provoke segmental reflex responses, while others are transmitted to higher centers via the spinothalamic and spinoreticular tracts, to produce suprasegmental and cortical responses.[1] Segmental reflex responses associated with surgery include increased skeletal muscle tone and spasm which leads to increased oxygen consumption and lactic acid production. Stimulation of sympathetic neurons causes tachycardia, increased stroke volume, cardiac work and myocardial oxygen consumption.[1]

Opioids are the mainstay of pain treatment since many years but are associated with unwanted effects like respiratory depression, sedation, nausea, vomiting and dependence. Non-steroidal anti-inflammatory drugs (NSAIDs) are alternatives to opioids for postoperative pain relief as they do not produce sedation, respiratory depression, constipation and substance abuse.[2]

Lornoxicam, an oxicam derivative, with a plasma elimination half-life of 3 - 5 hours is available for both oral and parenteral use. Treatment of postoperative pain after lumbar disc surgery with lornoxicam has been as effective as morphine, meperidine, and tramadol.[3, 4] Paracetamol is also a NSAID but it is a weak inhibitor of cyclooxygenase (COX) 1 and 2. Oral paracetamol has slow onset of analgesia and use after surgery limits its value in treating immediate postoperative pain.

Propacetamol, a water-soluble prodrug of paracetamol, was used for postoperative pain management, but its use is limited due to pain at injection site. Intravenous paracetamol available as a ready-to-use solution seems to be effective in the treatment of postoperative pain in hysterectomy, thyroid surgery and laparoscopic cholecystectomy.[5]

There is paucity of comparative studies between lornoxicam and paracetamol for management of postoperative pain in India. Both these drugs have opioid sparing effects with similar routes of administration and effective in reducing post-operative pain. Hence, this study was undertaken to compare the efficacy and safety of intravenous lornoxicam with paracetamol in patients undergoing elective laparotomy under general anesthesia.

Objectives

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2. To assess the time required for first rescue analgesic and total amount required in the first 24 hours after surgery
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4. To monitor the adverse effects of the above drugs

Review Of Literature

REVIEW OF LITERATURE

Historical aspects of pain

Primitive man perceived illness and pain as the work of evil spirits that had taken possession of the body. Incantations, charms, amulets, special ceremonies, and faith in the power of medicine men were the methods for alleviation or abolition of pain. A kind of psychological anaesthesia was therefore established during surgical interference. Testimony to this are found on Babylonian clay tablets, in Papyri written in the days of pyramid builders, in Persian leather documents, in inscriptions from Mycenae, on parchment rolls from Troy.

In ancient India, the earliest concepts of pain and other medical knowledge were attributed to the god Indra, as recorded in the Vedas and Upanishads. Buddha, about 500 B.C., quoted that pain was due to the frustration of desires: "Birth is attended with pain, decay is painful, and disease in painful. Union with the unpleasant is painful; painful is separation from the pleasant and any craving that is unsatisfied, that too is painful." Charaka, the first of India's great teachers of medicine, stated that all joy and pain was experienced in the heart, which was considered the seat of consciousness.

The ancient Chinese thought imbalance between the two forces, Yin and Yang results in deficiency or excess in the circulation of the CHI (the vital energy) which causes or ends up in disease and pain. E.H Hume described that Hunt O, a famous surgeon in Chinese medical history, born in 190 A.D had used acupuncture to perform operations on various organs. Acupuncture therapy, at one or more of the 365 specific points located along the meridians, corrects the imbalance and eliminates the disease

and pain. In Greece, Alcmaeon had the idea that the brain and not the heart was the center for pain.

Hippocrates' son-in-law Polypus emphasized that "Pain is felt when one of the humoral elements is in deficit or excess" in his book 'The Nature of Man'. Late 1800s, hot spring bathhouses were erected in England and United States to relieve pain and heal injuries. In 1939, methadone was first synthesized in Germany as a new painkilling medication. In 1972, dorsal column neurostimulators were first marketed to neurosurgeons in the United States. These devices were later renamed as spinal cord stimulators. In 1980s, the use of opioids administered directly to the spinal column via epidurals emerged as a treatment for chronic pain.

Ready in 1988 introduced Acute Pain Services (APS) to provide safe and effective management of severe post-operative pain. Patient-controlled analgesia (PCA) service became available for use. Epidural and intrathecal use of opioids and combination of opioids with local anesthetics has become popular, as a part of multimodal or balanced analgesic techniques. In 1997, Intra Discal Electrothermic Therapy (IDET) was introduced as an investigative treatment for chronic low back pain. This procedure involves killing nerve fibers by heating a catheter positioned inside the spinal disc.[6]

In 2004–2005, the first rechargeable spinal cord stimulation systems became available in the United States. Using rechargeable technology similar to a cell phone, these devices represent the new advancement in neuromodulation devices for the treatment of pain. In 2008 St. Jude Medical introduces the Eon Mini neurostimulator, the world's smallest, longest-lasting rechargeable neurostimulator to treat chronic pain of the trunk or limbs and pain from failed back surgery.[7]

Definition and classification of pain:

The Taxonomy Committee of International Association for the study of pain (IASP) defines pain as, "an unpleasant sensory and emotional experience associated with actual or potential tissue damage[8]." It is a subjective phenomenon perceived only by the sufferer. Pain is divided into two categories:

1) Acute Pain:

Acute pain warns about illness or injury that has occurred. It is usually confined to the affected area and is limited over time. Acute pain stimulates the sympathetic nervous system resulting in "fight or flight" response with symptoms like increased heart rate, respiratory rate, sweating, dilated pupils, restlessness and apprehension. Types of acute pain include somatic, visceral, and referred.

A) Somatic pain

Further classified into superficial or deep.

(a) Superficial somatic pain is due to nociceptive input from skin, tissues, and mucous membranes. It is well localized and either sharp, pricking, throbbing or burning in sensation.

(b) Deep somatic pain arises from muscles, tendons, joints or bones. It has a dull aching quality and is less well-localized.

B) Visceral Pain:

The visceral acute pain is due to a disease process or abnormal function of an internal organ or it's covering i.e. parietal pleura, pericardium, or peritoneum, and is described as:

(a) True visceral pain: It is dull, diffuse and usually midline. It is associated with abnormal sympathetic or parasympathetic activity causing nausea, vomiting, sweating and changes in blood pressure (BP) and heart rate.

(b) Localized parietal pain: It is typically sharp and often described as a stabbing sensation that is localized to the area around the organ.

(C) Referred pain:

It can be visceral or parietal. It is felt in an area distant from the site of the stimulus, because the area of referred pain is supplied by the same spinal segment as the site of the stimulus. Referred pain often occurs with visceral pain.[9]

2) **Chronic Pain**:

Chronic pain persists beyond the expected normal healing time which can vary from 1-6 months. Chronic pain may be nociceptive, neuropathic, or mixed. It can be continuous or intermittent. It is poorly understood, more complex and difficult to manage than acute pain. There is decreased autonomic nervous system response with prolonged pain because the sympathetic nervous system has adapted to persistent pain impulses.

There is evidence to indicate that chronic pain and depression share the same physiological pathway. Tricyclic antidepressants and selective serotonin reuptake inhibitors have been used for relief of many chronic pain syndromes such as neuropathic pain, low back pain, and fibromyalgia. These medications block the reuptake of neurotransmitters such as epinephrine and norepinephrine, thereby altering neurotransmission along pain pathways.[9]

Pain has been classified in two distinct types:

1. **Fast pain**. In the skin, it is mediated by free nerve endings and is rapidly transmitted by A delta fibers at velocities between 6 and 30 m/sec. It is opioid resistant.

2. **Slow pain**. It lasts longer than the provoking stimulus and is sensed in the deep visceral tissues. It may be secondary to actual tissue damage or inflammation. It is transmitted by unmyelinated C fibers at velocities between 0.5 and 2 m/sec and is relieved by both opioids and NSAIDs. Local anaesthetics block transmission in nerve fibers sub serving both types of pain.[9]

Post-operative pain and pain pathway mechanism:

Post- operative pain is one of the most common type of acute pain. It is a combined constellation of unpleasant sensory, emotional and mental experience precipitated by the surgical trauma and is associated with autonomic, endocrine-metabolic, physiological and behavioral responses. Nociceptive pain is often regarded as the key feature of acute postoperative pain. The analgesic requirement depends on the type of surgery and pharmacokinetic properties of the analgesic used.

Even though all pain receptors are free nerve endings, these endings use two separate pathways for transmitting pain signals into the central nervous system. On entering the spinal cord, the pain signals take two pathways to the brain, through

(1) The neospinothalamic tract and

(2) The paleospinothalamic tract

Spinal cord gray matter is divided into 10 laminae. The first six laminae which make up the dorsal horn receive all the afferent neural activity and represent the principal site of modulation of pain by ascending and descending neural pathways as shown in figure 1.[10]

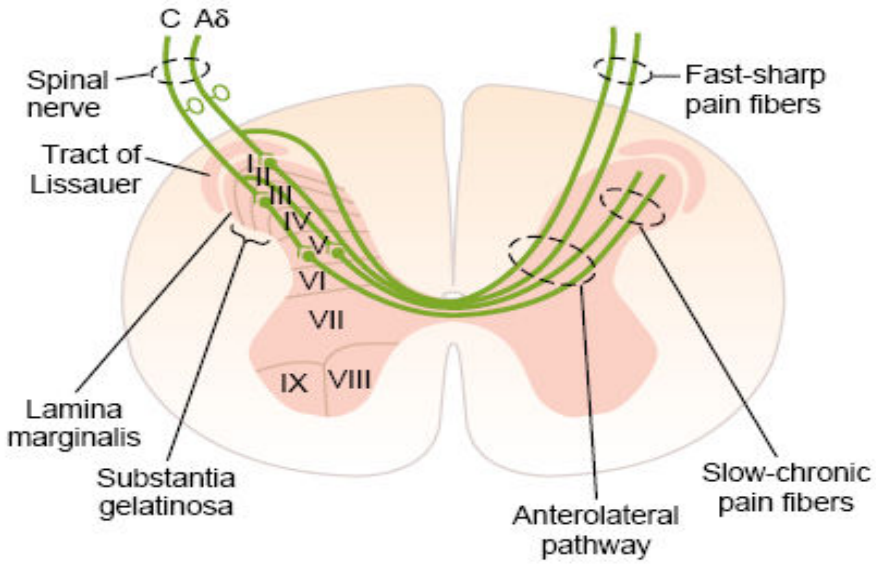


Figure 1: Transmission of "fast" and "slow" pain signals to the spinal cord

Neospinothalamic Tract for Fast Pain:

The fast type A delta pain fibers transmit mainly mechanical and acute thermal pain. They terminate mainly in lamina I (lamina marginalis) of the dorsal horns, as shown in figure 2 and they excite second-order neurons of the neospinothalamic tract. These give rise to long fibers that cross immediately to the opposite side of the cord through the anterior commissure and then turn upward, passing to the brain in the anterolateral columns.[10]

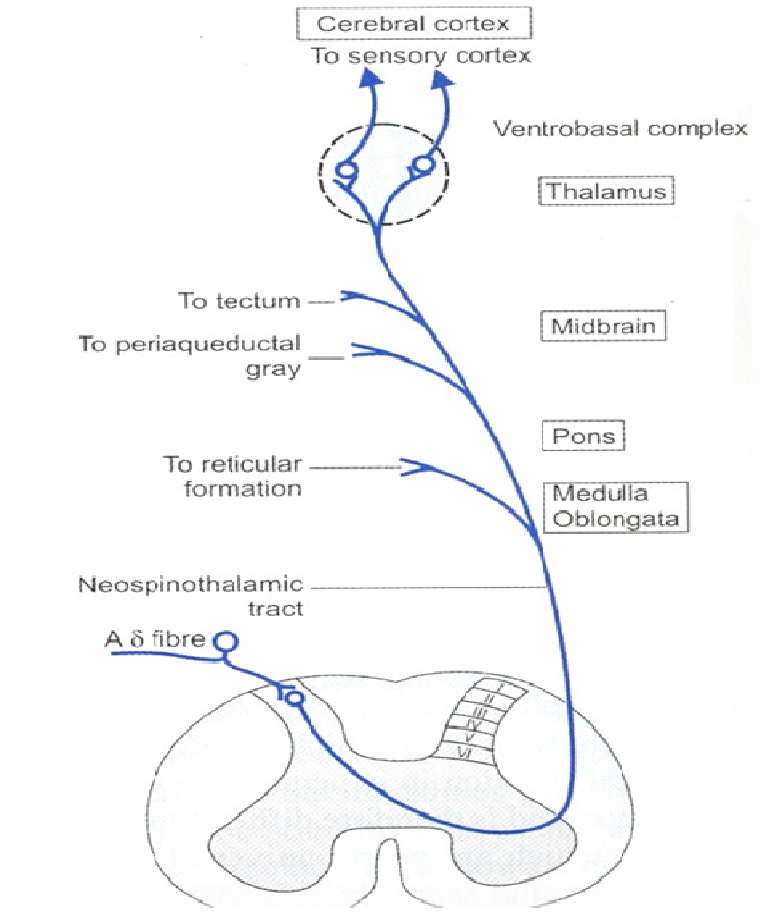


Figure 2: Neospinothalamic Tract

Termination of the Neospinothalamic Tract in the Brain Stem and Thalamus:

A few fibers of the neospinothalamic tract terminate in the reticular areas of the brain stem, but most pass all the way to the thalamus without interruption, terminating in the ventrobasal complex along with the dorsal column–medial lemniscal tract for tactile sensations. A few fibers also terminate in the posterior nuclear group of the thalamus. From these thalamic areas, the signals are transmitted to other basal areas of the brain as well as to the somatosensory cortex.

Paleospinothalamic Pathway for Transmitting Slow Pain:

The paleospinothalamic pathway is a much older system and transmits pain mainly from the peripheral slow type C pain fibers, although it does transmit some signals from type A delta fibers as well. In this pathway, the peripheral fibers terminate in the spinal cord almost entirely in laminae II and III of the dorsal horns, which together are called the substantia gelatinosa, as shown by the lateral most dorsal root type C fiber in figure 3. Most of the signals then pass through one or more additional short fiber neurons within the dorsal horns themselves before entering lamina V, also in the dorsal horn. Here the last neurons in the series give rise to long axons that mostly join the fibers from the fast pain pathway, passing first through the anterior commissure to the opposite side of the cord, then upward to the brain in the anterolateral pathway.[10]

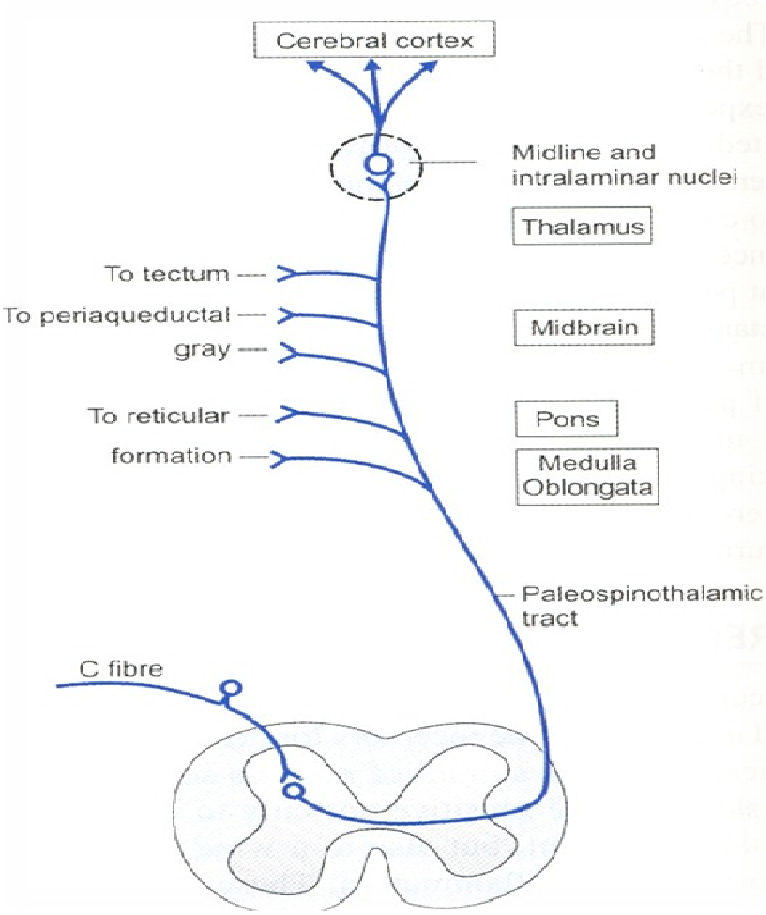


Figure 3: Paleospinothalamic tract

Projection of the Paleospinothalamic Pathway (Slow-Chronic Pain Signals) into the Brain Stem and Thalamus:

The slow-chronic paleospinothalamic pathway terminates widely in the brain stem as shown in figure 3 only one tenth to one fourth of the fibers pass all the way to the thalamus and the rest terminate in one of the three areas:

(1) The reticular nuclei of the medulla, pons and mesencephalon;

(2) The tectal area of the mesencephalon deep to the superior and inferior colliculi;

(3) The periaqueductal gray region surrounding the aqueduct of Sylvius.

These lower regions of the brain appear to be important for feeling the pain, because animals in whom the brains have been sectioned above the mesencephalon to block pain signals from reaching the cerebrum still suffer from pain when any part of the body is traumatized. From the brain stem pain areas, multiple short-fiber neurons relay the pain signals upward into the intralaminar and ventrolateral nuclei of the thalamus and into certain portions of the hypothalamus and other basal regions of the brain.[10]

Theories of pain:

- **The Specificity Theory**

The fundamental tenet of the Specificity Theory is that each modality has a specific receptor and associated sensory fiber (primary afferent) that is sensitive to one specific stimulus.

- **The Pattern Theory**

The theory stated that any somaesthetic sensation occurred by a specific and particular pattern of neural firing and that the spatial and temporal profile of firing of the peripheral nerves encoded the stimulus type and intensity

- **The Intensity Theory**

Pain occurred in any sensory system when sufficient intensity was reached rather than being a stimulus modality.[11]

- **Gate Control Theory:**

Ronald Melzack and Patrick Wall (1965) proposed that the gate in the spinal cord is the substantia gelatinosa in the dorsal horn, which modulates the transmission of sensory information from the primary afferent neurons to transmission

cells in the spinal cord. This gating mechanism is controlled by the activity in the large and small fibers. Large-fiber activity inhibits (or closes) the gate, whereas small-fiber activity facilitates (or opens) the gate. When nociceptive information reaches a threshold that exceeds the inhibition elicited, it "opens the gate" and activates pathways that lead to the experience of pain and its related behaviors as shown in figure 4.[11]

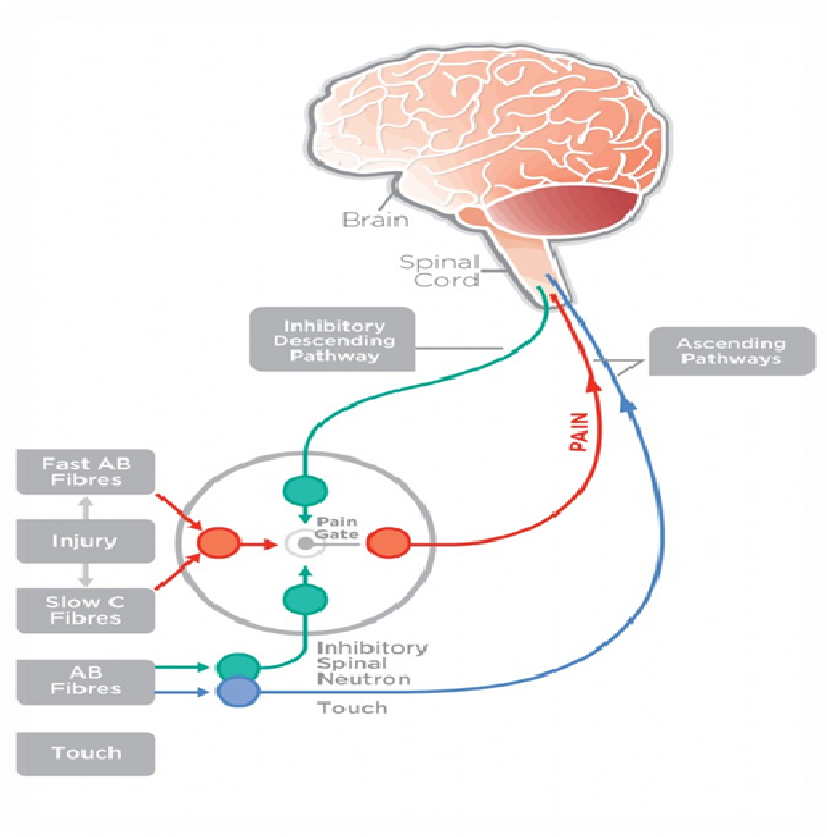


Figure 4: Gate control theory

Perception of pain

The pain impulses entering the brain stem reticular formation, the thalamus, and other lower brain centers cause conscious perception of pain. The cortex plays a special role in interpreting pain quality, even though pain perception might be principally the function of lower centers.[10]

Assessment of pain:

Valid and reliable assessment of pain is essential for effective pain management. The nature of pain makes objective measurement impossible. Acute pain can be reliably assessed with single dimensional tools such as numeric rating scales or visual analogue scales. Chronic pain assessment and its impact on physical, emotional, and social functions require multidimensional qualitative tools and health-related quality of life instruments.[12]

Single dimensional methods:

Pain is a complex experience involving sensory, emotional, psychological and social factors. The subjective nature of pain explains the difficulty with its measurement. The most commonly used pain evaluation tools are single dimensional and includes Verbal description scale, Visual analogue scale and Pain faces scale.

Verbal Description Scale:

This is a simple five-point scale, wherein words are used to assess the degree of pain. Melzack and Torgerson introduced the following scale for pain intensity.[13]

No pain	Mild	Moderate	Severe

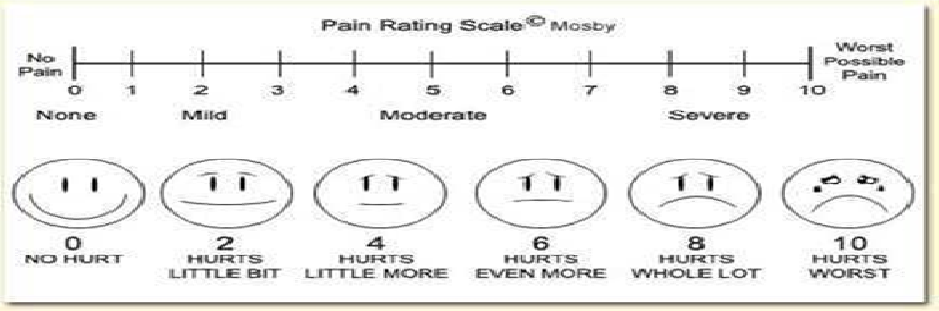
Visual Analogue Scale (VAS):

Currently, the most commonly used method; first described by Aitken is 1966. In this method, the subject makes a mark on a 10 cm line – horizontal or vertical, one end of which is marked as "No pain" and the other as "The worst pain one can imagine". Zero indicates patient has no pain and 10 refer to maximum pain. The position of the mark on the line measures how much pain the subject experiences. 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.[12]

0 ___1___2____3____4____5____6____7____8____9___ 10

Pain faces scale:

This rating scale is recommended for children aged 3 years and older. The child is asked to choose the face that best describes his or her own pain, and notes the appropriate number.



Multi-dimensional methods:

Mc Gill pain Questionnaire (MPQ)

The McGill Pain Questionnaire is used to evaluate a person experiencing pain. It can be used to monitor the pain over time and to determine the effectiveness of any intervention. It was developed at by Dr. Melzack at McGill University in Montreal Canada and has been translated into several languages. Other questionnaires are Dartmouth pain questionnaire (DPQ) and Haven-Yale pain questionnaire (HYPQ). 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.[14]

Behavioral rating scale

The behavioral pain assessment scale is designed for use with non-verbal patients unable to provide self-reports of pain. Observe the patient for 10 minutes. Assess the patient on the four behaviors (restlessness, tense muscles, frowning/grimacing, patient sounds from none-severe). Obtain a pain score based on the highest behavior observed.

Functional activity scale

This is an activity-related score. The patient is asked to perform an activity related to their painful area (for example, deep breathe and cough for thoracic injury or move affected leg for lower limb pain).

The patient is observed during the chosen activity and scored A, B or C.

A – No limitation meaning the patient's activity is unrestricted by pain

B – Mild limitation means the patient's activity is mild to moderately restricted by pain

C - Severe limitation means the patient ability to perform the activity is severely limited by pain

CHEOPS scoring - pediatrics

The CHEOPS (Children's Hospital of Eastern Ontario Pain Scale) is a behavioral scale for evaluating postoperative pain in young children. It can be used to monitor the effectiveness of interventions for reducing the pain and discomfort.[12]

Complications of post-operative pain:

Cardiovascular: Tachycardia, increased myocardial oxygen consumption, myocardial ischemia, altered regional blood flow, deep-vein thrombosis and pulmonary embolism

Respiratory: Reduced lung volumes, atelectasis, decreased cough, sputum retention, infection and hypoxemia

Gastrointestinal: Decreased bowel motility

Genitourinary: Urinary retention

Neuroendocrine/metabolic: Increased catabolic hormones like glucagon, growth hormone, Vasopressin, aldosterone, renin and angiotensin. Anabolic hormones like insulin, testosterone are raised. This leads to catabolic state with hyper glycaemia, increased protein breakdown, negative nitrogen balance which impaired wound healing.

Musculoskeletal: Muscle spasm, immobility and muscle wasting leading to prolonged recovery of function.

Psychological: Anxiety, fear, sleep deprivation leading to increased pain.

Central nervous system: Chronic (persistent) pain due to central sensitization.[15]

Post-operative pain management:

Modes of analgesia:

1. **Preemptive analgesia**

Preemptive analgesia is defined as a treatment that is initiated before surgery in order to prevent the establishment of central sensitization evoked by the incision and inflammatory injuries occurring during surgery and in the early postoperative period. It has 'protective' effect on the nociceptive system. Preemptive analgesia has the potential to be more effective than a similar analgesic treatment initiated after surgery. Thus preemptive analgesia can reduce immediate postoperative pain and also prevent the development of chronic pain by decreasing the altered central sensory processing.[16]

2. **Multimodal analgesia**

It is defined as two or more analgesic agents with different mechanism of action or techniques (includes non – pharmacological measures) used in combination to produce additive or synergistic analgesia for the control of post-operative pain. The benefits of this approach are reduction in the total dose of analgesia required in the post-operative period, improvement in pain relief, fewer adverse effects, early discharge from the hospital and decreased cost.[17]

3. **Patient controlled analgesia (PCA)**

Patient-controlled analgesia is a technique that provides effective postoperative pain relief. Using PCA, patients controls the application of pre-programmed doses of local anesthetics or opioids, via an indwelling catheter, which can be placed in different regions of the body depending upon the type of surgery. Infusions are controlled either by a staff-programmed electronic pump or a disposable

elastomeric pump. Morphine is the most commonly used drug in the dose of 1 – 1.5 mg with a lock out period of five to ten minutes.[18]

The common methods used for pain relief are pharmacologic and non-pharmacologic.

A. Pharmacological Management:[8]

1. Opioid analgesics

Opioids act as agonists on stereospecific opioid μ, δ and κ receptors occurring at presynaptic and postsynaptic sites within the CNS and in the peripheral tissues. Opioids mimic the actions of endogenous ligands by binding to opioid receptors, thus resulting in the activation of pain-modulating (anti nociceptive) systems (figure 5).

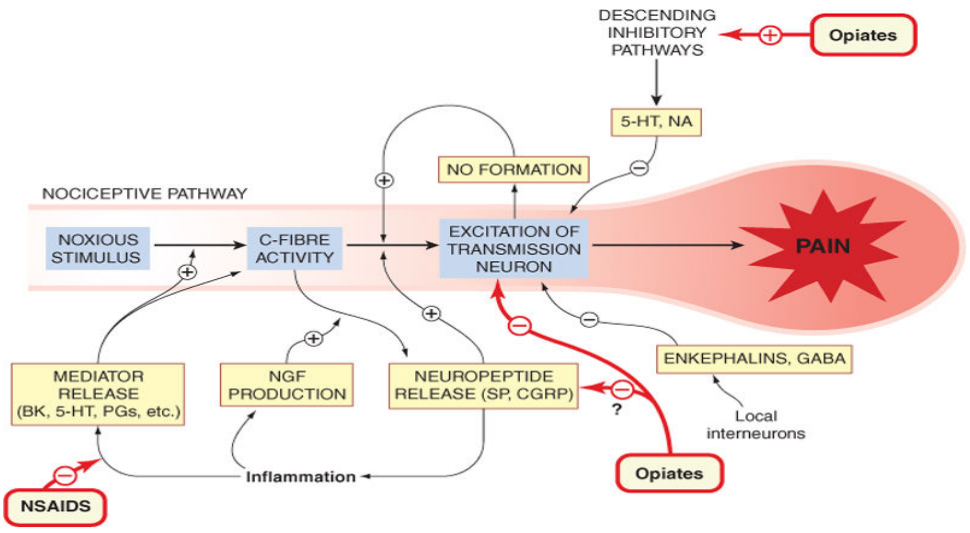


Figure 5: Nociceptive pathway

2. Non – opioids analgesics

NSAIDs are the most commonly used drugs because of their anti-inflammatory, analgesic and antipyretic properties. Its action is mediated through inhibition of cyclooxygenase enzymes 1 and 2, which convert arachidonic acid to prostaglandins, responsible for both peripheral and central sensitization.

3. **Local anesthetics**:

Continuous infusion of local anesthetics by epidural route results in effective pain relief and is recommended after major thoracic, abdominal and orthopedic surgeries for enhanced recovery. Addition of opioids to epidural local anesthetics improves analgesia. Local anesthetics may also be administered into the surgical wound (as continuous wound infusion), or intraperitoneal instillation or intra articular administration. They may also be used for peripheral nerve blocks like paravertebral, intercostal or intraperitoneal in order to provide postoperative pain relief.

4. **Other pharmacological modalities**:

Magnesium by blocking (N-methyl-D-aspartate) NMDA receptor prevents central sensitization and provides post-operative pain relief. Intrathecal and epidural administration of neostigmine is effective in preventing postoperative pain. Adenosine has anti-nociceptive and anti-hyperalgesic properties in surgical patients. A variety of other drugs like cannabinoids and glucocorticoid also have a role in treatment of postoperative pain.

B. Non – pharmacological measures:[8]

Transcutaneous electrical nerve stimulation (TENS) applied with a relevant, strong, sub noxious intensity and adequate frequency in the wound area may reduce analgesic consumption in the postoperative period. Acupuncture is another non-pharmacological means which may prove to be of value in acute pain management especially in the postoperative period.

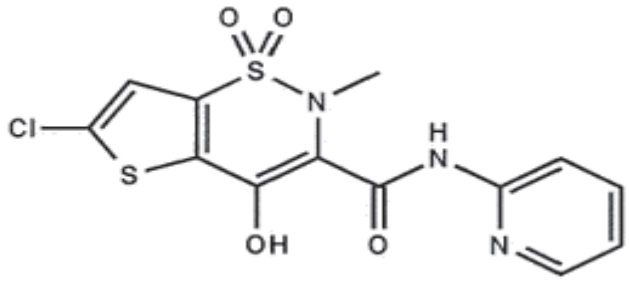
PHARMACOLOGY OF LORNOXICAM

Introduction:

Lornoxicam, a congener of tenoxicam, is a new NSAID belonging to the oxicam class. It has a strong analgesic and anti-inflammatory activity compared to other NSAIDs with a wide range of application in painful and/or inflammatory conditions, including postoperative pain and rheumatoid arthritis.[19] The analgesic activity is comparable to opioids.[20]

Physio-chemical characteristics:

The active drug substance is 6-chloro-4-hydroxy-2-methyl-N-2-pyridyl-2H-thieno-[2, 3-e]-1, 2-thiazine-3-carboxamide-1, 1-dioxide (Figure 6). It is present as a yellow crystalline solid with a pKa of 4.7. It is highly ionized at physiological pH and relatively low lipophilicity limits its distribution to fatty tissues. It has a molecular weight of 371.82 Da[21].



(C13H10ClN3O4S2)

Figure 6: Chemical structure of Lornoxicam [21]

Mechanism of action:

Lornoxicam (chlortenoxicam) inhibits prostaglandin (PG) synthesis by inhibiting cyclooxygenase enzyme (COX-1 and COX-2). It inhibits both the isoforms in the same concentration range i.e. COX-1/COX-2 = 1 resulting in balanced inhibition of both the enzymes (figure 7). COX-1 is a constitutive enzyme expressed in many cells as a house keeping enzyme and provides homeostatic prostaglandins. COX-2 is an inducible enzyme and is expressed at the onset of inflammation in many cell types involved in inflammatory response. Prostaglandins are involved in physiological functions like intestinal motility, vascular tone, renal function, gastric acid secretion. It mediated fever, pain and all phases of inflammatory events.[22]

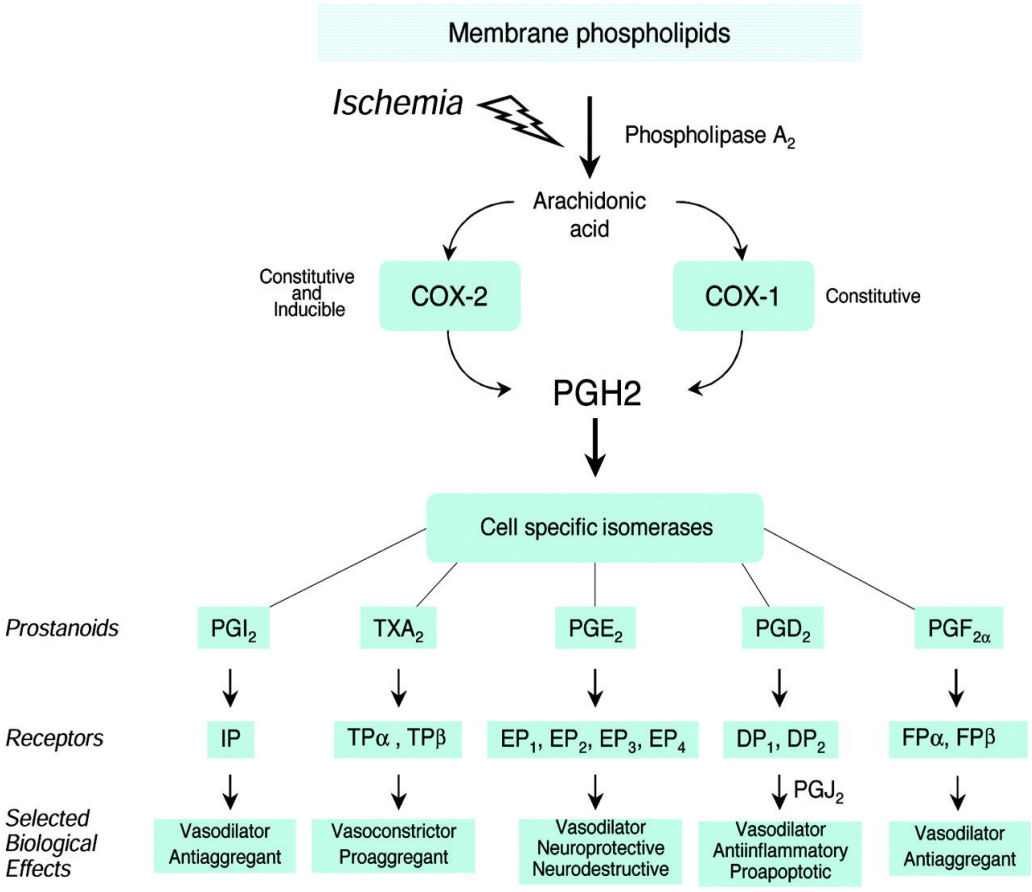


Figure 7: Mechanism of action of NSAIDs

It inhibits polymorphonuclear (PMN)-leukocyte migration, release of superoxide from human PMN-leukocytes and platelet derived growth factor (PDGF) from human platelets. It stimulates the synthesis of proteoglycans in cartilage in tissue culture. It also increases endogenous dinorphin and beta-endorphin levels promoting central analgesic and anti-inflammatory effects by inhibiting the synthesis of prostaglandins.[23] Its peripheral analgesic effects may be mediated through nitric oxide, cGMP and the opening of K^+ channels.[24, 25] It has also shown marked inhibitory activity on endotoxin induced IL-6 formation in Tamm-Horsfall Protein 1(THP 1) monocytes with less activity on tumor necrosis factor (TNF) alpha and interleukin 1 (IL-1).[26]

Pharmacokinetics

Absorption and distribution:

Lornoxicam is absorbed rapidly and almost completely from the gastro-intestinal tract with an oral bioavailability of 90-100%. Food reduces the absorption of the drug. Peak plasma concentration is achieved within 2.5 hrs following oral use. On repeated administration, Cmax increases in a dose dependant manner without accumulation. Almost 99% is protein bound exclusively to albumin. It readily penetrates into synovial fluid.[27] Lornoxicam is found in the plasma in unchanged form and as hydroxylated metabolite which is pharmacologically inactive. It has a relatively short plasma half-life of 3 to 5 hours.[28]

Metabolism and elimination:

CYP2C9 has been shown to be the primary enzyme responsible for the metabolism of the lornoxicam to its major metabolite, 5'-hydroxylornoxicam which does not undergo entero-hepatic circulation. Approximately 2/3rd is eliminated via the

liver and 1/3rd via the kidneys as an inactive substance with a half-life of about 11 hours.[29]

Uses:

Analgesia: Acute and Chronic Pain

Its analgesic potency in pain exceeds that of tenoxicam and piroxicam by approximately 12 and 13 fold respectively; whereas it is 4 to 6 fold more potent as compared to indomethacin and diclofenac. Intravenous lornoxicam (8mg) has been shown to be as effective as morphine (20mg), pethidine (50mg) and tramadol (50mg) in the treatment of postoperative pain.[23] The duration of analgesic effect of lornoxican is approximately 4.5 hrs with maximum pain relief occurring at approximately 2 hrs. The analgesic effects of parenteral lornoxicam is not immediate as some time is required for inhibition of the arachidonic acid pathway. Thus pre-operative administration may be more appropriate for procedures requiring less than 2 hrs.

Lornoxicam has been shown to produce dose related analgesia, with 16 mg and 32 mg being significantly superior to 4 mg with respect to pain relief. It is a useful agent in the treatment of acute traumatic painful conditions such as fractures.[30] Lornoxicam is also effective in acute sciatica, lumbosciatica and chronic low back pain. Lornoxicam can decrease the opioid requirement when used as an adjunctive analgesic in patients with cancer pain. It decreases the number of headache episodes and also reduces the analgesic intake in migraine attacks.[30-32]

Anti-Inflammatory effects:

In osteoarthritis, 8mg twice daily relieves pain and functional disability. Other area where lornoxicam is found useful is ankylosing spondylitis and rheumatoid arthritis.[33] Anti-inflammatory and antipyretic effects of lornoxicam include prevention

of the degenerative boneloss seen in chronic inflammation by inhibiting polymorphornuclear leucocyte migration (for this effect an additional dose of 0.1 mg/kg is required). Antipyretic effect is observed at a dose 10 fold higher than that required for inflammation.[34]

Dosage and Route:

It is available for oral and parenteral use. Its oral dose is 4mg thrice daily or 8 mg twice daily. Quick-release formulation is also available. It is available in powder form as vial of 8mg both for intramuscular as well as intravenous use twice daily. The powder is to be dissolved in 2ml of water for injection immediately prior to use. Maximum dose 24 mg/day.[23]

Adverse effects:

Lornoxicam combines the high therapeutic potency of oxicams with an improved gastrointestinal toxicity profile. The most common side effects reported with the regular use of oral lornoxicam include dizziness, headache, abdominal pain, diarrhea, nausea, vomiting and indigestion. Following an injection, most commonly reported adverse effects are headache, flushing, insomnia and redness and irritation at the injection site. Severe but seldom side effects include bleeding, bronchospasms and the extremely rare stevens-johnson syndrome.[23]

Drug Interaction:

- Clonazepam and diazepam inhibit metabolism of lornoxicam. Concomitant administration of lornoxicam and anticoagulants or anti-platelet agents prolong the bleeding time. [23]

- Cimetidine co-administration inhibits elimination of lornoxicam resulting in significant increase in steady state Cmax and AUC (Area under curve) values and a reduction in apparent plasma clearance.[35,36]
- Lornoxicam displaces glibenclamide from its protein binding site leading to enhanced glibenclamide effect.[37]
- Lornoxicam decreases the plasma digoxin clearance and increases methotrexate concentration.[38]

Contra-indications:

The drug is contraindicated in patients with salicylate sensitivity, gastrointestinal bleeding, bleeding disorders and severe impairment of heart, liver or kidney function. Lornoxicam is not recommended during pregnancy and breastfeeding and is contraindicated during the third trimester of pregnancy. Caution is recommended when using lornoxicam in patients with impaired renal function (although dosage adjustment does not appear to be necessary) and in those receiving warfarin, oral sulphonylureas, loop or thiazide diuretics, or digoxin.[23]

PHARMACOLOGY OF PARACETAMOL

Introduction:

Paracetamol (N-acetyl-p-aminophenol; Acetaminophen) was first described as an analgesic and antipyretic by Von Mering in 1893. In the 1940s Brodie and Axelrod confirmed its analgesic and antipyretic activity.[39]

Chemistry and Structure:

N-(4-hydroxyphenyl) acetamide

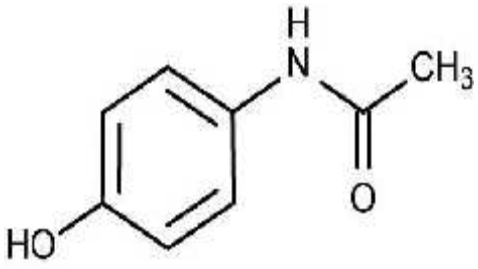


Figure 8: Chemical structure of paracetamol [40]

The molecular weight of paracetamol is 151.2 g/mol. It is both water and lipid-soluble, weak organic acid with a pKa of 9.5. Thus, it is unionized over the physiological range of pH.[4] Paracetamol consists of a benzene ring core, substituted by one hydroxyl group and the nitrogen atom of an amide group in the para (1, 4) pattern.[41]

Mechanism of action:

Analgesic effects:

The analgesic effect of paracetamol is well established but its site and mode of action have not been clearly elucidated. Its analgesic effect is probably produced by inhibiting the prostaglandin synthesis in the central nervous system and elevating

the pain threshold. Recent research suggests that it inhibits a specific site on the prostaglandin H_2 synthase (PGHS) molecule, the 2 isoforms of which are PGHS1 and PGHS2, also referred to as COX-1 and COX-2 (figure 7). PGHS has 2 active sites: the COX site and the peroxidase (POX) site. Paracetamol acts as a reducing substrate at the POX site, while other NSAIDs bind at the COX site noncovalently, obstructing the entry of arachidonic acid. Paracetamol inhibit prostaglandin synthesis in different cell and tissue types to varying capacities. The cell selectivity is thought to be derived from sensitivity to the ambient peroxide levels in various cell types. The central analgesic and antipyretic effects of paracetamol may be exerted through PGHS inhibition within vascular endothelial cells and neurons, where peroxide concentrations are low. In activated leukocytes and platelets, where peroxide concentrations are high, paracetamol is prevented from affecting inflammation and platelet thrombosis.[42]

Another recently proposed hypothesis suggests that paracetamol is mediated by indirect activation of cannabinoid CB_1 receptors, as evidenced by complete inhibition of the analgesic effects of paracetamol in the presence of CB_1-receptor antagonists.[43] Other suggested mechanisms of action include modulation of the serotoninergic and opioid systems, inhibition of nitric oxide generation and hyperalgesia induced by substance P.[44]

Antipyretic Effects:

In animal models, a putative cyclooxygenase (COX) isoenzyme, COX-3, has been suggested as the target for the analgesic and antipyretic effects of paracetamol.[45] However, there is no evidence that humans express COX-3. Therefore, there is no basis for postulating that COX-3 play a role in the mechanism of action of paracetamol in humans.[46] Studies have shown that endogenous pyrogens produced by

leukocytes cause an elevation of prostaglandin E in the cerebrospinal fluid. Paracetamol reduces fever by blocking the formation and release of prostaglandins in the central nervous system and inhibiting the action of endogenous pyrogens at the hypothalamic thermoregulatory centers.[47]

Pharmacokinetics:

Absorption:

Paracetamol absorption from stomach is negligible but very rapid from small intestine. Absorption is by passive transport. It undergoes first-pass metabolism, the peak concentration is reached in 30 to 60 minutes and the plasma half-life is about 2 hours after therapeutic doses. The duration of the action is 4 – 6 hours. The usual therapeutic doses produce plasma concentration of 5 to 20 µg/ml. After 8 hours, only small amount of unchanged paracetamol is detectable in plasma. Paracetamol absorption is dependent on the rate of gastric emptying, therefore any drug, disease, or other condition which alters the rate of gastric emptying may influence the rate of paracetamol absorption.[48]

Distribution:

Paracetamol is distributed to most of the tissues and fluids, reaching a tissue: plasma concentration ratio of one in all tissues except fat and cerebrospinal fluid. At normal therapeutic dose, paracetamol is slightly bound to plasma proteins where during acute intoxication only 20 to 50% may be bound. The apparent volume of distribution of paracetamol is about 1 L/kg and is similar in healthy subjects, children and elderly. The volume of distribution of paracetamol is more in men than in women (0.99 and 0.86 l/kg).[48]

Metabolism and excretion:

Paracetamol is metabolized by microsomal enzymes in the liver, with 85–90% of the drug undergoing glucuronidation and sulfation to inactive metabolites that are eliminated in the urine. A smaller amount is conjugated with cysteine and mercapturic acid. Only 5% of the drug is eliminated unchanged in the urine.[41] A small proportion of paracetamol undergoes CYP-mediated N-hydroxylation to form N-acetyl-p-benzoquinoneimine (NAPQI), a highly reactive intermediate. This metabolite normally reacts with sulfhydryl groups in glutathione (GSH) and thereby is rendered harmless as shown in figure 9. However after ingestion of large dose of paracetamol, the metabolite is formed in large amount sufficient to deplete hepatic GSH and contributes to toxic effects.[47] Total urinary recovery of paracetamol in 24hrs is reported to be 71.5 – 95%, as free and/or conjugated. The clearance ranges between 11.8 - 22.3L/h and the elimination half-life is reported to be between 1.9 - 4.3 hrs.[41]

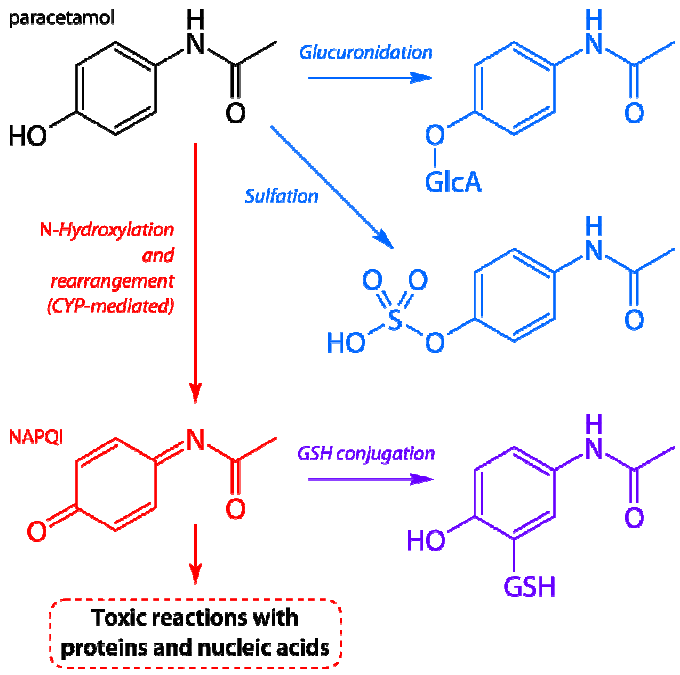


Figure 9: Metabolism of paracetamol

Therapeutic uses:

In most countries, paracetamol is the most commonly used analgesic-antipyretic drug in children. The paracetamol has a ceiling effect at the oral dose of 1000 mg in adults. Further increase in dosage do not produce further increase in the analgesic activity. The analgesic-antipyretic effect of a dose of paracetamol lasts for 3–4 hrs. Paracetamol is indicated for mild-to-moderate pain, such as those due to headache, cold, flu, muscle aches, sprains, backache (including low back pain), dysmenorrhea, minor arthritis pain and toothache.

Paracetamol is the drug of choice for treating mild to-moderate, non-inflammatory conditions in patients who are prone to gastric damage, preferable to aspirin in patients receiving anticoagulants or in patients with coagulation disorders. Paracetamol, at oral doses of 15–20 mg/kg every 4 hour, is the mainstay of treatment in childhood headache; since rectal absorption is variable, doses up to 45 mg/kg may be required for this route of administration. Paracetamol has been shown to be effective in the treatment of moderate pain associated with minor surgical procedures.

The dose of 1000 mg was effective up to 5 hrs after oral surgery, although pain relief was maximal at 1 to 2 h after administration and was shown to be an effective treatment for extraction of impacted third molars and for various other oral surgeries, including difficult extractions, alveolectomy, multiple extractions, apicoectomy, biopsy, and deep gingival curettage.

Paracetamol must be considered as a safe alternative to NSAIDs for the relief of mild to -moderate pain in elderly patients, in patients with kidney disease, hypertension and congestive heart failure. It can also antagonize the platelet inhibition induced by low dose aspirin and lessens its cardioprotective effect.[48] In November 2010, the Food and Drug Administration (FDA) approved the use of intravenous

paracetamol for the management of moderate to severe pain with adjunctive opioid analgesics.[49]

Dosage and routes:

The conventional oral dose of paracetamol is 325–1000 mg (650 mg rectally); total daily dose should not exceed 4000 mg (2000 mg/day for chronic alcoholics). At daily dose of 1000 mg, gastrointestinal adverse effects are less common. Higher doses, accomplish complete inhibition of COXs and may approach the adverse effect profile of NSAIDs, so no more than five doses should be administered in 24 hours.[48]

Adverse effects and toxicity:

Paracetamol usually is well tolerated. Erythematous or urticarial rash may occur and may be accompanied by drug fever and mucosal lesions. Patients who show hypersensitivity reactions to the salicylates only rarely exhibit sensitivity to paracetamol. The most serious acute adverse effect of overdosage of paracetamol is a potentially fatal hepatic necrosis. Renal tubular necrosis and hypoglycemic coma may also occur.

The mechanism by which overdosage with paracetamol leads to hepatocellular injury and death involves its conversion to the toxic N-acetyl-p-benzoquinone imine (NAPQI) metabolite. The glucuronide and sulfate conjugation pathways become saturated, and increasing amounts undergo CYP-mediated N-hydroxylation to form NAPQI. This is eliminated rapidly by conjugation with glutathione (GSH) and then further metabolized to mercapturic acid and excreted into the urine. In the setting of paracetamol overdose, hepatocellular levels of GSH become depleted. The highly reactive NAPQI metabolite binds covalently to cell macromolecules, leading to dysfunction of enzymatic systems, structural and metabolic disarray. Furthermore,

depletion of intracellular GSH renders the hepatocytes highly susceptible to oxidative stress and apoptosis.[48]

Management of paracetamol overdose:

Paracetamol overdose is a medical emergency. Severe liver damage occurs in 90% of patients with plasma concentrations of paracetamol being >300 mg/ml at 4 hours or 45 mg/mL at 15 hours after the ingestion of the drug. Early diagnosis and treatment is essential to optimize outcome. 10% of poisoned patients who do not receive specific treatment develop severe liver damage; 10–20% of these eventually die of hepatic failure despite intensive supportive care. Activated charcoal, if given within 4 hours of ingestion, decreases paracetamol absorption by 50–90% and is the preferred method of gastric decontamination. Gastric lavage is not recommended.

N-acetylcysteine (NAC) is indicated for those at risk of hepatic injury. NAC therapy should be instituted in suspected cases of paracetamol poisoning before blood levels become available. Treatment can be terminated if assay results indicate that the risk of hepatotoxicity is low. NAC detoxify NAPQI. It repletes GSH stores and may conjugate directly with NAPQI by serving as a GSH substitute. Even in the presence of activated charcoal, there is ample absorption of NAC, and neither should activated charcoal be avoided nor NAC administration be delayed because of concerns of a charcoal-NAC interaction.

Adverse reactions to NAC include rash (including urticaria, which does not require drug discontinuation), nausea, vomiting, diarrhea and rare anaphylactic reactions. An oral loading dose of 140 mg/kg is given, followed by the administration of 70 mg/kg every 4 hours for 17 doses. Where available, the intravenous loading dose is 150 mg/kg by intravenous infusion in 100 mL of 5% dextrose over 15 minutes (for those weighing less than 20 kg), followed by 50 mg/kg by intravenous infusion in

250 mL of 5% dextrose over 4 hours, then 100 mg/kg by intravenous infusion in 500 mL of 5% dextrose over 16 hours.[48]

Drug interaction:

- Paracetamol potentiates the anticoagulant effects of acenocoumarol and warfarin, with increased risk of bleeding. The suggested mechanisms are inhibition of the metabolism of oral anticoagulants or interference with the hepatic synthesis of factors II, VII, IX, and X. Patients receiving oral anticoagulants should be cautioned to limit their intake of paracetamol.
- Carbamazepine increases the risk of paracetamol hepatotoxicity by inducing the hepatic metabolism of paracetamol and thus increasing the formation of toxic metabolite.
- Paracetamol have lower bioavailability in epileptic patients receiving enzyme inducing anticonvulsants like phenytoin and fosphenytoin. Paracetamol enhances the urinary elimination of lamotrigine.
- Sulfinpyrazone and carbamazepine increases the risk of paracetamol toxicity by increasing the formation of hepatotoxic metabolite.
- Coadministration of paracetamol with zidovudine may result in neutropenia or hepatotoxicity.
- Concurrent use of alcohol and paracetamol may increase the CYP2E1-mediated metabolism of paracetamol to the highly hepatotoxic metabolite, N-acetyl-p-benzoquinoneimine (NAPQI). In non-alcoholics, NAPQI is detoxified by conjugation with glutathione. In alcoholics, the combination of CYP2E1 induction and glutathione depletion results in NAPQI accumulation. In these subjects, the highest risk of paracetamol toxicity occurs after a brief

(12hrs) abstinence of alcohol, since CYP2E1 is still induced, but alcohol is not present to compete for CYP2E1 metabolism.[39]

Contra-indications:

- It is not advocated for those allergic to its ingredients.
- Not advocated in severe hepatocellular insufficiency and hepatic failure.
- Paracetamol injection especially must be advocated with caution in those with a creatinine clearance <30 ml/minute, chronic alcoholism, chronic malnutrition (low reserves of glutathione stores) and dehydration.
- In pregnancy and lactation it should be given only if strictly required.
- There is inadequate safety data for intramuscular (IM) / IV paracetamol use in neonates, infants and children < 6 months of age.[48]

Materials & Methods

MATERIALS AND METHODS

This prospective study was conducted by departments of Pharmacology and Anesthesiology on patients admitted for elective laparotomy under general anesthesia in R. L. Jalappa Hospital and Research Centre attached to Sri Devaraj Urs Medical College, Kolar. The study was done from January 2013 to June 2014. The study was approved by the Institutional Ethics Committee and written informed consent was obtained from all the patients willing to participate in the study. The patient's details were collected as per the protocol designed for the study. A total of 69 patients were recruited and allocated to two groups – Group P and Group L using computer generated random numbers. It was a single blinded study.

Inclusion Criteria:

1. Patients of either gender aged between 20 – 55 years
2. Patients undergoing elective laparotomy under general anesthesia

Exclusion Criteria:

1. Patient undergoing emergency surgery
2. History of peptic ulcer, gastrointestinal bleeding
3. Renal or hepatic dysfunction, hemorrhagic disorders
4. Hypersensitivity to the test drugs

Method of collection of data:

Name, age, gender, address, educational status, hospital number of patients were recorded at the time of recruitment into the study. Among 69 patients who were recruited were randomly divided into two groups i.e., 35 patients in group P and 34 patients in group L. Patients in group P received a single dose of paracetamol 1gm intravenous infusion and group L received lornoxicam 8 mg intravenous infusion in 100 ml normal saline. Both the drugs were administered as intra-venous infusion over 20 minutes half an hour before skin closure. Duration of surgery was noted.

Pain was assessed using Visual Analogue Scale (VAS), which is divided into 10 equal parts where "0" is no pain and "10" is the worst pain. VAS score is classified as painless (0), mild (1 – 3), moderate (4 – 7), and severe (8 – 10). It was explained to patient prior to surgery and pain was assessed at 2, 4, 8, 12 and 24 hours post operatively. Rescue analgesic tramadol 100mg intravenously was administered to the patients if VAS score was more than three during post-operative period. The time required for first rescue analgesic and total amount required in the first 24hrs after surgery were assessed. Heart rate and blood pressure were monitored immediately after recovery from anesthesia and at 2, 4, 8, 12 and 24 hours post operatively. Sedation was scored using five point scale with zero being alert, 1– sedated, 2 – drowsy, 3 – asleep and 4 – comatose. Sedation was assessed at 2, 4, 8, 12 and 24 hours post operatively. Patient's satisfaction was assessed at the end of 8 hours on a four point scale graded as score 1= poor, 2= fair, 3= good and 4= excellent. Adverse effects were monitored. Injection Ondansetron 8mg was administered intravenously, if the patient complained of nausea and vomiting.

Statistical methods:

Taking into consideration a power of 80% and an alpha error of 5% to detect a difference of 0.4 in total VAS score in 24hours with an effect size of 0.8 and a dropout rate of 10%, the sample size was calculated to be 31 patients per group. The demographic data were analyzed using descriptive statistics. The VAS score was analyzed by repeated measures ANOVA within the group (Bonferroni post hoc test) and unpaired t test between the groups at each interval. Time to first rescue analgesic between the groups was analyzed by using Kaplan-Meier and log-rank test. Total amount of rescue analgesic used between the groups by unpaired t-test. Patient's satisfaction score and sedation score was analyzed between the groups by Mann Whitney U test. Adverse effects was analyzed by chi-square test. P value less than 0.05 was considered to be statistically significant.

Results

RESULTS

Sixty nine patients undergoing elective laparotomy under general anaesthesia were randomized into two groups – Group P (Gp P) and Group L (Gp L). Patients in Gp P received a single dose of injection paracetamol 1gm 100 ml infusion and Gp L received injection lornoxicam 8mg in 100 ml normal saline. Both the drugs were administered as intra-venous infusion over 20 minutes half an hour before skin closure.

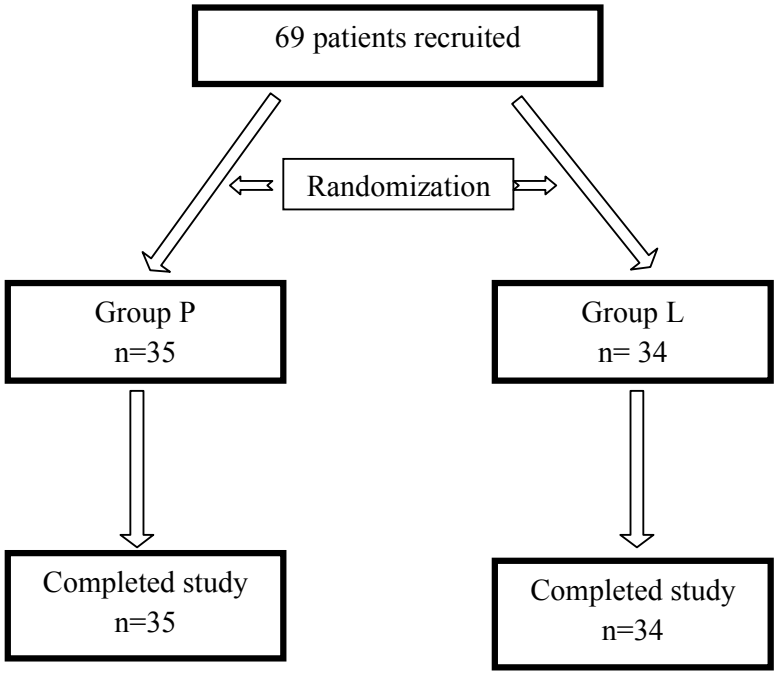


Figure 10: Flow chart representing recruitment of patients

Table 1 – Demographic parameters

Variables	Group P	Group L
Male/Female	24/11	21/13
Age (yrs) (Mean ± SD)	41.60 ± 12.71	37.41 ± 12.18
Duration of surgery (minutes) (Mean ± SD)	136.57 ± 59.28	146.03 ± 58.53

The groups were similar with respect to the demographic variables like age, gender and mean duration of the surgery. Parameters like haemoglobin, blood urea, serum creatinine were in normal range in both the groups and was comparable. Among 69 patients, 45 were males and 24 females with their literacy rate of 53.6%.

Table 2- Comparison of mean VAS scores between two groups

	VAS Score				
	2 hrs	4 hrs	8 hrs	12 hrs	24 hrs
Group P	3.26 ± 1.59	3.34 ± 1.03	3.60 ±1.45	3.66 ±1.06	3.40 ±1.41
Group L	2.68 ± 1.12	3.09 ±0.83	3.56 ±1.19	3.21 ±0.69	2.85 ±0.89
p value	0.08	0.26	0.89	0.04*	0.06

*p = 0.04

Mean VAS score in Gp P was more compared to Gp L at 2, 4, 8, 12 and 24 hours, but it was statistically significant only at 12^{th} hour (p = 0.04) as shown in table 2

Table 3- Graded VAS score in paracetamol and lornoxicam groups

Time intervals	Mild VAS score (1-3)			Moderate VAS score (4-7)		
	Group P (n=35)	Group L (n=34)	p value	Group P (n=35)	Group L (n=34)	p value
2hrs	22	29	0.03*	13	5	0.03*
4hrs	23	26	0.32	12	8	0.32
8hrs	18	17	0.91	17	17	0.91
12hrs	17	25	0.03*	18	9	0.03*
24hrs	23	26	0.32	12	8	0.32

*p=0.03

At 2nd and 12th hours, number of patients having mild VAS scores in Gp P was less than Gp L and moderate VAS score was more in Gp P compared to Gp L which was statistically significant as shown in table 3. Patient's having moderate pain at 2hrs were 37.1% and 14.7% in Gp P and Gp L respectively, but at 8th hour it was 48.6% and 50% of patients.

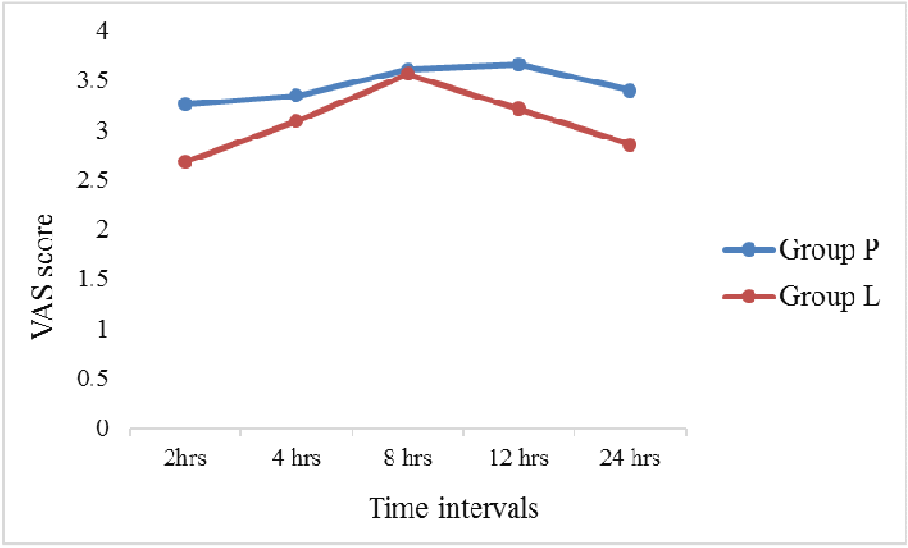


Figure 11: Intensity of post-operative pain in both the groups

In paracetamol group, analysis of VAS score using R-ANOVA followed by Bonferroni's post hoc test was statistically not significant at different intervals, whereas in lornoxicam group it was significant between 2nd and 8th hour only (p=0.03) as shown in figure 11.

Table 4- Rescue analgesic in paracetamol and lornoxicam group

	Group P (Mean ± SD)	Group L (Mean ± SD)	p value
Time to first rescue analgesic (minutes)	351.62 ± 296.92	395.76 ± 273.91	0.543
Total amount of rescue analgesic used (mg)	194.12 ± 73.61	151.52± 56.57	0.018*

*p =0.018

Time to first rescue analgesic was less in Gp P compared to Gp L. Lornoxicam group required significantly lesser amount of rescue analgesic compared to paracetamol group as shown in table 4

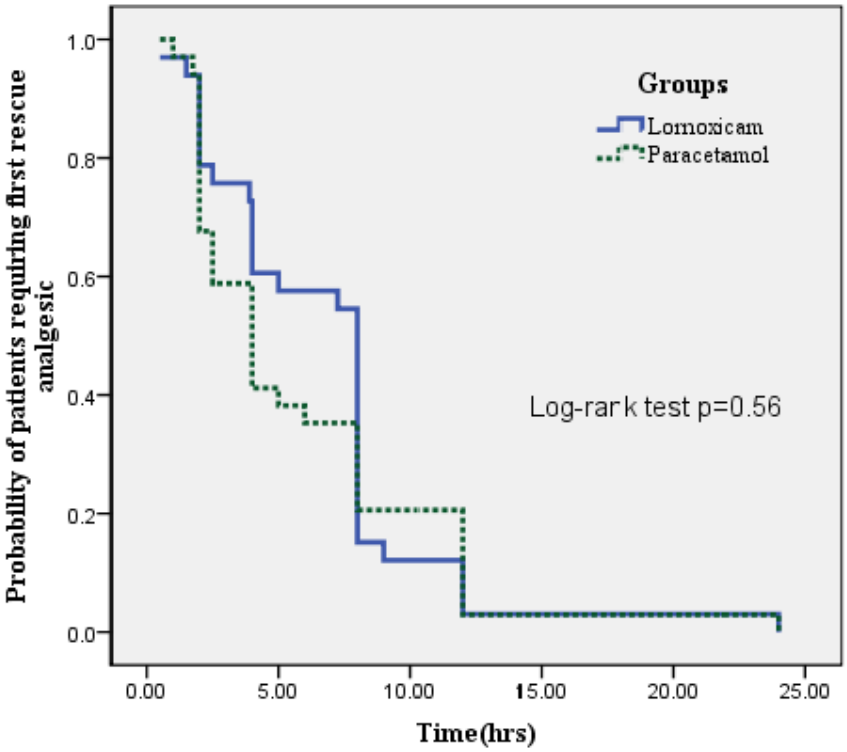


Figure 12: **Kaplan Meier curve for first rescue analgesic between two groups**

Log-rank test, p = 0.56

Kaplan-Meier curve (Figure 12), shows the time from the administration of study drug to the first rescue analgesic postoperatively in patients receiving lornoxicam and paracetamol was not significant.

Table 5– Number of patients requiring rescue analgesic

Number of times patients requiring rescue analgesic	Group P (n= 35)	Group L (n=34)	p value
0	1	1	0.98
1	9	17	0.03*
2	19	15	0.41
3	5	1	0.09
4	1	0	0.32

*p = 0.03

Majority of the patients in lornoxicam group received single rescue analgesic as compared to paracetamol group and it was found to be significant (p=0.03) as shown in table 5

Table 6 – Blood pressure and heart rate of two groups at each time interval

Parameters	Group P				Group L			
	Baseline	2 hrs	8 hrs	24 hrs	Baseline	2 hrs	8 hrs	24 hrs
Systolic BP (mmHg)	119.1 ± 12.4	120.7 ± 10.3	121.4 ± 9.4	122 ± 9.9	118.2 ± 12.4	120.2 ± 2.1	121.1 ± 11.7	122.6 ± 11.6
Diastolic BP (mm Hg)	78.1 ± 7.6	78.2 ± 6.8	78.6 ± 6.9	79.7 ± 6.1	77.6 ± 8.5	79.3 ± 8.2	79.3 ± 8.9	77.4 ± 7.4
Heart rate (beats/min)	84.5 ± 8.8	85.5 ± 8.1	84.5 ± 5.9	83.1 ± 8.0	83.5 ± 7.0	82.7 ± 2.9	83.1 ± 4.6	82.8 ± 4.8

Values: Mean ± SD

The systolic blood pressure was increased in both the groups up to 24 hours from baseline but diastolic blood pressure and heart rate did not alter as shown in table 6.

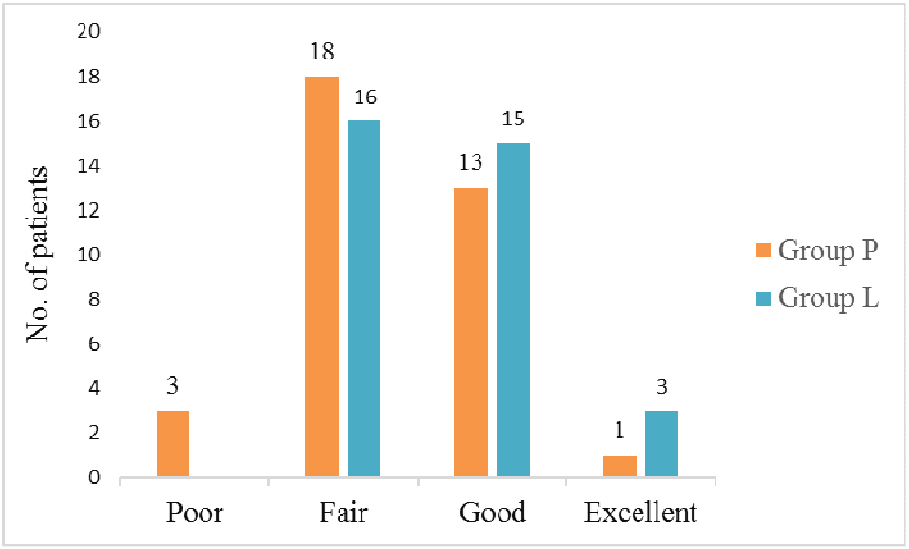


Figure 13: Patient satisfaction score

At the end of 8 hours, 44.1% of patients graded their satisfaction score as good and 8.8% as excellent in lornoxicam group whereas 37.1% as good and 2.8% as excellent in paracetamol group. It was not significant between two groups ($p = 0.133$) as shown in figure 13. All patients had sedation score of zero in both the groups.

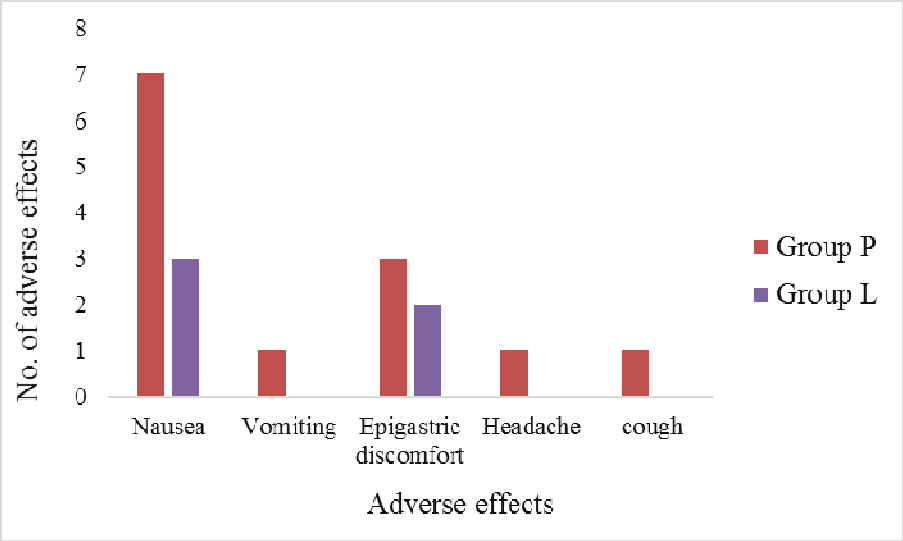


Figure 14: Adverse effects in both the groups

Total number of patients showing adverse effects were 10 in Gp P and 5 in Gp L. Number of adverse effects noted were 13(37.1%) and 5(14.7%) in Gp P and Gp L respectively as shown in figure 14. The most common adverse effect in both the groups was nausea, otherwise the drugs were well tolerated. Adverse effect compared between two groups was not significant, p = 0.16.

Discussion

DISCUSSION

Postoperative pain is a subjective sensation which varies from person to person depending upon psychosomatic personality, age, nature and type of surgery.[50] Early and effective pain relief in post-operative period is necessary to improve patient comfort and restore patient's daily activities as early as possible.[51] Poorly controlled post-operative pain can lead to increased use of medications, slower recovery and longer hospital stay.[50] Post-operative pain is treated with opioids and N-acetyl-p-benzoquinoneimine (NSAIDs). Opioids are associated with sedation and respiratory depression which needs intensive post-operative monitoring. NSAIDs are devoid of these effects but have the risk of gastrointestinal disturbance and bleeding.[52]

Paracetamol, a NSAID is a safe and effective analgesic for mild to moderate pain.[53] The intravenous formulation is used for management of postoperative pain as monotherapy or as an adjuvant to opioids. The advantage of intravenous paracetamol over oral is ability to cross blood brain barrier quickly and produce analgesic effect within 15-20 minutes and can be used in conditions where oral use is restricted. Intraoperative administration of 1 gm intravenous paracetamol results in an effective plasma level in the early postoperative period compared to an equal dose given orally preoperatively.[54]

Paracetamol 1 gm intravenous infusion has provided statistically significant greater efficacy in treating postsurgical dental pain when compared to oral paracetamol 650 mg.[55] Similarly 1 gm intravenous paracetamol was statistically superior to 500 mg oral formulation in reducing acute pain.[56] Lornoxicam, a NSAID has better efficacy with reduced gastrointestinal adverse effect as compared to other oxicams. This could be due to the shorter half-life of lornoxicam (3–5 h) when

compared to the other oxicams.[51] Intravenous lornoxicam 8 mg was found to be equianalgesic to 20 mg of morphine, 50 mg of pethidine and 50 mg of tramadol.[57]

In this study 69 patients were recruited, 35 received paracetamol 1 gm intravenous infusion and 34 lornoxicam 8 mg intravenous infusion in 100 ml normal saline. The gender distribution was comparable (Table 1). Patients were in age group between 25 - 54 years, which is in concordance with another study by Goel et al where it was between 30 - 45 years.[50] In this age group patients usually present with conditions like hernia, appendicitis, cholelithiasis requiring laparotomy. Number of male patients undergoing laparotomy were more compared to females which was similar to another study.[58]

The duration of surgery was two to three hours in both the groups in our study which was also observed in another study by Murthy et al.[59] This is usually the time required for performing elective abdominal surgeries under general anesthesia. In our study, mean VAS scores recorded at different intervals of time (Table 2) ranged from 3.2 to 3.7 for paracetamol which implies sustained analgesic effect of paracetamol over 24 hrs. In lornoxicam group, it ranged between 2.7 to 3.5 over 24 hours probably due to early onset and sustained effect.

In the present study, there was no significant difference between the pain scores in patients receiving paracetamol or lornoxicam. In a study conducted by Coskun et al, patients received 8 mg lornoxicam and 1 gm paracetamol intravenously 30 minutes before intubation but they also did not observed significant difference between the two drugs in terms of VAS scores at 2, 4, 8 and 12 hours post operatively following elective abdominal surgeries.[60] Similar observation was noticed in another study using the same study drugs in the same dose for shock wave lithotripsy.[61]

In our study, patients with moderate pain at 2 hours were more in paracetamol group compared to lornoxicam group, which probably denotes early onset of action of lornoxicam (Table 3). The peak effect of lornoxicam and paracetamol were 20-30 minutes and 1 hour respectively as per literature.[62] One gram intravenous paracetamol was observed to be equally efficacious as other NSAIDs like ketorolac, diclofenac, naproxen, ibuprofen, bromfenac, parecoxib for control of post-operative pain due to major abdominal and orthopaedic surgeries.[62-64] But in minor procedures like tooth extraction other NSAIDs were superior to 1 gm intravenous paracetamol.[63] Guzel et al concluded that following oral administration of lornoxicam 8 mg showed lower VAS score compared to oral paracetamol 500 mg at all assessment time intervals after endometrial sampling.[65]

In our study, the mean time to first rescue medication with injection tramadol 100mg intravenous was six hours with paracetamol and six and a half hours in lornoxicam groups (Table 4). Similar findings were observed by Murthy et al, five hours in lornoxicam group and Sinatra RS et al 3 hours in paracetamol group.[60, 66] This shows the duration of action of lornoxicam as 3-5 hours and paracetamol 4-6 hours as documented in literature.[67] Even though their action is of shorter duration, their effect has been observed to last for 24 hours in the presence of rescue analgesic. This can be explained on the basis that majority of patients required only one to two doses of tramadol whose duration of action is 4 to 6 hours.

VAS score remained constant at 8^{th} and 24^{th} hour in patients receiving paracetamol but in lornoxicam group VAS score was less at 24^{th} hour compared to 8^{th} hour. This implies that lornoxicam when administered along with tramadol, have greater analgesic activity compared to paracetamol. In a study conducted by Inan et al in patients undergoing total knee replacement surgery, received morphine as patient

controlled analgesia (PCA) postoperatively. Other group additionally received lornoxicam 16 mg intravenously 15 minutes before surgery and 8 mg postoperatively at 12th and 24th hour. Morphine consumption in patients receiving lornoxicam was significantly lower than in morphine alone at 2, 3, 6, 8, 24, 36 and 48 hours postoperatively.[68]

Patients who received lornoxicam required single dose of rescue analgesic whereas in case of paracetamol two doses of rescue analgesic were administered (Table 5). Dilmen et al compared the analgesic effects of 1 gm paracetamol with 8 mg lornoxicam in patients undergoing surgical repair of lumbar disc hernia. They found that although morphine consumption and pain scores were decreased in patients receiving paracetamol, this difference was not significant compared to those receiving lornoxicam. Both groups had similar morphine consumption over 24hours.[69] Pal et al study observed that paracetamol group required significantly higher amount of rescue analgesic compared to diclofenac in patients undergoing lower abdominal gynecological surgeries.[70]

Blood pressure and heart rates are important indicators of hemodynamic stability, hence in our study they were monitored post operatively upto 24 hours. There was an increase in the systolic blood pressure in both groups, but was not significant. NSAIDs induced increase in systolic blood pressure could be due to inhibition of COX-1 and COX-2 causing depletion of vasodilating prostaglandins leading to water retention and increased total peripheral resistance. Increase in heart rate during the post-operative period could be due to patient's agony with pain.[71] In our study, in both the groups heart rate was within normal limits probably due to intra-operative administration of paracetamol and lornoxicam. The hemodynamic

stability was observed in post-operative period in both the groups as evidenced by the normal heart rate and blood pressure without gross deviations.

More number of patients graded their satisfaction score as good and excellent in paracetamol group compared to lornoxicam group (Figure 13), which is similar to study a conducted by Coskun et al in which 83 % and 100 % of patients graded completely satisfied with paracetamol and lornoxicam respectively.[61] In Gupta et al study, patients in the parecoxib group were more satisfied with the control of postoperative pain compared to paracetamol group.[64]

Commonest adverse effect was nausea in both the groups. In another study the commonest adverse effects observed with lornoxicam were nausea and vomiting accounting to 16.6 % in patients undergoing abdominal hysterectomy.[72] In another study 23.3% patients had nausea and vomiting with paracetamol.[50] In this study, both the drugs were well tolerated and adverse effects were mild.

Conclusion

CONCLUSION

- Postoperative pain management helps to minimize patient discomfort, facilitate early mobilization, faster recovery and reduces risk of deep vein thrombosis.
- Opioids are the main stay for management of postoperative pain, but their side effects such as sedation, constipation, urinary retention and respiratory depression limit their use
- NSAIDs are used in postoperative pain management because of their analgesic, anti-inflammatory properties and relative tolerability. Studies suggested that the addition of NSAIDs reduce opioid requirement but improves analgesia
- NSAIDs used in the study are paracetamol 1gm and lornoxicam 8 mg intravenous infusions in 100 ml normal saline
- The groups were comparable with respect to the demographic variables
- Mean VAS scores in patients who received paracetamol was more than lornoxicam but it was significant only at 12^{th} hour
- Time to first rescue analgesic was less in patients who received paracetamol compared to lornoxicam but it was not significant
- Lornoxicam group required significantly lesser amount of rescue analgesic
- More percentage of patients graded their satisfaction score as good and excellent in lornoxicam group. The most common adverse effect in both the groups was nausea but both the drugs were well tolerated
- We observed that intra-operative administration of 1 gm intravenous paracetamol is non-inferior to lornoxicam for post-operative analgesia.

Summary

SUMMARY

Pain is the most common complaint after abdominal surgery that restricts the physical activity of the patients as well as early recovery. Commonly used pharmacological agents for post-operative pain management are opioid analgesics and non-steroidal anti-inflammatory drugs (NSAIDs). Opioids are associated with unwanted effects like sedation and respiratory depression so NSAIDs which are devoid of these adverse effects are frequently used.

In our study 69 patients undergoing elective laparotomy under general anaesthesia and were randomized into two groups, 35 patients in Gp P received a single dose of paracetamol 1gm intravenous infusion and 34 in Gp L received lornoxicam 8 mg intravenous infusion in 100 ml normal saline. Both the drugs were administered as intra-venous infusion over 20 minutes, half an hour before skin closure.

The analgesic effect of paracetamol and lornoxicam in post-operative pain was assessed using Visual Analogue Scale (VAS) score at different intervals of time post operatively. Rescue analgesic injection tramadol 100mg was administered intravenously if VAS was more than three. Time required for first rescue analgesic, total amount required in the first 24hrs after surgery and patient's satisfaction score at the end of 8 hours were assessed. Adverse effects were monitored.

There were 45 males and 24 females. Mean age of 41.60 ± 12.71 and 37.41 ± 12.18 in Gp P and Gp L respectively. The baseline demographic variables were comparable between two groups. Mean VAS scores in patients who received paracetamol was more than lornoxicam but it was significant only at 12th hour

(p=0.04). Time to first rescue analgesic was less in patients who received paracetamol compared to lornoxicam but it was insignificant. Lornoxicam group required significantly lesser amount of rescue analgesic (p=0.018).

At the end of 8 hours, 37.1 % of patients graded their satisfaction score as good in paracetamol group and 44.1% in lornoxicam group. The common adverse effect in both the groups was nausea but these drugs were well tolerated. Our observation is that intra operative administration of 1 gm intravenous paracetamol is non-inferior to 8 mg lornoxicam for post-operative analgesia following elective laparotomy under general anesthesia.

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Annexures

PROFORMA

Serial No: Date:

OP No:

1. Name:

2. Age/Gender:

3. Educational status:

4. Occupation:

5. Date of Admission:

6. Address with phone no.:

7. Present history:

8. Personal history:

9. General Physical Examination:

    Per abdomen:

    CVS:

    RS:

    CNS:

10. Diagnosis:

11. Date of Surgery:

12. Duration of Anaesthesia:

13. Time of start of surgery:

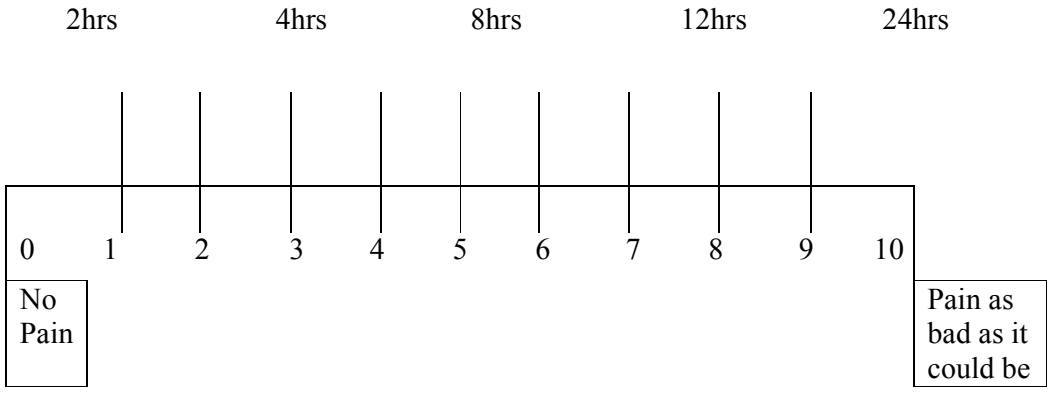
14. Time of end of surgery:

15. Duration of Surgery:

ROUTINE LABORATORY ANALYSIS REPORT

Complete hemogram:		
Bleeding time :		Clotting time :
Fasting blood sugar:		
Blood urea:		Serum Creatinine:
Urine a)Sugar :	b) Albumin :	c) Microscopy:

VISUAL ANALOG SCALE FOR ASSESMENT OF PAIN [0 – 10]



Directions – Ask the patients to indicate on the line where the pain is in relation to the two extremes. Measure from left side to mark

Post-Operative Parameters

	Heart rate	Blood pressure
Baseline		
2hrs		
4hrs		
8hrs		
12hrs		
24hr		

Additional post-operative analgesic - Rescue medication

Additional post-operative analgesic used					Total amount of analgesic used
Drug	Dose mg	Route	No. of doses	Time of drug administration	
Tramadol	100	i.v			

Patient's assessment of the analgesic used (patient satisfaction score) at 8 hours

How would you rate the medication you have received for pain after the operation?

1 = Poor 2 = Fair 3 = Good 4 = Excellent

Sedation Score

Alert = 0, Sedated = 1, Drowsy = 2, Asleep = 3, Comatose = 4

Side effects

	2hrs	4hrs	8hrs	12hrs	24hrs
Nausea					
Vomiting					
Epigastric discomfort					
Any other					

VAS Score [73]

Painless = 0
Mild = 1-3
Moderate=4-7
Severe=8-10

Sedation Score [74]

Alert = 0
Sedated = 1
Drowsy = 2
Asleep = 3
Comatose = 4

Satisfaction score [75]

1 = Poor 2 = Fair 3 = Good 4 = Excellent

Key to master chart

- S. No. - Serial number
- M - Male
- F - Female
- Bl - Baseline
- VAS - Visual Analogue Scale
- DOS - Duration of surgery
- yrs - Years
- h - Hours
- mins - Minutes
- BP - Blood pressure
- P - Poor
- F - Fair
- G - Good
- E - Excellent
- Adverse effects
    - ✓ 1 – Nausea
    - ✓ 2 – Vomiting
    - ✓ 3 – Epigastric discomfort
    - ✓ 4 – Headache
    - ✓ 5 – Cough

Masterchart : Lornoxicam

S.No	OP NO.	Gender	Age In yrs	Education	Occupation	Diagnosis	Hb g/dl	B.urea mg/dl	S.creat mg/dl	VAS score					Heart rate						BP systolic/diastolic												DOS In mins	Rescue medication-Tramadol		Number of rescues					Patient satisfaction score				Adverse effects				
		M/F								2h	4h	8h	12h	24h	Bl	2h	4h	8h	12h	24h	Bl		2h		4h		8h		12h		24h			First Rescue (mins)	Total Amount	0	1	2	3	4	P	F	G	E	2 h	4 h	8 h	12 h	24 h
1	828998	F	35	PUC	Housewife	Cholelithiasis	10.9	25	0.76	7	3	2	4	3	80	80	80	90	82	80	130	80	130	80	120	90	130	90	110	80	110	80	105	90	300				1			1							
2	836409	F	45	illitrate	Agriculture	Ano rectal ca	12.2	30	0.6	2	3	2	3	2	84	86	86	88	82	80	130	90	130	90	130	90	110	70	110	70	118	72	300	150	200			1					1						
3	809077	M	48	illitrate	Agriculture	Incisional hernia	14.5	17	1	1	1	1	1	1	76	82	80	86	76	78	120	80	130	80	130	80	120	80	122	80	120	80	240	NA	NA	1								1					
4	879576	M	55	illitrate	Agriculture	Antral ca	11.6	17	0.9	4	2	2	4	3	84	84	86	80	80	88	100	70	130	90	130	90	130	90	130	90	130	80	210	120	200			1				1							
5	878437	F	45	illitrate	Housewife	Incisional hernia	13	17	0.59	3	4	3	3	3	82	86	86	82	84	80	140	90	130	90	130	100	130	100	130	90	130	80	120	120	100		1					1							
6	878227	F	50	illitrate	Housewife	Gall bladder stone	12.6	15	0.42	2	3	4	3	4	80	82	84	82	82	84	120	70	120	80	110	70	110	70	120	80	120	70	210	480	200			1				1				3	3	3	3	3
7	876455	F	50	illitrate	Housewife	Retro peritoneal tumor	14.1	10	0.69	2	3	4	3	2	80	80	84	86	84	80	110	70	110	70	130	70	130	70	130	70	130	70	270	540	100		1					1							
8	896902	M	35	SSLC	Cooley	Right inguinal hernia	12.2	12	0.9	2	3	4	3	3	80	86	82	82	82	86	110	80	120	70	110	80	110	70	120	80	130	90	150	435	100		1					1							
9	901575	M	55	illitrate	Cooley	Lf. Inguinal hernia	11.4	27	0.69	2	4	3	4	3	82	84	88	84	82	82	110	80	110	80	110	70	110	70	110	70	110	70	190	235	200			1				1							
10	916348	M	36	illitrate	Cooley	Appendicitis	18.4	44	1.4	2	4	3	3	4	80	80	80	82	80	80	130	90	130	90	130	90	130	90	130	90	130	80	120	240	200			1				1							
11	909409	M	50	SSLC	Agriculture	Cholelithiasis	13.9	36	1	3	4	3	4	2	78	80	84	90	90	100	130	90	140	90	140	90	146	90	134	92	132	90	150	30	200			1				1							
12	921471	M	23	6th std	Auto driver	Lf. Inguinal hernia	15.9	16	0.65	3	5	3	2	2	94	88	90	94	84	78	130	80	130	76	130	76	130	76	130	80	130	80	90	300	100		1					1							
13	922159	M	23	5th std	Car driver	Cholecystitis	15	59	1.4	2	2	4	3	2	86	82	80	80	80	80	110	60	130	80	110	80	120	80	110	80	110	80	150	480	100		1					1							
14	924231	M	25	10th std	Mechanic	Recurrent peptic ulcer	16	27	1.3	2	3	4	3	4	72	86	82	80	80	80	100	70	110	80	120	80	120	70	120	80	120	80	150	480	200			1				1							
15	929425	M	55	illitrate	Agriculture	Antral ca	12.9	55	0.72	2	2	4	3	4	116	84	84	84	76	92	130	70	146	90	130	80	154	90	140	80	150	90	180	480	200			1				1							
16	930415	M	38	illitrate	Agriculture	Rt inguinal hernia	11.6	33	1	2	3	5	3	2	82	82	82	80	80	82	120	80	120	80	110	80	120	80	120	80	120	80	60	480	100		1						1	1	1	1	1	1
17	929794	M	26	SSLC	Bus driver	Cholecystitis	11.1	22	0.7	3	3	4	3	3	82	80	82	82	86	88	130	80	130	80	130	80	130	80	130	80	140	80	180	480	100		1						1						
18	933254	M	25	illitrate	Tracter driver	Recurrent peptic ulcer	17.6	22	0.5	2	3	5	3	3	88	88	82	96	80	82	110	70	124	80	122	70	126	90	120	70	122	70	110	480	100		1						1						
19	934734	M	20	B com	Student	Sub ac intestobst	12.4	26	0.7	2	3	4	3	3	84	82	80	74	80	76	110	70	110	70	110	70	120	80	120	80	120	80	150	480	100		1						1			1	1	1	1
20	941507	M	23	5th std	Cooley	Intestobst	15.3	52	1	3	5	3	3	3	82	86	86	82	84	80	140	90	130	90	130	90	130	90	130	90	130	80	60	240	100		1						1						
21	942284	F	37	8th std	Housewife	Incisional hernia	12.5	14	0.7	4	3	6	3	2	82	84	82	80	82	84	100	60	110	70	110	70	120	70	120	70	120	70	180	120	200			1				1							
22	942220	F	35	illitrate	Housewife	Sub ac intestobst	11.4	12	0.6	4	3	7	3	2	88	82	86	82	84	86	110	80	110	80	110	70	110	80	110	80	110	80	180	120	200			1					1			3	3	3	3	3
23	954522	F	28	4th std	Housewife	Para umbilical hernia	13.5	22	0.9	2	3	4	3	2	84	82	78	80	82	86	110	80	110	80	120	80	120	80	110	80	110	70	120	480	100		1						1						
24	954470	F	21	8th std	Housewife	Appendicitis	13.7	28	0.9	2	2	3	4	3	90	86	80	80	80	82	130	80	120	80	110	70	110	80	110	80	110	80	95	720	100		1						1						
25	958541	M	50	illitrate	Cooley	Cholelithiasis	10.4	30	1	3	3	3	4	5	82	82	86	88	86	88	110	80	100	70	100	70	100	70	110	70	110	70	180	720	200			1				1							
26	973414	F	30	8th std	Housewife	Incisional hernia	11.2	17	0.4	2	3	2	3	4	82	78	80	78	72	84	120	80	120	70	118	80	110	80	110	80	110	80	120	1440	100		1						1						
27	974698	M	50	illitrate	Agriculture	Rt inguinal hernia	13.9	35	0.7	3	3	5	3	4	82	84	82	80	84	84	120	70	120	80	120	70	120	80	120	70	120	80	180	480	200			1				1							
28	985424	M	27	7th	Cooley	Para umbilical hernia	11.8	14	0.8	3	2	3	5	3	82	82	82	82	82	82	130	80	130	80	130	80	130	80	130	80	130	80	120	720	100		1						1						
29	991968	F	52	8th std	Housewife	Sub ac intestobstr	10.4	42	0.5	2	4	3	4	3	82	82	82	82	82	84	130	80	110	60	110	80	110	70	120	80	120	70	120	240	200			1				1				1	1	1	1	1
30	998528	M	32	illitrate	Cooley	Lf. Inguinal hernia	12.5	30	1.2	5	3	3	4	3	82	82	82	82	82	82	130	90	130	90	130	90	130	90	130	90	130	90	150	120	200			1				1							
31	1002480	F	45	illitrate	Housewife	Cholelithiasis	11.2	24	0.8	3	3	4	3	2	88	76	80	76	72	72	120	80	110	80	120	80	110	70	110	70	110	70	100	480	100		1						1						
32	1003036	M	55	illitrate	Agriculture	Rt inguinal hernia	5.9	29	0.7	2	3	4	3	4	76	76	80	82	82	82	100	80	100	80	130	80	120	80	120	80	120	80	60	480	200			1				1							
33	1003432	M	18	12th std	Student	Appendicitis	13.6	23	0.9	3	4	3	3	2	84	84	84	84	84	84	100	60	100	60	100	60	100	60	100	60	100	60	45	240	100		1						1						
34	1004329	F	30	illitrate	Housewife	Para umbilical hernia	8.2	17	0.4	2	3	4	3	2	82	84	82	82	82	82	100	80	100	80	110	80	120	80	120	80	120	80	120	480	100		1						1						

Masterchart : Paracetamol

S No	OP No	Gender	Age in yrs	Education	Occupation	Diagnosis	Hb g/dl	B.Urea mg/dl	S.creat mg/dl	VAS SCORE					Heart rate						BP												DOS in mins	Rescue medication - Tramadol		Number of resques				Patient satisfaction score				Adverse effects				
		M/F								2h	4h	8h	12h	24h	Bl	2h	4h	8h	12h	24h	Bl		2h		4h		8h		12h		24h			First Rescue (mins)	Total Amount	0	1	2	3	4	P	F	G	E	2h	4h	8h	12h	24h
1	882182	F	55	illitrate	Housewife	Sub ac Inteobst	7.7	23	0.7	4	3	4	3	3	80	76	76	86	86	82	110	80	120	80	100	70	100	70	100	70	100	70	180	60	200			1				1							
2	879624	M	46	10th std	Attender	Ca sigmoid colon	11	19	1.4	3	4	3	2	2	82	72	80	80	80	82	120	80	120	70	120	80	120	80	120	70	120	80	180	300	100		1						1						
3	829755	F	40	6th std	Cooley	Intesobst	13.2	28	0.6	5	3	2	2	1	90	80	86	82	90	86	110	80	110	80	140	80	120	80	130	90	130	80	165	105	300				1				1		4				
4	892356	M	37	12th std	Worker	Rt inguinal hernia	11.3	22	0.9	4	3	3	4	3	84	80	82	82	80	82	130	80	130	70	130	80	130	80	130	80	120	90	90	120	200			1				1							
5	864277	F	54	4th std	Staff	Incision hernia	12.9	35	1.1	3	4	3	4	3	80	84	86	90	82	80	110	80	120	80	120	80	130	90	110	70	120	80	120	240	200			1				1							
6	903057	M	54	Bsc	Agriculture	Ca rectum	10.2	18	0.7	5	3	5	3	6	80	82	80	82	88	80	110	80	110	70	110	80	120	70	120	80	120	70	180	150	200			1				1							
7	907624	M	32	6th std	Cooley	Lf. Inguinal hernia	10.3	19	0.7	3	4	3	4	3	100	96	96	82	78	76	90	60	130	80	108	80	110	80	110	70	110	70	150	360	200			1				1							
8	966528	M	23	illitrate	Cooley	Appendicitis	14.9	28	0.8	6	4	6	4	3	82	80	82	82	84	82	120	80	120	80	120	80	120	80	120	80	120	80	120	120	200			1				1							
9	908647	F	55	illitrate	Agriculture	Colo-colic intuss	13.7	26	0.5	6	3	6	5	6	84	80	84	82	86	82	110	70	110	80	110	80	110	80	120	70	110	70	120	150	400					1		1							
10	902329	M	55	SSLC	Bussiness	Calcucholecystitis	11.4	28	1.1	3	6	3	6	3	82	84	84	82	82	80	140	90	140	90	130	90	140	90	140	90	140	80	150	240	200			1				1							
11	912679	M	31	illitrate	Cooley	Lf. Inguinal hernia	12.4	28	0.6	5	4	6	4	2	86	82	84	82	82	80	120	80	110	80	120	80	120	80	120	80	120	80	120	120	200			1				1							
12	918948	M	18	Bsc	Student	Appendicitis	14.8	35	1	5	4	4	5	4	82	82	82	84	84	84	130	80	110	70	110	70	120	80	120	80	130	90	120	120	200			1				1							1,3
13	915481	F	45	illitrate	Housewife	Incision hernia	4.4	23	0.3	2	3	4	4	3	80	90	84	86	82	82	120	90	140	90	130	90	140	100	130	90	136	88	180	480	200			1					1			1				
14	926222	M	50	illitrate	Milk man	Rt inguinal hern	14.8	19	0.7	5	3	6	2	6	80	84	80	84	74	74	100	60	110	70	110	80	110	80	110	80	110	80	60	120	300				1			1							
15	930148	F	18	illitrate	Housewife	Appidicularabsc	12.8	30	0.6	3	4	3	3	4	84	80	72	72	72	76	110	70	120	80	120	80	120	80	120	80	130	80	150	240	200			1				1							
16	931110	M	50	illitrate	Agriculture	Recurr pep ulcer	11.2	21	0.7	3	5	3	5	3	86	90	88	86	86	86	140	80	140	80	140	80	140	80	140	80	140	80	150	150	200			1				1				1	1	1	1	1
17	936776	F	26	12th std	Housewife	Appendicitis	9.2	25	0.4	2	3	6	3	6	82	84	82	80	84	80	110	80	110	70	110	80	110	70	110	80	110	70	90	480	200			1					1			1	1	1	1	1
18	934421	F	47	10th std	Housewife	Cholilithiasis	12.6	18	0.5	7	3	6	3	6	72	80	80	78	82	76	130	90	124	80	120	80	120	80	140	90	114	80	210	120	300				1		1					1,3	1,3	1,2,3	1,3	1,3
19	945302	M	50	illitrate	Driver	Sub ac intestobst	9.3	53	0.9	4	3	4	3	4	80	84	78	82	84	80	120	80	120	80	110	80	120	80	110	80	110	70	120	120	300				1			1				1	1			
20	953265	M	35	4th std	Cooley	Incision hernia	14.4	20	0.5	3	3	2	3	5	112	90	80	86	82	86	100	60	100	60	120	80	120	80	120	80	110	80	45	1440	100		1					1							
21	953236	M	40	illitrate	Agriculture	Cholilithiasis	13.8	15	0.8	3	3	4	2	3	82	88	86	82	86	88	110	80	120	80	120	80	120	70	120	80	120	80	150	720	100		1					1			5	5	5	5	5
22	945304	M	50	illitrate	Agriculture	Jeju tube block	12.8	30	0.6	4	3	5	3	3	80	82	88	80	82	82	120	70	130	80	120	70	120	70	130	80	130	80	120	120	200			1			1				3	3	3	3	3
23	971411	F	45	6th std	Housewife	Para umbilical her	10.6	33	0.7	1	2	4	2	3	80	82	80	82	80	80	120	80	120	80	120	80	120	80	120	80	120	80	90	480	100		1					1							
24	958392	M	54	4th std	Cooley	Lf Inguinal hernia	12	36	0.7	2	2	3	4	3	80	80	88	86	86	86	130	80	130	80	120	80	120	80	130	80	120	80	120	720	100		1					1							
25	978113	M	50	illitrate	Cooley	Sub ac intestobst	12.2	39	1	2	3	3	5	3	72	84	86	84	86	84	110	70	130	90	100	70	110	70	120	80	130	90	120	720	100		1					1			1	1	1	1	1
26	979628	M	50	illitrate	Mechanic	Rt inguinal hern	11.5	27	0.9	1	2	1	4	2	86	84	82	82	84	82	120	80	120	80	120	80	120	80	120	80	120	80	75	720	100		1					1							
27	980396	M	32	Bsc	Worker	Appendicitis	15.8	10	0.7	2	4	3	4	3	90	96	96	90	86	100	110	80	110	80	130	80	130	90	120	90	130	90	120	240	200				1				1						
28	984281	M	24	10th std	Driver	Ch appendicitis	12.4	27	0.9	1	2	2	4	3	78	84	86	82	82	84	130	80	110	70	120	80	120	80	120	80	120	80	90	720	100		1					1							
29	980007	M	28	2nd std	Cooley	Sub ac intstobst	17.3	20	0.7	4	3	4	3	4	80	80	82	84	82	80	110	80	110	80	110	80	110	80	110	80	110	80	360	120	300				1			1							
30	985404	M	50	8th std	Cooley	Lf Inguinal hernia	14.8	30	0.9	1	1	1	2	2	82	82	84	82	82	82	130	80	130	80	130	80	130	80	130	80	130	80	120	NA	NA	1								1						
31	985723	M	28	6th std	Worker	Recurr pep ulcer	12.2	20	0.7	1	3	3	4	3	108	110	94	100	100	110	120	80	110	70	110	80	120	70	120	70	120	80	280	720	100		1					1							
32	986702	M	55	B com	Worker	Rt inguinal hernia	13.6	14.2	0.8	2	3	4	4	3	84	86	84	84	86	84	130	70	130	70	130	70	130	70	130	70	130	70	120	480	200			1					1						
33	1007640	M	25	6th std	Cooley	Appendicitis	13.4	26	0.8	3	4	2	3	4	96	100	98	96	98	98	120	80	120	80	120	80	120	80	120	80	120	80	120	240	200			1				1							
34	1012899	F	50	illitrate	Housewife	Para umbilical her	11.4	17	0.5	3	4	3	4	2	102	104	106	104	86	88	130	80	130	80	130	80	120	70	130	80	130	80	120	240	200			1				1							
35	1014503	F	52	10th std	Housewife	Cholilithiasis	12.8	34	0.8	3	3	5	3	5	84	84	86	86	84	88	150	90	130	90	140	90	140	70	140	90	140	90	75	480	200			1					1						