A COMPARATIVE STUDY OF EFFICACY AND SAFETY OF FLUPIRTINE VERSUS PIROXICAM IN POSTOPERATIVE PAIN IN PATIENTS UNDERGOING LOWER LIMB SURGERY

BY

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IN

PHARMACOLOGY

Under the guidance of

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April 2017

DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation entitled "**A COMPARATIVE STUDY OF EFFICACY AND SAFETY OF FLUPIRTINE VERSUS PIROXICAM IN POSTOPERATIVE PAIN IN PATIENTS UNDERGOING LOWER LIMB SURGERY**" is a bonafide and genuine research work carried out by me under the direct guidance of **Dr. SARALA N, MD** Professor and Head, 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. SOWMYA C**, a postgraduate student in the Department of Pharmacology of Sri Devaraj Urs Medical College entitled "**A COMPARATIVE STUDY OF EFFICACY AND SAFETY OF FLUPIRTINE VERSUS PIROXICAM IN POSTOPERATIVE PAIN IN PATIENTS UNDERGOING LOWER LIMB SURGERY**" to be submitted to Sri Devaraj Urs Academy of Higher Education and Research, Tamaka, Kolar.

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Dedicated with

REVERENCE

to

My Parents

LIST OF ABBREVIATIONS

NSAID	Non-steroidal anti-inflammatory drug
NMDA	N-methyl-D-aspartate
$GABA_A$	Gamma aminobutyric Acid
VAS	Visual analogue scale
WHO	World Health Organization
A.D.	Anno Domini
B.C.	Before Christ
TENS	Transcutaneous Electric Nerve Stimulation
IDET	Intra Discal Electrothermic Therapy
™	Trademark
IASP	International Association for the Study of Pain
CGRP	Calcitonin gene-related peptide
5-HT	5-Hydroxytryptamine (serotonin)
B_2	Bradykinin receptor type 2
NO	Nitric oxide

NRS	Numerical Rating Scale
FRS	Faces Rating Scale
BPAS	Behavioural Pain Assessment Scale
FAS	Functional Activity Score
MPQ	McGill Pain Questionnaire
CNS	Central Nervous System
TRPV1	Transient receptor potential vanilloid 1
HIV	Human immunodeficiency virus
gp	Glycoprotein
AIDS	Acquired immune deficiency syndrome
V_d	Volume of distribution
CSF	Cerbrospinal fluid
COX	Cyclooxygenase
FDA	Food and Drug Administration
CYP	Cytochrome P450 group of enzymes
ASA	American Society of Anaesthesiologists
F	Flupirtine

P	Piroxicam
$TOTPAR_{24}$	Total pain relief for 24 hours
PSS	Patient Satisfaction Score
ANOVA	Analysis of variance
n	Number
PO	Per oral
SD	Standard deviation
Bl	Baseline
h	Hours

ABSTRACT

BACKGROUND:

Effective control of pain postoperatively is essential in providing enhanced patient care and cost-effective hospital stay.[1] Though many treatment modalities exist for postoperative pain management in orthopaedic surgeries, they are often accompanied by adverse effects.[2] Piroxicam, a non-steroidal anti-inflammatory drug (NSAID), inhibits prostaglandin mediated pain and inflammation and is used for postoperative pain relief, musculoskeletal disorders and arthritis. flupirtine, a non-opioid, non-NSAID drug exerts its action by exhibiting indirect antagonism on N-methyl-D-aspartate receptors of glutamate and via $GABA_A$ergic receptors.[3, 4] It has an unique analgesic and skeletal muscle relaxing property and hence used in the management of musculoskeletal ailments.

OBJECTIVES:

1. To assess the efficacy of flupirtine and piroxicam in postoperative pain using visual analogue scale (VAS) score
2. To assess the total amount of rescue analgesic required and patient's satisfaction score
3. To evaluate safety profile of the above drugs using WHO causality scale

MATERIALS AND METHODS:

A randomized, open label, parallel group, comparative study was conducted on patients undergoing lower limb orthopaedic surgery, randomized into two groups of 38 patients each. Six hours postoperatively they received either flupirtine 100 mg or piroxicam 20 mg twice daily orally for five days. Intensity of pain was measured

using VAS score, Total Pain Relief Score ($TOTPAR_{24}$) and Patient Satisfaction Score (PSS); the other scales used for assessment were Behavioural Pain Assessment Scale (BPAS) and Functional Activity Score (FAS). Rescue medication used was tramadol 100 mg intravenously. WHO causality scale was used for assessing adverse effects. Descriptive and inferential statistics were used for assessment of various parameters.

RESULTS:

A total of 76 patients with mean age of 35.08±10.3 years were recruited, 34 and 37 in flupirtine and piroxicam group completed the study. Patients in both the groups were comparable in terms of age, gender, type and duration of surgery. Flupirtine and piroxicam reduced VAS score significantly after 48 hours of surgery compared to baseline ($p = 0.006$ and 0.001), however piroxicam produced significant reduction in pain at 8, 12 and 120 hours compared to flupirtine ($p = 0.028$, 0.032 and 0.021). $TOTPAR_{24}$ and PSS at 24 hours were comparable between the treatments. BPAS scores reduced significantly in patients receiving either drug at 24 hours ($p = 0.001$). FAS improved earlier (72 hours) in all patients receiving piroxicam. Most patients required one to two doses of the rescue medication and there was no significant difference between the groups ($p = 0.365$). Adverse effects were similar with both the medications.

CONCLUSION:

Flupirtine and piroxicam reduced pain effectively but onset of pain relief was earlier with piroxicam.

Keywords: Postoperative pain, flupirtine, piroxicam, orthopaedic surgeries

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Introduction

INTRODUCTION

Pain has been the most common problem encountered in the immediate postoperative period. Effective control of this pain has become essential as it helps in providing early mobilization, better recovery and cost-effective hospital stay, especially in patients undergoing orthopaedic surgeries. Acute pain if left untreated may lead to chronicity and become persistent which imposes a greater burden on the patient, as treatment modalities for chronic pain is limited and rarely effective.[1] The existing medications used to relieve pain following orthopaedic surgeries are non-steroidal anti-inflammatory drugs (NSAIDs), opioids, local anaesthetics, gabapentinoids, antiepileptics and steroids, but they are often accompanied by adverse effects.[2] Hence the need for further studies in this regard has become necessary.

Piroxicam, an oxicam derived NSAID, inhibits prostaglandin mediated pain and inflammation. The advantages of this group of drugs over the other analgesics are decreased sensitisation of peripheral receptors, absence of addiction potential and cognitive impairment. It is used for postoperative pain relief, musculoskeletal disorders and arthritis.

Flupirtine, a non-opioid, non-NSAID drug, belongs to K_V7 potassium channel openers, exerting its action by exhibiting antagonism on N-methyl-D-aspartate (NMDA) receptors of glutamate. In addition it also exerts therapeutic action via $GABA_A$ergic receptors.[3,4] It has an unique analgesic and skeletal muscle relaxing property and hence used in the management of musculoskeletal ailments. It is devoid of adverse effects like gastritis, renal compensation, respiratory depression and therefore found to be safe in most patients. Though earlier studies have shown that flupirtine produces analgesia,[4,5] there is dearth of research related to its ability in yielding postoperative analgesia and hence the present study was carried out.

Aims and Objectives

AIMS AND OBJECTIVES

1. To assess the efficacy of flupirtine and piroxicam in postoperative pain using visual analogue scale (VAS) score
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Review of Literature

REVIEW OF LITERATURE

"For all the happiness, mankind can gain

Is not in pleasure, but in rest from pain."

- John Dryden

Pain is one of the physiological responses to tissue injury which serves as a protective function. However, it can become a disease when it occurs or persists despite absence of tissue damage or following healing of injured tissues.[6] Relief of pain is one of the greatest concerns of treatment as it is the most common symptom reported to physicians. It affects millions of people worldwide, altering the physical and emotional functions, impairing the ability to work, decreasing their quality of life and thus affecting the general, psychological, social health and economic well-being.

HISTORY OF PAIN

Theories of pain

The word pain is derived from the Latin word 'ponea', shares its etymological origin with the words punishment and penalty.[7] A number of theories have been hypothesized to describe the mechanisms of pain perception ranging from ancient civilizations to the current Melzack and Wall's Gate Control Theory of pain, of which the most influential theories include the specificity, intensity, pattern and gate control theories as depicted in Figure 1.[8]

Specificity theory of pain[8]

The specificity theory refers to the presence of specific pathways for each somatosensory modality; each stimulus encoded by specific receptor (primary afferent) which projects to the second-order neurons in the spinal cord. Later, these

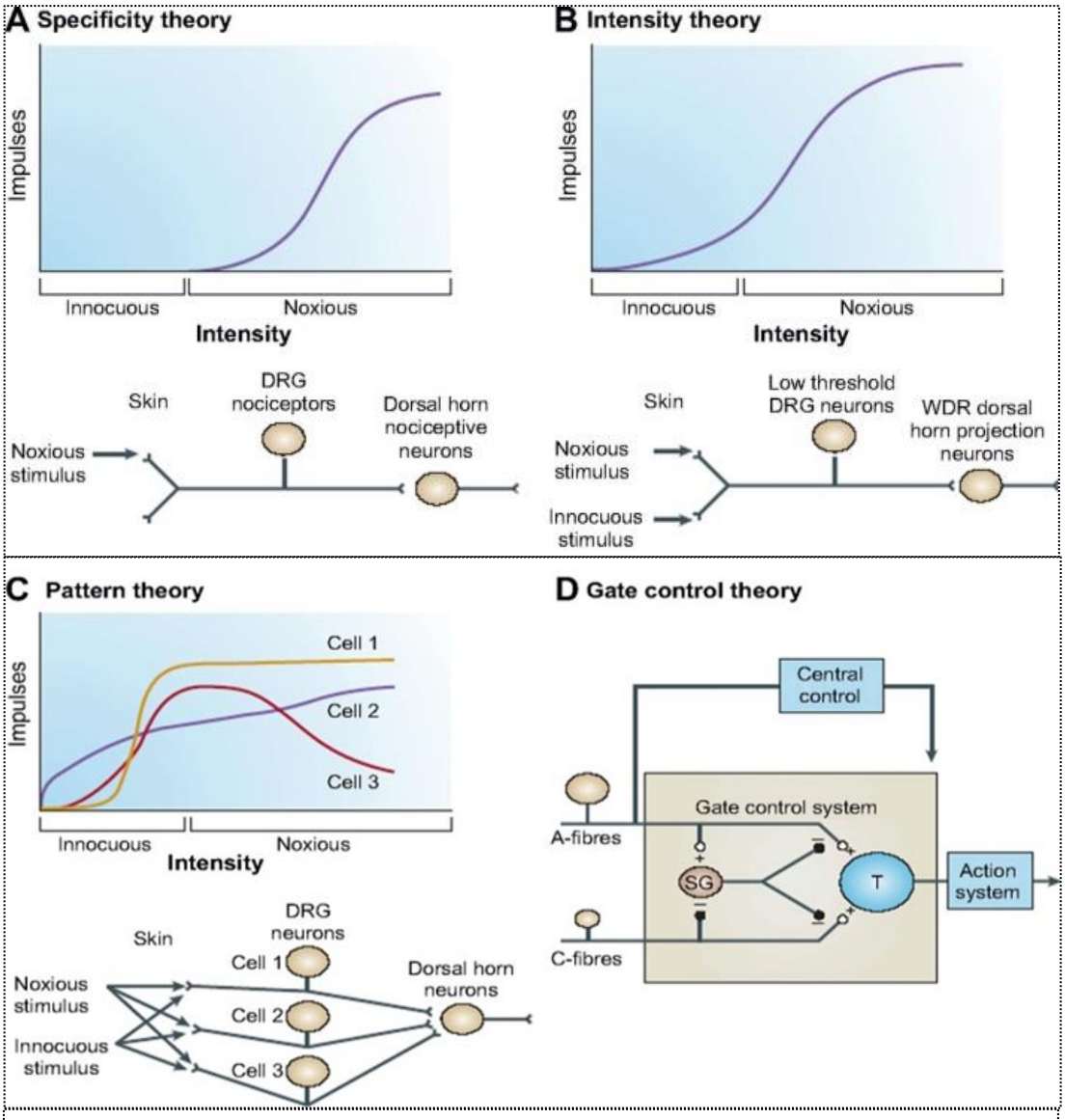

Figure 1: Schematic diagrams of theories of pain

project to the "higher" areas in the brain. The ideas were tested and formally postulated in the 19th century by physiologists in Western Europe. Rene Descartes (Figure 2)[9] described somatosensory pathway in humans. He perceived nerves as hollow tubules that convey both sensory and motor information and in his manuscript, Treatise of Man, described pain as a perception present in the brain. He also described the difference between the neural phenomenon of sensory transduction (nociception) and the perceptual experience of pain.

Figure 2: Rene Descartes

Galen demonstrated that dissecting the spinal cord produced sensory and motor deficits. He postulated that three conditions are to be met for pain perception namely, potential of the organ to receive the stimulus, connection between the organ and the brain and the ability of the sensations to convert to a conscious perception. Descartes added to Galen's model by speculating that a gate existed between the brain and the tubular structures, which was unlocked by a sensory cue. This would allow "animal spirits" to flow through these tubes and within the muscles. La Forge's drawing of a foot near a flame is one of the most famous figures in neuroscience, was based on this concept and La Forge's understanding of its anatomy (Figure 3).[8] Descartes also believed that the pattern and rate of firing of a fibre provided adequate information to the brain about the intensity and quality of the stimulus.

Figure 3: Line drawing of the pain system by Louis La Forge based on Descartes' description

The modern concept of specificity theory developed by Charles Bell in 1811 postulated that there is a dedicated fibre that leads a dedicated pain pathway to the sensory modality's region of the brain. Eleven years later Francois Magendie (Figure 4),[9] a French physician established the sensory characteristic of the nerve root and proved Bell's findings about the presence of both motor and sensory nerves with separate paths to and from the spinal cord, named ventral and dorsal roots,

Figure 4: Francois Magendie

respectively. This distinction of spinal nerves is known as the Bell-Magendie Law. Concurrently, Johannes Müller, a German physiologist, developed the law of specific nerve ending which states that specific receptors must have precise energy of stimulation. In line with these findings, Erasmus Darwin provided the first evidence for a set of specific nerves for the perception of heat. The discovery of specific, cutaneous touch receptors (Figure 5),[10] such as Pacinian corpuscles, Meissner's corpuscles, Merkel's discs and Ruffini's end-organs provided further evidence that specific sensory perceptions were encoded by dedicated nerve fibres.

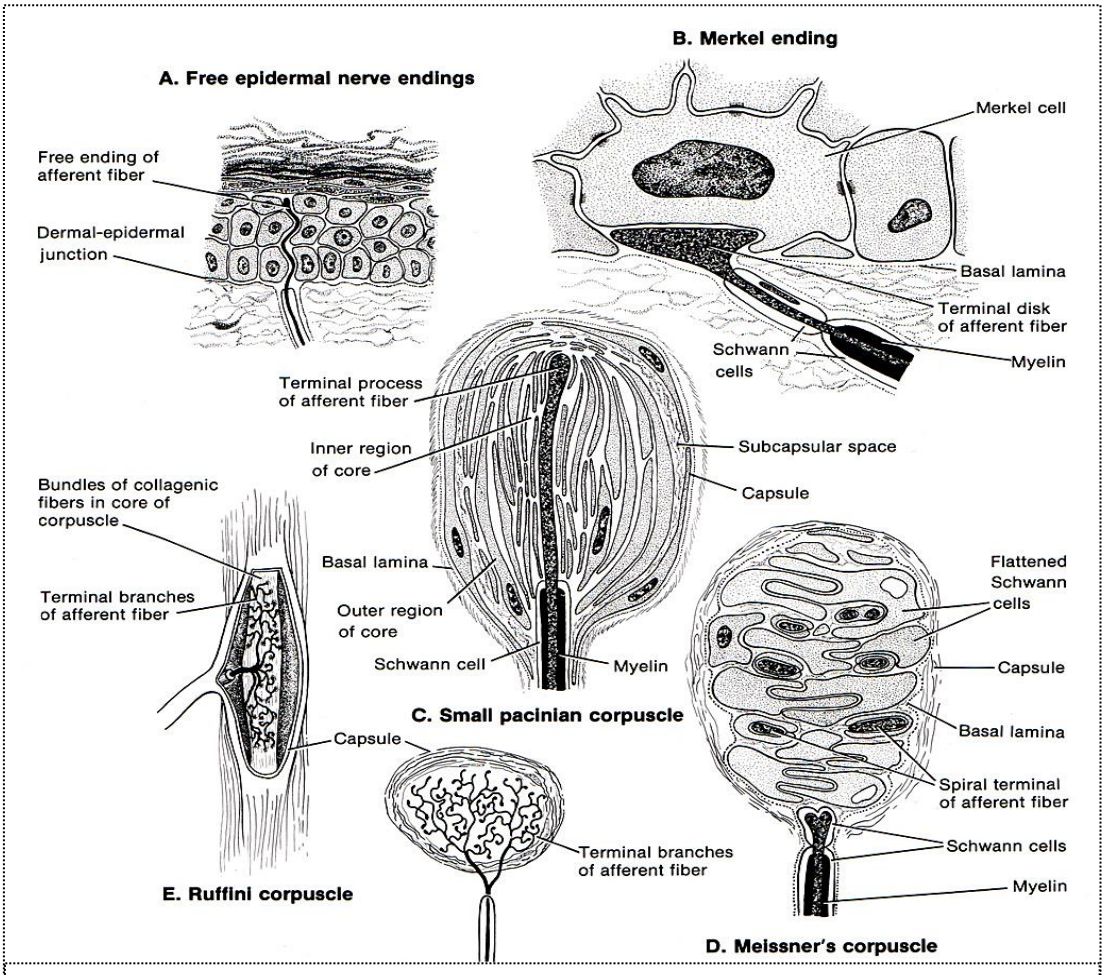

Figure 5: Cutaneous touch receptors

Further data for the specificity theory came from Schiff and Woroschiloff's findings that identified the presence of two pathways namely, the anterolateral pathway for pain and temperature and the posterior bundles for tactile sensibility. Blix and Goldscheider (Figure 6)[9] reported that sensory spots present on the skin elicit a specific sensation when touched and this response was specific to warmth, cold, pressure or pain. This led the specificity theory to gain momentum and pain to become one of the five accepted senses.

Figure 6: Alfred Goldscheider

Between 1894 and 1896, Max von Frey conducted experiments that determined four somatosensory modalities namely cold, heat, pain and touch. To prove this further he developed "von Frey hairs", with the use of which he determined the pressure required to evoke a sensation at each skin spot identified by Blix and Goldscheider. Charles Scott Sherrington (Figure 7)[9] in 1947, addressed some of the assumptions of the specificity theory in his proposed framework of nociception. He examined the simple reflex arc to understand the nervous system and concluded that the main function of the receptor was to lower the excitability threshold of the reflex arc for one kind of stimulus and heighten it for the rest. He also coined the term "nocicipient" to describe the specificity of the cutaneous end-organ for noxious stimuli. Bessou and Perl in 1969,

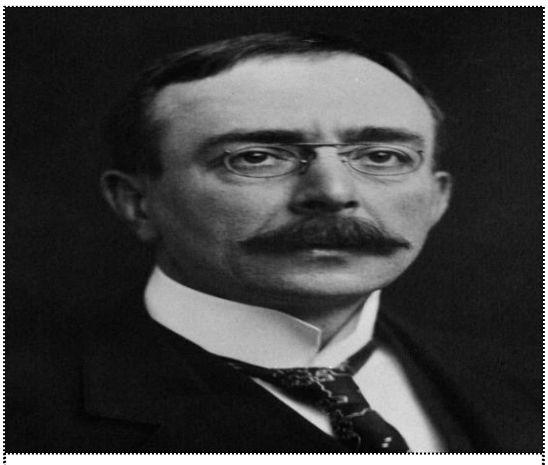

Figure 7: Charles Scott Sherrington

discovered polymodal nociceptors and high-threshold mechanoreceptors which were nociceptive, unmyelinated afferent fibres and this revolutionized the field of pain research.

Intensity theory of pain[8]

An intensive or summation theory of pain was formulated in the fourth century by Plato in his book Timaeus, where he defined pain as an emotion that occurs to a stimulus stronger than usual. Experiments performed by Bernhard Naunyn in 1859, showed that repeated subthreshold tactile stimulation, produced pain in patients with syphilis. Arthur Goldscheider further advanced the theory by suggesting a neurophysiological model to describe this summation effect and told that repeated subthreshold or suprathreshold hyperintensive stimulation could also cause pain.

Pattern theory of pain[8]

In an attempt to modernise theories of pain, J P Nafe postulated a "quantitative theory of feeling" in 1929. This theory ignored findings of specialized nerve endings and many of the observations supporting the specificity and/or intensive theories of pain. It stated that a specific and particular pattern of neural firing produced a somaesthetic sensation and the stimulus type and intensity was encoded by the spatial and temporal profile of firing of the peripheral nerves. To support this, they showed that distorting a nerve fibre would cause action potentials to discharge in any nerve fibre and intense stimulation of any of these nerve fibres would cause perception of pain.

Gate control theory of pain[8]

In 1965, Ronald Melzack and Patrick David Wall (Figure 8 and 9)[9] proposed this theory that revolutionized pain research. They provided a model that described

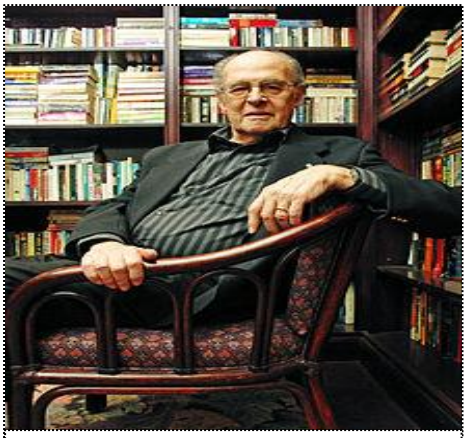

Figure 8: Ronald Melzack

Figure 9: Patrick David Wall

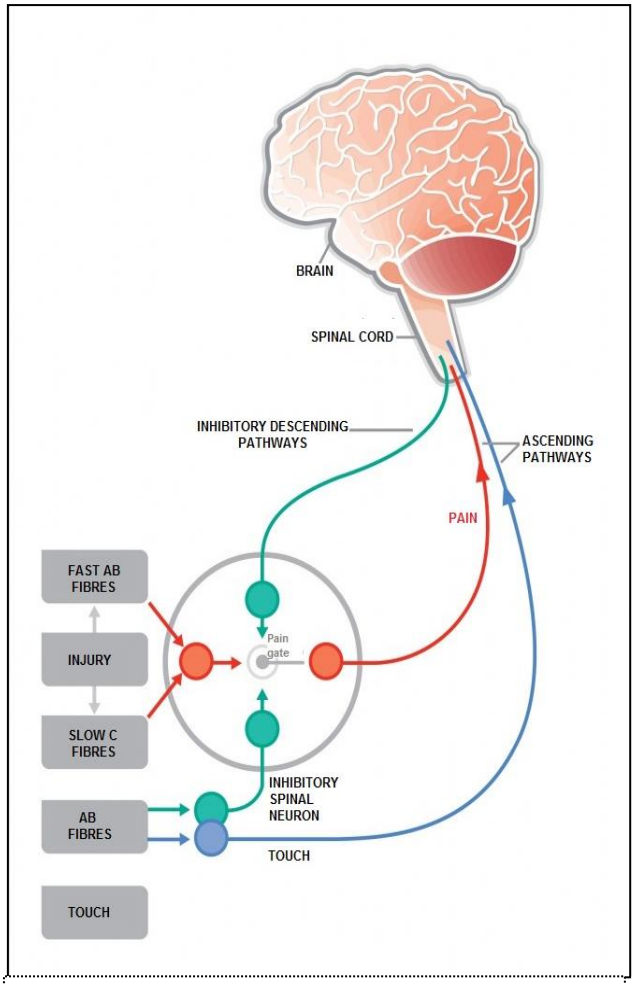

Figure 10: The gate control theory of pain

nociceptors and touch fibres to synapse at two different sites within the dorsal horn of the spinal cord. The model proposed that signals produced in primary afferents from stimulation of the skin were transmitted to substantia gelatinosa, dorsal column and transmission cells. They proposed that the gate in the spinal cord is the substantia gelatinosa in the dorsal horn which regulates 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 of large and small fibres which inhibit or facilitate it respectively. 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. Therefore, the gate control theory of pain (Figure 10)[11]

provided a neural basis for the findings that supported and helped to reconcile the apparent differences between the pattern and specificity theories of pain.

HISTORY OF ANALGESIA

Primitive treatment of pain consisted of extracting the intruding object or frightening away the spirit which was implicated as the causative agent of pain. Acupuncture, a method prevalent in China since 2700 B.C, consists of inserting metal needles at certain points of skin to varying depths, to counteract pain and other symptoms. F H Fume, a Chinese surgeon used this method for carrying out operations.[12] Leeches were used for treatment of pain and inflammatory diseases in the middle ages (500-1500 A.D). Dioscorides reported that the torpedo fish could be applied to the skin to relieve headaches.

European physicians judiciously used opium to relieve pain. After 1680, Thomas Sydenham compounded laudanum, a mixture of opium.[13] During early 1800s, morphine was obtained from opium by European chemists and was found soon after in the United States, where it replaced opium in patented pain medicines. In 1874, the Cannabis plant from which marijuana is obtained, became a well-regarded headache remedy. In1898, Heroin the newest opium derivative, was first produced commercially by Germany's Bayer Company. British scientist, Michael Faraday discovered that an electric current can produce a magnetic field and vice-versa was also true which served as the basis for neurostimulation. French scientist Gaiffe, constructed an electrical nerve stimulating device called the Gaiffe's Transcutaneous Electrical Nerve Stimulation (TENS) unit, which had all of the basic components of a modern neurostimulation device except that, the low electrical output made it ineffective for neurostimulation.[14] Neurosurgeon Norman Shealy was the first to begin implanting neurostimulators in humans for pain relief.

In 1980s the use of opioids administered directly to the spinal column via epidural injections emerged as a treatment for chronic pain. In 1991, the first prototype of a radio-frequency spinal cord stimulation system was developed for the relief of chronic neuropathic pain. Later in 1997, Intra Discal Electrothermic Therapy (IDET) was introduced as an investigative treatment for chronic low back pain. This procedure involved killing of nerve fibres by heating a catheter positioned inside the spinal disc. In 2002, the United States department of health and human services reported that narcotic analgesics were involved in 16% of total drug abuse-related emergency room visits. Therefore, use of these drugs became largely restricted to severe illness. In 2004-05 the first rechargeable spinal cord stimulation system became available in the United States. In 2008 St.Jude introduced 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.[12,14]

DEFINITION AND CLASSIFICATION OF PAIN

Somatosensation is the physiologic process by which neural substrates are activated by physical stimuli resulting in the perception of touch, pressure and 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, or described in terms of such damage."[15] This definition clearly states that pain is subjective and is associated with sensory, affective and cognitive responses. Painful stimuli initiate potent withdrawal and avoidance responses which can be highly variable between persons as well as in the same person at different times.[16]

The term nociception is derived from "noci", Latin word for harm or injury. It is the physiologic process of activation of high threshold peripheral sensory neurons

(nociceptors) in neural pathways by intense mechanical, chemical or thermal noxious stimuli that are potentially damaging to tissues.[17] Clinically the degree of nociception is inferred by overt evidence of tissue damage contrary to pain being a conscious experience. Stimulus-induced activation of afferent neural pathways, alterations in somatosensory processing following injury and psychosocial factors play an important role in the perception of pain.

Pain can be classified according to pathophysiology, etiology, duration or the site involved. However most of the times it has been classified into two major types namely, fast and slow pain. Fast pain is felt within about one tenth of a second after a pain stimulus is applied and also been described by many alternative names such as sharp, pricking, acute and electric pain. Slow pain begins only after a second or more and then the intensity increases slowly over time and is referred to as burning, aching, throbbing, nauseous and chronic pain.[18]

Many patients experience pain in the absence of noxious stimuli, therefore clinically pain is divided into one of the two categories:

Acute pain: It is described as being "the normal, predicted physiological response to an adverse chemical, thermal or mechanical stimulus associated with surgery, trauma and acute illness". It is sudden in onset and recedes during the healing process. It can be considered as "good pain" as it serves an important protective mechanism, confined to the affected area and is limited over time. Acute pain stimulates the sympathetic nervous system resulting in increased heart rate, respiratory rate, sweating, dilated pupils, restlessness and apprehension. Types of acute pain include somatic, visceral and referred.

i. **Somatic pain:** Superficial somatic pain is due to nociceptive input arising from skin, tissues and mucous membranes. It is well localized and sharp, pricking, throbbing or burning in character. Deep somatic pain arises from muscles, tendons, joints or bones and has a dull-aching quality and is less localized.

ii. **Visceral pain:** The type of acute pain is due to a disease process or abnormal function of an internal organ or its covering i.e., parietal pleura, pericardium or peritoneum and is described as true localized visceral pain. It is dull, diffuse in character and associated with abnormal sympathetic or parasympathetic activity causing nausea, vomiting, sweating, changes in blood pressure and heart rate.[19]

iii. **Referred pain:** It can be visceral or parietal, felt in an area distant from the site of the stimulus, because the area is supplied by the same spinal segment as the site of the stimulus. It often occurs with visceral pain.[20]

Chronic pain: Chronic pain is a prolonged pain, persisting beyond the expected normal healing time which can vary from one to six months. It may be nociceptive, neuropathic or psychological and behavioural factors often play a major role. It can be continuous or intermittent; more complex and difficult to manage than acute pain. Chronic pain can be considered as a "bad pain" because it persists long after recovery from an injury and is often refractory to common analgesic agents. It can result from nerve injury including diabetic neuropathy, toxin-induced nerve damage and ischemia. There is evidence to indicate that chronic pain and depression share the same physiological pathway.[16]

PHYSIOLOGY OF ACUTE PAIN

Pain receptors are free nerve endings which are widespread in the superficial layers of the skin as well as in certain internal tissues such as periosteum, arterial walls, joint surfaces, falx and tentorium in the cranial vault. Mechanical, thermal,

chemically sensitive nociceptors respond to strong pressure, skin temperatures above 45°C or severe cold and various agents like bradykinin, histamine, high acidity, environmental irritants respectively.

The variability in pain reflects the physiology of the input from periphery to the cerebral areas that interpret the information. Signals from nociceptors travel primarily along small myelinated A-δ and unmyelinated C-sensory afferent fibres to the dorsal horn of the spinal cord where they make synaptic contact with second order neurons. These signals then travel along the spinothalamic tract of the spinal cord to the thalamus and sensory cortex.[21] This spino-cerebral signalling continues also partly to the hypothalamus and the limbic system, the loci being important in determining the individuals´ emotional reactions to pain. This transmission is under the influence of both local and bulbo-spinal neural activity and can be either inhibitory or facilitatory.

Inflammatory pain results from release of sensitizing mediators that lead to a reduction in the threshold of nociceptors that innervate the inflamed tissue (peripheral sensitisation). The peripheral sensitisation is augmented by important biological processes that result in central sensitisation of the spinal cord and rostral sites. As a consequence, inflammation is associated with exaggerated responses to normal sensory inputs. These phenomena, named allodynia or hyperalgesia, although evoked within a few minutes, can outlast the precipitating tissue injury for several hours or days. Spinal cord nociceptive neurons may become sensitized by repeated brief stimulation, which leads to prolonged spontaneous discharge. This can lead to increase in intensity and duration of pain, not proportional to tissue damage and thus interfere with pain assessment and analgesic efficacy. Neuropathic pain is the pain that arises after injury to peripheral nerves or to sensory transmitting systems in the

spinal cord and brain. As with inflammatory pain, allodynia and hyperalgesia also reflects neuropathic pain.

POSTOPERATIVE PAIN

Postoperative pain is considered a form of acute pain due to the surgical trauma accompanied by an inflammatory reaction. It is a combination of several unpleasant sensory, emotional and mental experiences precipitated by the surgical trauma and associated with autonomic, endocrine-metabolic, physiological and behavioural responses.[22] Pain following surgery occurs mainly due to the sensitisation of central and peripheral nociceptive fibres. While peripheral sensitisation is due to the primary afferent fibres causing pain at the site of tissue injury, central is involved with pain transmission to the brain and is responsible for pain in the undamaged sites surrounding the injured area.[22] Various factors such as type and site of surgery, patient related factors affect the severity of postoperative pain

Mechanism of postoperative pain

Surgical procedures cause damage to the skin and various other tissues. Application of thermal and chemical stimuli to the wound and manipulation of somatic structures also contribute to damage and destruction of tissues. In response to this tissue injury, chemical mediators can sensitize and activate nociceptors which contribute to hyperalgesia and allodynia. Tissue injury releases bradykinin and prostaglandins that sensitize or activate nociceptors, which in turn releases substance P and calcitonin gene-related peptide (CGRP). Substance P acts on mast cells to cause degranulation and release histamine, which further activates nociceptors. Substance P causes plasma extravasation and CGRP dilates blood vessels resulting in edema. Serotonin (5-HT) is released from platelets and activates nociceptors.[16]

Modulation of postoperative pain

Modulation of nociceptive transmission occurs at multiple levels (peripheral, spinal, supraspinal) which are referred to as the descending modulatory pain pathways and these can lead to either an increase in the transmission of pain impulses or a decrease in transmission.

Peripheral sensitisation

Transient receptor potential family and tetrodotoxin-resistant sodium channel are the important receptors involved in the transduction of a pain signal. Many chemicals cause peripheral sensitisation via these receptors (Figure 11).[23] Bradykinin activates G-protein coupled receptors (B_2) which then stimulates protein kinase C, resulting in release of prostaglandins which cause vasodilation and increased vascular permeability at the site of surgery. Prostaglandins formed by the action of cyclooxygenase on arachidonic acid, PGE_2 and PGI (via their EP_1 and IP receptors respectively) are thought to activate protein kinases C and A respectively, thus enhancing nociception transmission. PGE_2 has also been involved in the enhancement of activity at the primary afferents in the spinal cord. Substance P is released by the

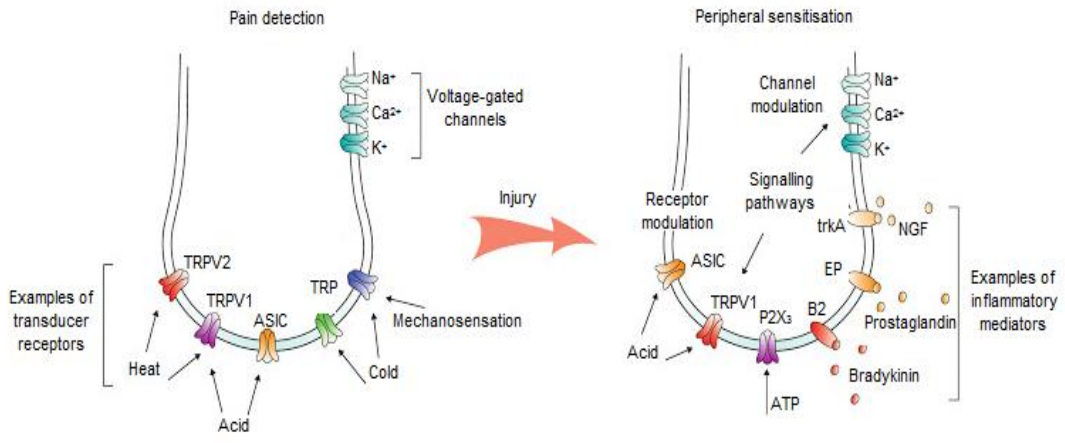

Figure 11: Pathway of peripheral sensitisation

sensory nerve endings locally by noxious stimuli and also via the axon reflex. It activates the neurokinin-1 receptor which causes vasodilatation, increased vascular permeability and synthesis of prostaglandins.

Neurotrophic factors such as fibroblasts and mast cells are over expressed in tissue injury, promoting thermal sensitivity. Nerve growth factors sensitize nociceptors to substance P and other noxious stimuli and also exert long term gene expression changes in nerve cells. Histamine released by activation of mast cells causes vascular smooth muscle contraction, vasodilation and encourages immune cells to reach the injury site. Serotonin is another important mediator released from mast cells and platelets, capable of directly or indirectly activating nociceptive afferent fibres. All the above mediators take variable time frames to produce their effects. Hence, after an initial period of injury, pain becomes worse with further stimuli including low intensity stimuli. This hyperalgesia and allodynia due to various chemical mediators with one facilitating the other, causes peripheral sensitisation.[24]

Central sensitisation

Central sensitisation refers to hyperexcitability of the neuron. Repeated stimulation of nociceptors initially causes a gradual increase in the frequency of dorsal horn neuron firing known as "wind-up." NMDA receptor plays a key role in this process where activation induces calcium entry into the sensory neurons in the dorsal horn, induces activation of Nitric oxide (NO) synthase, leading to the synthesis of NO. This can affect the nociceptor terminals and enhance the release of sensory neuropeptides (substance P) from presynaptic neurons, therefore contributing to the development of hyperalgesia and maintenance of central sensitisation. Repeated or prolonged input from C-nociceptors or damaged nerves causes a longer-lasting increase in dorsal horn neuron excitability and responsiveness (Figure 12).[23]

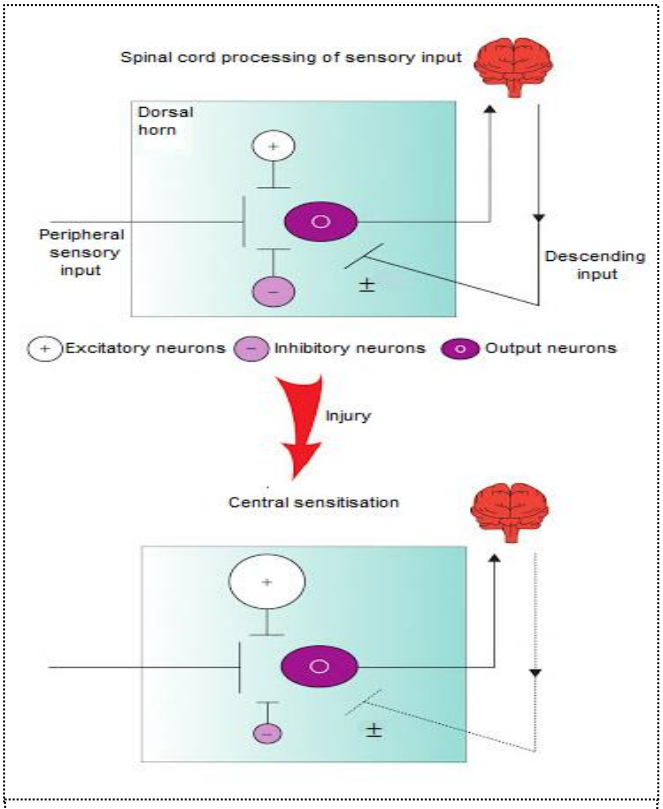

Figure 12: Pathway of central sensitisation

Central sensitisation is associated with a reduction in central inhibition, less recruitment of responses from neurons that normally respond to low intensity stimuli. Clinically, these changes may either manifest as hyperalgesia, allodynia, prolonged pain after a transient stimulus (persistent pain) or the spread of pain to uninjured tissue (referred pain).

Pathways involved in transmission of postoperative pain

There are two separate pathways for transmitting pain signals to the central nervous system corresponding to the two types of pain – an acute/ fast pain pathway and a chronic/ slow pain pathway (Figure 13).[18] The acute pain elicited by either mechanical or thermal pain stimuli are transmitted in the peripheral nerves to the spinal cord by small type Aδ fibers at velocities between six and thirty metre per second. The

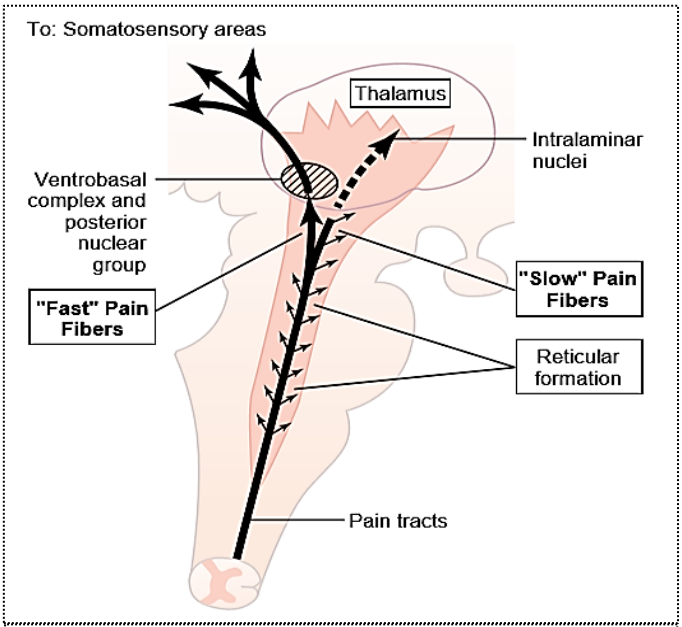

Figure 13: Transmission of pain signals into the brain stem, thalamus and cerebral cortex

slow, chronic type of pain elicited by chemical types of pain stimuli and also by persisting mechanical or thermal stimuli, is transmitted to the spinal cord by type C fibres at velocities between half and two metre per second. The Aδ and C-fibres are involved in the transmission of pain impulses through the peripheral nerves. Spinal cord gray matter is divided into ten lamina (Figure 14).[18] 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. The two ascending pathways are the neospinothalamic tract and the paleospinothalamic tract,[18] of which, the former tract is the main pathway for transmission of acute postoperative pain.

The fast type Aδ pain fibres transmit mainly mechanical and acute thermal pain. They terminate in lamina I (lamina marginalis) of the dorsal horns and there excite second-order neurons of the neospinothalamic tract. These give rise to long fibres 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. A few fibres 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.[18]

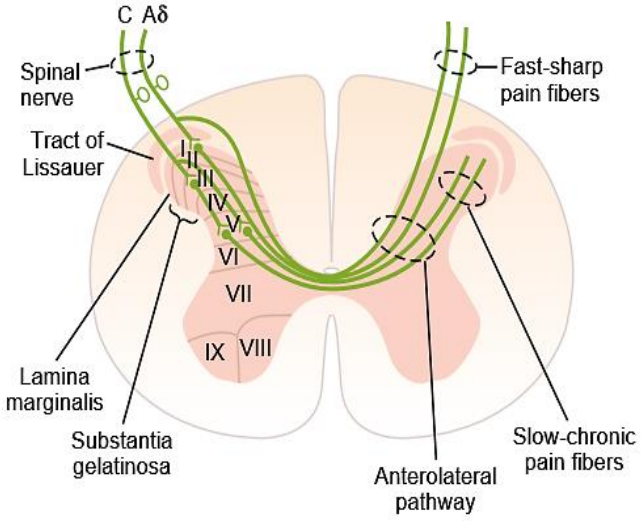

Figure 14: Transmission of fast and slow pain fibres through the spinal cord

Patients with moderate to severe pain during postoperative period and those who have undergone operation with risk of nerve damage are more likely to develop chronic pain. Chronic type of pain is carried by type C fibres in the paleospinothalamic tract which terminate in the spinal cord in laminae II and III of the dorsal horns, together called the substantia gelatinosa. Most of the signals then pass through one or more additional short fibre neurons within the dorsal horns themselves before entering mainly lamina V, also in the dorsal horn. Here the last neurons in the series give rise to long axons that mostly join the fibres 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.[18]

ASSESSMENT OF PAIN

The aim of assessment is to determine the intensity, quality and duration of pain, to help decide on the choice of therapy and to evaluate the relative effectiveness of different therapies.

Pain rating scales

Pain assessment scales are useful for eliciting responses from patients about their comfort or discomfort, for enhancing clarity in communications and for supporting an individualized pain management program.[25,26]

Visual analogue scale (VAS)

The most common and traditional method for assessment of pain is the visual analogue scale score from zero to ten (Figure 15),[27] with zero being no pain and ten being the worst pain. It is a psychometric response scale, used to measure the subjective characteristics or attitudes that cannot be directly measured. The respondents specify their level of agreement to a statement by indicating a position

along a continuous line between two end-points. This continuous aspect of the scale differentiates and makes it superior to discrete scales such as the numerical rating scale and thus a wider range of statistical methods can be applied to the measurements. The patient is instructed to point to the position on the line between the faces to indicate how much pain they are currently feeling. The far left end indicates 'No pain' and the far right end indicates 'Worst pain ever'. Ease and brevity of administration and scoring, minimal intrusiveness and conceptual simplicity makes VAS advantageous over the other methods. The major disadvantage however is its assumption that pain is a uni-dimensional experience.

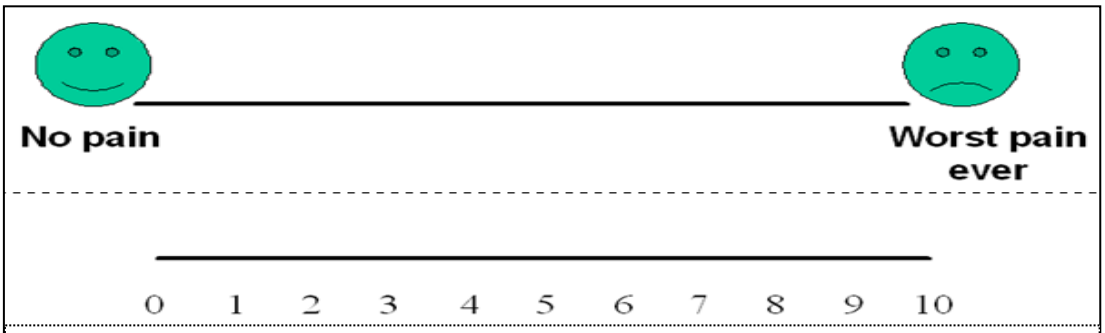

Figure 15: Visual analogue scale

Numerical Rating Scale (NRS)

The Numeric Rating Scale is a simple reporting instrument that can help to quantify a patient's subjective pain. NRS is administered by asking the patient to verbally estimate his or her pain on a scale of zero to ten (Figure 16),[27] which best describes their current pain. Zero represents no pain and ten represent the worst possible pain.

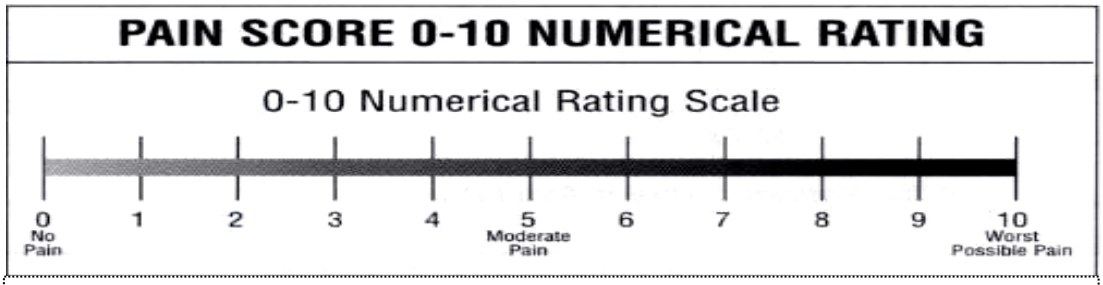

Figure 16: Numerical rating scale

Faces Rating Scale (FRS)

Adults who have difficulty using the numbers on the visual or numerical rating scales can be assisted with the use of the six facial expressions suggesting various pain intensities. Ask the patient to choose the face that best describes how they feel. The far left face indicates 'No hurt' and the far right face indicates 'Hurts worst' (Figure 17).[27] Document the number below the face chosen. This rating scale is recommended for children ages three and older. Ask the child to choose the face that best describes his or her own pain and note the appropriate number.

Figure 17: Faces rating scale

Behavioural Pain Assessment Scale (BPAS)

The behavioural pain assessment scale is designed for use with non-verbal patients unable to provide self-reports of pain. Observe the patient for ten minutes. Assess the patient on the five behaviours (facial expression of pain, restlessness, muscle tone, vocalisation and consolability). Obtain a pain score based on the highest

behaviour observed. Rate each of the five measurement categories as zero, one or two with a highest score of ten.

Functional Activity Score (FAS)

This is an activity-related score. Patient is asked to perform an activity related to their painful area and based on the observation of limitation of patient's activity they are graded as A, B or C.

McGill Pain Questionnaire (MPQ)

The McGill pain questionnaire can be used to evaluate significant pain experienced by the patient. 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.

MANAGEMENT OF POSTOPERATIVE PAIN

Postoperative pain is said to be of mild to moderate intensity in 62-65% of patients undergoing orthopaedic surgeries.[28] The associated negative outcomes such as insomnia, high risk of infections, thromboembolic events due to prolonged immobility and impaired rehabilitation suggest that effective pain management contributes to quick recovery.[29]

Pharmacological measures

Opioid analgesics

Opioids act as agonists on stereospecific opioids receptors (μ, δ and κ) at presynaptic and postsynaptic sites within the CNS and in the peripheral tissues. They have been the most widely used analgesics in control of postoperative pain but due to

the adverse effects such as nausea, vomiting, sedation, dependence and respiratory depression, their use is restricted.[30]

Non-opioid 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 type 1 and 2, which convert arachidonic acid to prostaglandins, responsible for both peripheral and central sensitisation.

Non-opioids, non-NSAIDs

Flupirtine is neither an opioid nor a NSAID, produces analgesic action through indirect blockade of NMDA receptor via activation of potassium channels. It also has muscle relaxant, neuroprotective and antiparkinsonian property. It is devoid of the classical adverse effects of the commonly used analgesics because of its unique mechanism of action. It is used in musculoskeletal, postoperative, neurogenic and cancer pain.[31]

Adjuvants

Drugs which by themselves have undesirable side effects or low potency but in combination with opioids, allow a reduction of narcotic dosing for postoperative pain control. Examples include ketamine, gabapentin, pregabalin, dexmedetomidine, clonidine and neostigmine.

Local anaesthetics

A local anaesthetic is a drug that causes reversible local anaesthesia and loss of nociception. It interferes with pain transmission in the spinal cord by blocking sodium channels leading to analgesia. When it is used on specific nerve pathways (nerve block), effects such as analgesia and paralysis (loss of muscle power) can be

achieved. It allows patients to undergo surgical and dental procedures with reduced pain and distress. Use of local anaesthetics pre-emptively reduces the dose of required general anaesthesia and thus the adverse effects of general anaesthetics. Local anaesthetics in use are lignocaine, bupivacaine, ropivacaine, tetracaine and prilocaine.

TRPV1 antagonists

TRPV1 is expressed on small myelinatedn and unmyelinated sensory neurons in dorsal root and trigeminal ganglia. They are also found in muscles, joints, urinary bladder and kidneys. The functional activity of TRPV1 is seen in the spinal cord and specific sites in the brain including the hypothalamus, cerebellum, locus coeruleus, periaqueductal gray and cerebral cortex. Activation of these receptors causes influx of calcium and sodium ions which in turn initiates a cascade of events that result in membrane depolarization, neuronal firing and transduction of neural impulses. Orally active TRPV1 antagonist substances have progressed into clinical development and several more are in preclinical development. Capsazepine blocks the painful sensation caused by capsaicin which activates the TRPV1 ion channel and is therefore considered to be a capsaicin antagonist. It blocks only the activation of the channels by chemicals but not by other painful stimuli like heat.

Non-pharmacological measures

TENS applied with a strong, subnoxious intensity and adequate frequency in the wound area reduces analgesic consumption in the postoperative period. Acupuncture is another non-pharmacological means which is helpful in acute pain management in the postoperative period.[19]

PHARMACOLOGY OF FLUPIRTINE

Introduction

Flupirtine is a centrally acting non-opioid, non-NSAID analgesic, without antipyretic and anti-inflammatory properties. It has a unique pharmacologic profile via the activation of potassium K_v7 channels with additional $GABA_A$ergic mechanisms. Flupirtine was first synthesized by Chemiewerk Homburg, Degussa pharma group of Frankfurt, Germany in 1981.[32] It was approved for the treatment of pain in 1984 in Europe.[33]

Chemistry

Flupirtine is a triaminopyridine derivative having a chemical structure (Figure 18)[32] of 2-amino-3-ethoxy-carbonylamino-6,4-fluoro-benzylamino-pyridine.[34] The basic molecule used for synthesis is 2,6-dichoro-3-nitropyridine.[35] Flupirtine is a basic, weakly lipophilic drug and a poorly water soluble molecule, hence available as the maleate salt.

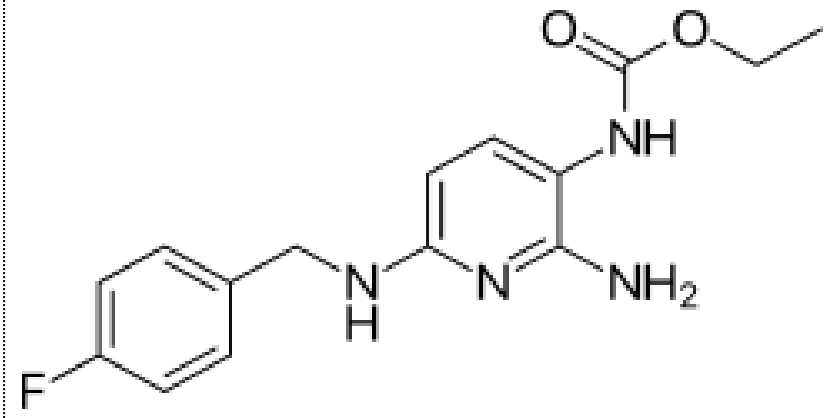

Figure 18: Structure of flupirtine

Mechanism of action

Flupirtine acts as a functional NMDA receptor antagonist by activation of K_v7 channels.[4] It also enhances GABA-induced effects in the dorsal root ganglia and dorsal horn neurons via action on $GABA_A$ receptors.[36]

Pharmacodynamics

The spectrum of action of flupirtine includes analgesia, muscle relaxation and neuroprotection.

Analgesic action

Flupirtine was introduced as an alternative analgesic to opioids and NSAIDs. It binds and activates G-protein coupled inwardly rectifying potassium channels, the opening of which leads to stabilisation of the resting membrane potential of the neuronal cells. Thus flupirtine exhibits its analgesic action via inhibition of the neuronal hyperexcitability and nociceptive impulse.[4]

Muscle relaxant action

The muscle relaxing activity that was discovered by serendipity,[4] is due to inhibition of both mono and polysynaptic reflexes. The spinal polysynaptic flexor reflex, mediated by NMDA receptors, was depressed whereas the monosynaptic Hoffmann reflex, mediated by non-NMDA receptors was spared from the action of flupirtine[37,38] This effect is partly attributed to the action of the drug in reinforcing GABA binding to its receptor.[4] Flupirtine possesses analgesic as well as muscle-relaxing effect in same dose ranges; thus, it can be used in the treatment of painful diseases of the motor system presenting with spasticity and chronic musculoskeletal pain.

Neuroprotective action

Apoptosis, a programmed cell death, is caused by increased intracellular calcium levels, mitochondrial dysfunction, cell membrane disruption and nucleolysis. In vitro studies with primary cortical neurons from rat embryos have shown that lead acetate; prions like PrPsc, HIV coat protein gp120, and β amyloid peptide will cause apoptotic cell death. Preincubation with flupirtine completely protects apoptotic cell death caused by above agents in the neurons. It has been found that flupirtine also antagonizes both glutamate and NMDA induced increase in intracellular levels of calcium ions, as observed in in-vitro cultures of cortical and hippocampal neurons.[39]

The expression of Bcl-2, an anti-apoptotic agent and glutathione, a scavenger of reactive oxygen, are reduced during NMDA-induced apoptosis in cells. Flupirtine is found to increase the levels of Bcl-2 and glutathione of human Ntera/D_1 (hNT) neurons as well as cultured retinal pigment cells.[33,40] It also reduced the expression of oncogenes and formation of reactive oxygen radicals in experimental models which explains its action of preventing ischemia-induced apoptosis.[34] This explains the role of flupirtine in future for treatment of neuroinfections such as AIDS, prion diseases and neurodegenerative disorders such as Alzheimer's disease.[4]

Pharmacokinetics

Absorption - Flupirtine is a hydrophilic compound. It is rapidly and completely absorbed from gastrointestinal tract with a bioavailability of 90%, by oral route and 72.5% by rectal route as compared with that for an intravenous dose of flupirtine tartrate 80 milligram.[41] The onset of action is within 15-30 minutes after oral administration, attaining peak concentrations of approximately 0.8 and 2.0 milligram per litre at 1.6 hours. Peak concentration following rectal administration of flupirtine

maleate 150 milligram was 0.89 milligram per litre after 5.7 hours. Steady-state concentrations were achieved after two days in four healthy volunteers who received 75 milligram of flupirtine orally at 12 hour intervals.[42] Plasma drug accumulation was not observed after oral administration of flupirtine 100 milligram times daily for 28 days.

Distribution - Flupirtine has a large Volume of distribution (V_d) and gets equally distributed into both extravascular and intravascular compartments. V_d for a dose of 100 milligram is 154 L, 212 L and 195 L in healthy volunteers, patients with renal impairment and elderly respectively on intravenous administration.[33,41] It is 80-84% bound to human albumin,[41] CSF concentration is same as that in plasma whereas it is higher in liver, exocrine glands and lower in kidneys.[42] Its half-life following intravenous administration is 1.8 hours,[34] while the plasma elimination half-life in healthy young volunteers following single dose administration by the intravenous, oral and rectal routes is 8.5, 9.6 and 10.7 hours respectively.[37]

Metabolism and elimination - The carbamate group in flupirtine is hydrolysed by carboxyl esterases. The decarbamylated product in liver is further metabolized to 4-fluorohippuric and N-acetylated analogue D13223 by peroxidase enzymes, of which the later retains 20-30% of activity of its parent compound.[34] The two metabolites are further oxidized and then conjugated with glutathione to form inactive metabolites.[35,43] Thus the rate of formation of the toxic intermediates with diimine structure in hepatocytes, is dependent on the activity of NAT1/NAT2, UGTs and GSTP1. As NAT2, UGT1A1 and GSTP1 are highly polymorphic enzymes, the risk of hepatotoxicity may be dependent on the genotype of the subjects that are treated with the drug, however this theoretical concept has not proven to influence its metabolism.[44] The apparent clearance in healthy volunteers following an oral dose is

16.5 L/h[41] and following oral administration of 100 milligram of the drug is found to be 275, 263 and 161 ml/minute in healthy volunteers, renal impairment patients, and elderly respectively.[33,41] Of the total dose administered, 72% appears in urine as parent drug and its metabolites, whereas 18% is excreted in feces.[40,45]

Uses[4,46-50]

In Europe, flupirtine is being used for the management of pain following surgery, trauma, dental extraction, pain associated with muscle spasm, cancer, degenerative joint diseases and conditions such as headache and dysmenorrhoea. It has proven to be clinically effective in the treatment of acute low back-ache, headache, in the management of postoperative pain following episiotomy, fistulectomy, appendicectomy, hernioplasty surgeries, as well as in chronic pain such as fibromyalgia and neurogenic pain. It is effective and better tolerated for the treatment of cancer pain but lacks anti-inflammatory effect which limits its use in inflammatory conditions. It is shown to have beneficial effects on cognitive function and its anti-apoptotic, cytoprotective, antioxidant properties favour its use in the treatment of neurodegenerative diseases such as multiple sclerosis. It has been postulated to be useful in glaucoma, overactive bladder syndrome and preterm labour.

Dosage and formulation

Flupirtine can be administered by oral and rectal routes. It is available as capsules or rectal suppositories at strengths of 50 to 150 milligram.[51] Adult dose is 300-400 milligram per day and in children 150-200 milligram per day in three to four divided doses.[33,35] The duration of treatment should not exceed eight days without review by a medical practitioner, or four weeks on repeated prescription. Monitoring of transaminases is recommended on prolonged administration in elderly patients or

those with mild to moderate renal impairment.[35] Safety in pregnant, lactating women and children less than six years is not established.

Adverse effects

Flupirtine is well tolerated with mild and infrequent adverse effects. In long-term trials done for rheumatic disease, majority of adverse reactions occurred within six months of treatment, among which most common were dizziness (11%), drowsiness (9%), pruritis (9%), dry mouth and gastric fullness (5%), nausea and muscle tremor (2%).[52] Others were heart burn, vomiting, disturbed sleep, sedation, headache, fatigue and mood elevation. A dose of 100 and 200 milligram caused an insignificant increase in systolic blood pressure with not much alteration in heart rate. A slight increase in transaminases levels, leucocyte counts, blood urea nitrogen and creatinine were reported in a few patients and none were reported to be clinically significant.[51] Rare but serious adverse effects were hepatitis, ataxia, tremors, restlessness and nervousness.

In elderly individuals, it was reported to cause transient faintness, dizziness and lethargy, whereas in patients with renal dysfunction produced light headedness and headache. Patients with liver disease presented with encephalopathy due to increased plasma concentration of the drug.[42]

Drug interactions

Flupirtine has shown to increase warfarin toxicity, hence patients on oral anticoagulant therapy should be monitored for prothrombin time. It also enhances hepatotoxic potential of paracetamol thus, hepatic transaminases levels should be assessed when both the drugs are given concomitantly.[34] Alcohol and other sedatives including benzodiazepines potentiate tiredness and dizziness.[42] Co-administration

with carbamazepine is not advisable as it induces hepatic enzymes. A slight degree of enzyme induction has been described on long term administration to epileptic patients.[51]

PHARMACOLOGY OF PIROXICAM

Introduction

Piroxicam, an oxicam derivative is a non-selective cyclooxygenase (COX) inhibiting NSAID, has a long half-life of approximately 50 hours and is highly bound to plasma proteins. This may allow improved compliance through once daily dosing. The FDA approved piroxicam in April 6, 1982 for rheumatoid arthritis and osteoarthritis.[53]

Structure and chemistry

Chemical name of piroxicam is 4-hydroxyl-2-methyl-N-2-pyridinyl-2H-l,2-benzothiazine-3-carboxamide-1,1-dioxide (Figure 19).[54,55] It occurs as a white crystalline, sparingly soluble in water, dilute acid and most organic solvents. It is slightly soluble in alcohol and aqueous solutions. It exhibits a weakly acidic 4-hydroxy proton (pKa 5.1) and weakly basic pyridyl nitrogen (pKa 1.8).[54]

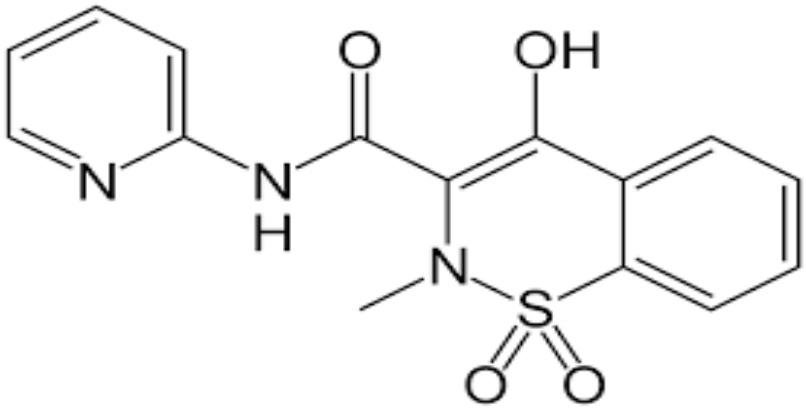

Figure 19: Structure of piroxicam

Mechanism of action

Piroxicam inhibits the cyclooxygenase enzymes non-selectively and hinders the formation of prostaglandins which are important mediators of pain. Hence decreases the postoperative pain by reducing the nociceptive transmission to the brain.

Pharmacodynamics

Analgesic activity

Piroxicam is less effective than indomethacin but more active than aspirin, fenoprofen, naproxen, phenylbutazone in reducing writhing frequency by 50%. This effect of piroxicam is shown to last for 12 hours.

Antipyretic activity

Piroxicam 10 mg/kg is as effective as aspirin 56 mg/kg in inhibiting pyrexia induced by intramuscular injection of E.coli lipopolysaccharide in mice.

Anti-inflammatory activity

Piroxicam inhibit polymorphonuclear leucocyte aggregation which are responsible for release of lysosomal enzymes and superoxide anions that tend to degrade cartilage. Piroxicam is twice as potent as indomethacin, seven times than naproxen and 14 times than phenylbutazone. Oral piroxicam suppresses both primary and secondary lesions of adjuvant arthritis in control rats. Topical and rectally administered piroxicam is equipotent to the orally administered drug.

Effect on gastrointestinal mucosa

The ulcerogenic dosages of piroxicam and other NSAIDs are related to the dosages that exhibit anti-inflammatory activity. After ingestion of single doses of

piroxicam 20 mg or fenbufen 600 mg, microbleeding was less with fenbufen than with piroxicam.[56]

Effect on prostaglandin synthesis

Piroxicam decreases plasma concentration of PGE_1 and $PGF_{2\alpha}$ in rheumatoid arthritis patients. It also suppress the synthesis of metabolic regulatory factors in conditioned medium derived from synovial cultural containing significant cartilage cell catabolic-inducing activity.

Pharmacokinetics

Absorption - Piroxicam is well absorbed from gastrointestinal tract. Peak concentration attained about three to five hours after oral administration. A second peak is observed between six and ten hours which are seen due to enterohepatic circulation. After intramuscular administration of piroxicam, maximum concentration attained after 45 minutes of administration and plasma levels are significantly higher than that after oral ingestion. An almost identical plasma concentration-time curve is obtained after oral, rectal, intramuscular and intravenous administration, signifying near complete oral absorption. Because of its long elimination half-life, plasma concentrations of piroxicam vary less between consecutive doses than those of other NSAIDs.

Distribution - The apparent volume of distribution is 0.14 L/kg body weight, which is about 10L for a 70kg man. It penetrates into the synovial fluid of patients with rheumatoid arthritis and osteoarthritis, where mean concentration is 40% of that in plasma and into synovial tissue and cartilage tissues. Piroxicam is 99% bound to plasma proteins and its concentration of piroxicam in breast milk is 1% of maternal plasma.

Metabolism - Piroxicam is metabolized in the liver by hydroxylation of the pyridyl ring (predominantly by an isozyme of the CYP2C subfamily) and glucuronidation. The metabolites of piroxicam have no anti-inflammatory activity and are inactive.

Elimination - Less than 5% of piroxicam is excreted unchanged in the urine. The elimination half-life of piroxicam is 30 to 60 hours.

Uses

Piroxicam is used in rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute gout, postoperative pain, mesothelioma and cmplex regional pain syndrome

Dosage and administration

The initial adult dosage in rheumatoid arthritis, osteoarthritis and ankylosing spondylitis is 20 mg daily as a single oral dose. Daily maintenance doses may vary between 10-30 mg. In acute musculoskeletal conditions, an initial dose of 40 mg daily for two days followed by 20 mg daily for two weeks is administered. However in postoperative pain 20 mg daily intramuscularly and 40 mg daily for prolonged operations as in orthopaedic surgeries is recommended. Piroxicam as dispersible tablets used in children above six years. Topical gel in a concentration of 0.5% is preferred for local painful inflammatory conditions, applied three or four times daily.[54]

Adverse effects

The incidence of adverse effects to Piroxicam are as follows - Local irritation is about 13%, skin rash, pruritis is 0.8%, peptic ulceration and gastrointestinal haemorrhage is 0.15% and increases upto 7% at higher doses.

Drug interactions

Aspirin with piroxicam results in decreased plasma concentrations of piroxicam to about 80% of normal. Ritonavir with piroxicam results in increased plasma concentrations of piroxicam and an increased risk of toxicity. Piroxicam potentiates the anticoagulant effect of acenocoumarin. It can reduce the renal excretion of lithium and lead to toxicity.

Materials and Methods

MATERIALS AND METHODS

Source of data

A randomized, open label, parallel group, comparative study was conducted by departments of Pharmacology and Orthopaedics on patients undergoing lower limb surgery in R L Jalappa Hospital and Research Centre, from January 2015 to July 2016.

Inclusion Criteria

1. Patients of either gender aged between 18 and 50 years
2. Patients undergoing either elective or emergency lower limb surgery with or without the requirement of implants
3. Patients belonging to American Society of Anaesthesiologists (ASA) grade I and II

Exclusion Criteria

1. Patients with hepatic and renal impairment, haemorrhagic disorders, bronchial asthma
2. Patients with addictive disorders such as smoking, alcoholism, any other drugs of abuse
3. Patients with history of peptic ulcer and gastrointestinal bleeding
4. Pregnant and lactating women
5. Patients with known hypersensitivity to the study medications

Method of collection of data

A proforma containing detailed information of each patient was designed according to the study protocol. Ethical clearance was obtained from the Institutional Ethics Committee. Patients undergoing elective or emergency lower limb surgery were recruited. After obtaining written informed consent, the patients were randomized using block randomization method. A block size of four was used and with the help of computer generated random numbers all the patients were assigned to two groups of 38 patients each. Baseline assessments included demographic details, clinical history and examination. The patients were acquainted to the pain scores prior to start of treatment with the study drugs and were requested to report any adverse events that they experienced during their stay in the hospital. Following surgery both the groups received single dose of injection tramadol 100 mg intravenously in the recovery room. Six hours after surgery, patients in Group F received flupirtine 100 mg twice daily and Group P received piroxicam 20 mg twice daily orally for five days.

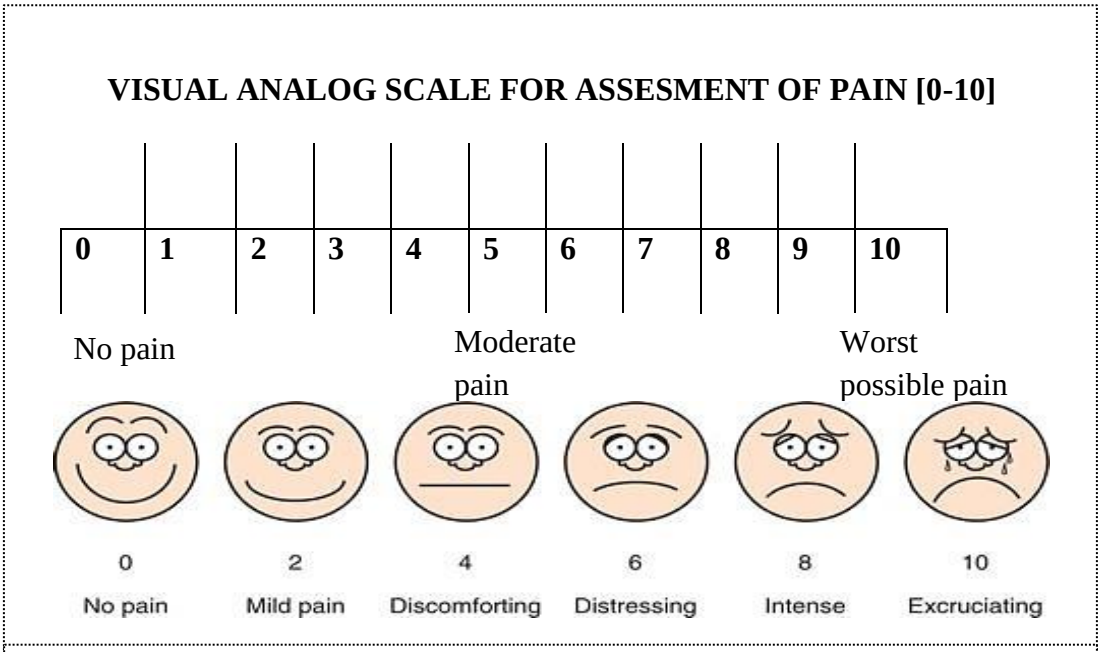

Figure 20: Visual analogue scale

Directions - Ask the patients to indicate on the line where the pain is in relation to the two extremes

Table 1: Graded visual analogue scale

VAS score	**Graded VAS** (Severity of pain)
0	No Pain
1-3	Mild
4-7	Moderate
8-10	Severe

Intensity of pain was measured using visual analogue scale (VAS) score from zero to ten (zero is no pain and ten is worst pain). VAS score was measured at baseline (before study medication was administered), 2, 4, 8, 12, 24, 48, 72, 96 and 120 hours. Total pain relief ($TOTPAR_{24}$) score for first 24 hours was also assessed. The objective evaluation of pain was done using Behavioural Pain Assessment Scale (BPAS) (scored zero to ten) and Functional Activity Score (FAS) (scored A-C) at 12, 24, 48, 72, 96 and 120 hours. The scales of assessment are depicted in figures 20, 21 and tables 1, 2.

Table 2: Behavioural pain assessment scale

Categories	Scoring			Total Score
	Score 0	**Score 1**	**Score 2**	
Face	Face muscles relaxed	Face muscle tension, grimace, frown	Frequent to constant frown, clenched jaw	
Restlessness	Quiet, Relaxed appearance, normal movement	Occasional restless movement, shifting position	Frequent restless movement may include extremities or head	
Muscle tone	Normal muscle tone	Increased tone, flexion of fingers and toes	Rigid tone	
Vocalization	No abnormal sounds	Occasional moans, cries, whimpers and grunts	Frequent or continuous moans, cries, whimpers or grunts	
Consolability	Content, relaxed	Reassured by touch, distractible	Difficult to comfort by touch or talk	
Behavioural pain assessment scale total (0-10)				

Instruction for BPAS:

1. Observe behaviours and rate each of the five measurement categories (0, 1 or 2) according to the descriptions provided
2. Add these ratings together
3. Document the total pain score out of ten

Score	Limitation	Yes/no
A	No limitation (perform task without pain)	
B	Mild limitation (perform task with minimal pain)	
C	Severe limitation (unable to perform the task)	

Observe the patient during the chosen activity / task (move the affected leg-i.e. toes, ankle) and scored as A, B, C

Instruction:

Patients who have received spinal anaesthesia for their surgical procedure will have some extent of motor blockade. Functional activity scoring should be done after return of motor function.

Exclusion:

Any pre-existing condition that the patient may already have restriction for chosen activity/task

Figure 21: Functional activity score

Table 3: Patient satisfaction score

Patient satisfaction score at the end of 24 hours	
1	Poor
2	Fair
3	Good
4	Excellent

Patient's pulse rate, blood pressure and respiratory rate were monitored immediately after recovery from anaesthesia and at 2, 4, 8, 12, 24, 48, 72, 96 and 120 hours postoperatively. Patients were administered injection tramadol 100 mg intravenously as rescue medication if VAS score was greater than three during the postoperative period. Patients' satisfaction with respect to pain relief was assessed using patient satisfaction score (Table 3) at the end of 24 hours post operatively. Adverse effects for both the drugs were monitored and causality assessed using WHO scale. The events were classified as –

- **Certain:** if it had a plausible time relationship to drug intake, if the adverse effect subsided on stopping the drug and if on rechallenge the adverse effect occurred
- **Probable:** if it had a reasonable time relationship to drug intake and if the adverse effect subsided on withdrawing the drug
- **Possible:** if it had a reasonable time relationship to drug intake, if the adverse effect could be explained by disease or other drugs
- **Unlikely:** if it had an improbable time relationship to drug intake, if the adverse effect could be explained by disease or other drugs
- **Conditional:** if more data for assessment was required
- **Unassessable:** if data could not be supplemented or verified

Sample Size Calculation

To detect a mean difference of 0.7 in visual analogue score with an effect size of 0.75, alpha error of 5%, power of 80% with a dropout rate of 10% the required sample size was calculated to be 38 patients per group.[5]

Statistical methods

1. The demographic data was assessed using descriptive statistics
2. The VAS and BPAS scores were assessed by Repeated measures ANOVA followed by Bonferroni post-hoc test within the group and unpaired 't' test between the groups
3. $TOTPAR_{24}$ and FAS was analysed using descriptive statistics
4. PSS and need for rescue analgesia were analysed using Mann-Whitney U test, Chi-square test respectively
5. Adverse effect was analysed using Fischer's exact test
6. p-value less than 0.05 was considered to be statistically significant

Results

RESULTS

A total of 76 patients undergoing lower limb surgeries were recruited in this study. They were randomized using computer generated, block randomization method to either group F or P. Following surgery all the patients received single dose of injection tramadol 100 mg intravenously in the recovery room. Patients in Group F received capsule flupirtine 100 mg and those in Group P received tablet piroxicam 20 mg respectively. Both the drugs were administered orally six hours after surgery and twice daily for the next five days. Seventy one patients completed the study. Figure 22 represents patient recruitment and follow-up.

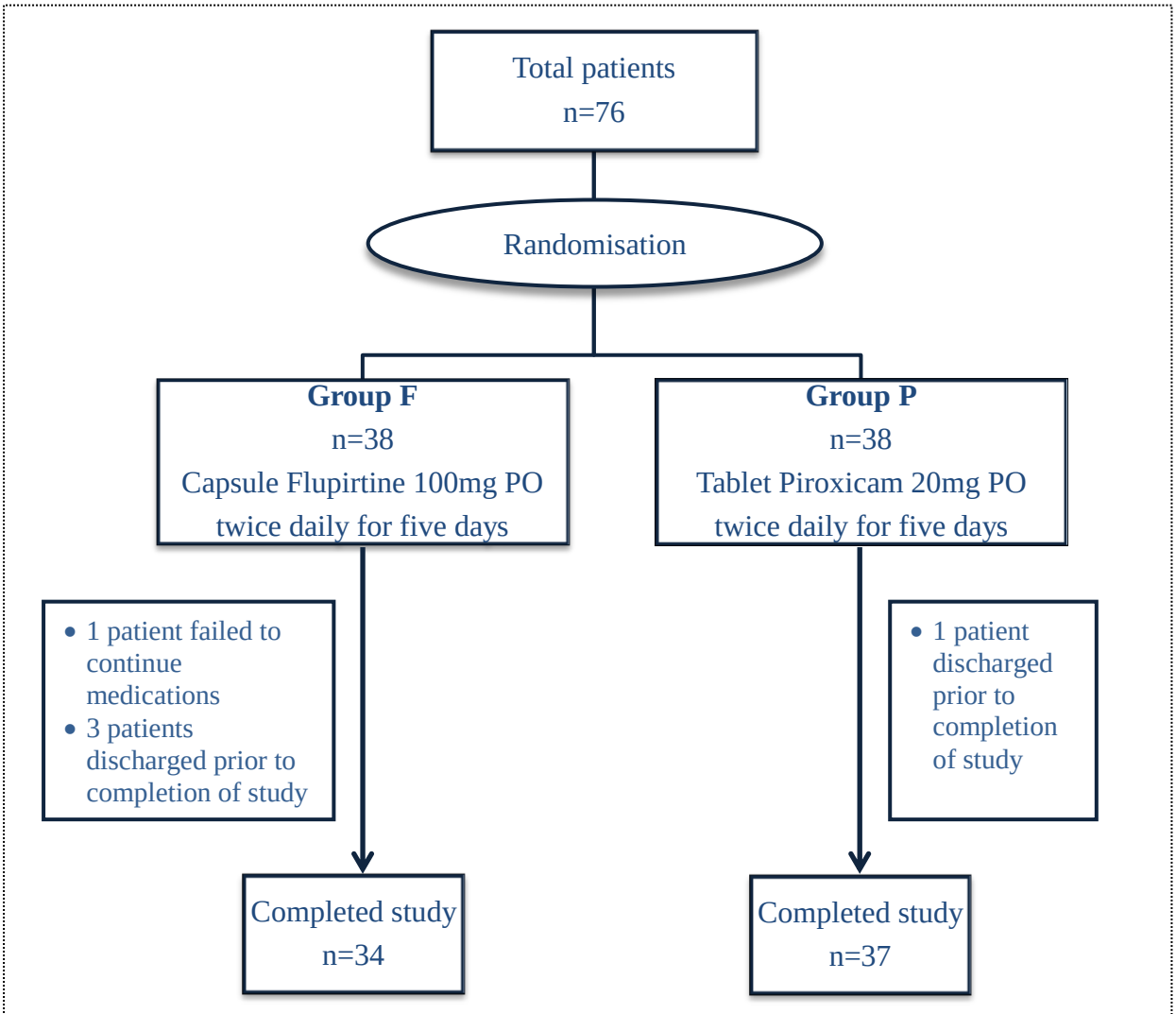

Figure 22: Flow chart representing recruitment of patients

Table 4: Baseline characteristics of all patients in both the groups

Variables	Group F (n = 38)	Group P (n = 38)	p-value
Male/Female	32/6	33/5	0.744
Age in years Mean±SD	35.08±10.42	35.08±10.22	1.000
Duration of surgery (in hours) Mean±SD	1.70±0.85	1.48±0.86	0.283

The baseline characteristics were comparable in both the groups (Table 4). The surgeries were performed under spinal anaesthesia using 3ml of 0.5% Bupivacaine. Among the 76 patients recruited, 65 were male and 11 female with an overall literacy rate of 59.21%. The type of surgeries are shown in figure 23, those requiring placement of orthopaedic implants contributed to 46.1% of the total patients and the distribution of type of surgeries between the groups was comparable (p = 0.054).

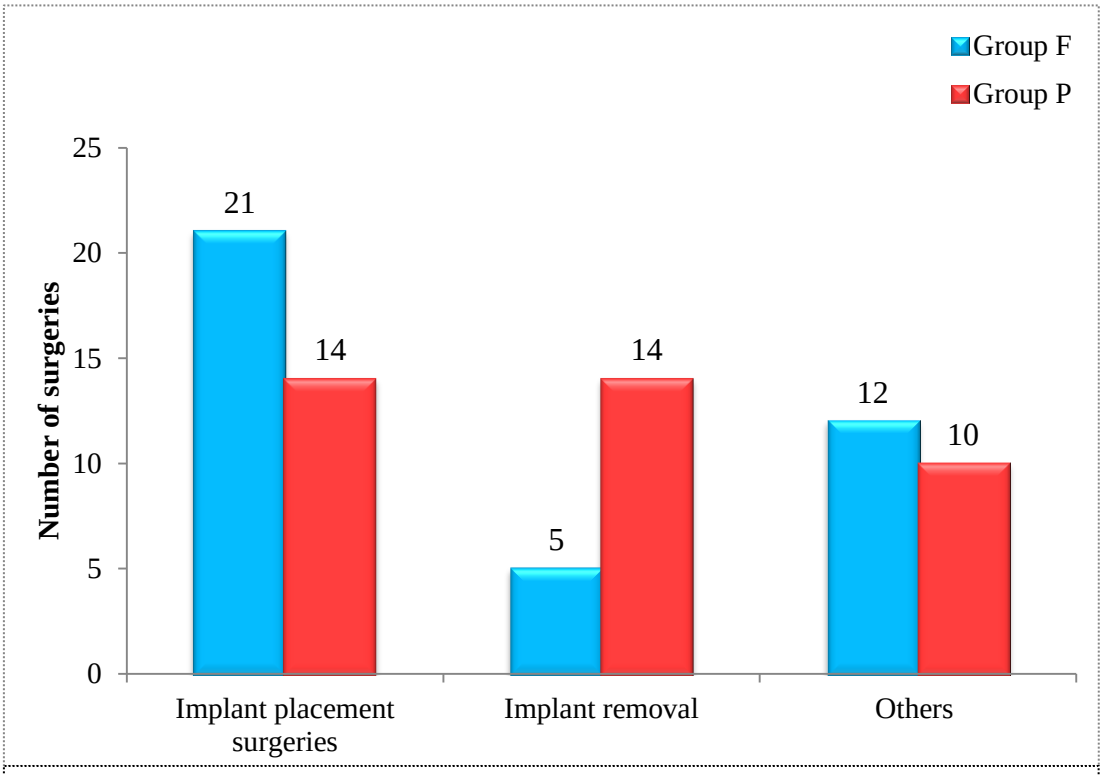

Figure 23: Types of surgeries in both the groups

Table 5: VAS score in patients of both the groups at various time points

Time in hours postoperatively	Group F (n = 34)		Group P (n = 37)		p-value
	Mean±SD	p-value	Mean±SD	p-value	
Baseline (Bl)	5.8±1.6		5.6±1.7		0.681
2h	5.4±1.2	1.000	5.1±1.4	0.660	0.253
4h	5.6±1.5	1.000	5.3±1.6	1.000	0.390
8h	5.8±1.3	1.000	5.1±1.5	1.000	0.028#
12h	5.3±1.1	1.000	4.5±1.6	0.060	0.032#
24h	4.8±1.3	0.171	4.7±1.4	0.058	0.713
48h	4.4±1.1	0.006*	4.1±1.5	0.0001*	0.354
72h	3.8±1.2	0.0001*	3.6±1.3	0.0001*	0.502
96h	3.1±1.1	0.0001*	2.8±1.3	0.0001*	0.346
120h	2.6±1.1	0.0001*	2.1±0.8	0.0001*	0.021#

* Comparison with baseline

Intergroup comparison

Table 5 shows the reduction in VAS score over time in patients of both the groups. The reduction in intensity of pain in Groups F and P was statistically significant at 48 hours and onwards compared to baseline. Piroxicam significantly reduced pain compared to flupirtine at 8, 12 and 120 hours. The pain experienced by the patient was also graded as mild, moderate and severe. Moderate pain was observed up to 72 hours by 55.9% patients in Group F and 48.6% in P, thereafter the intensity reduced to mild pain in both the groups.

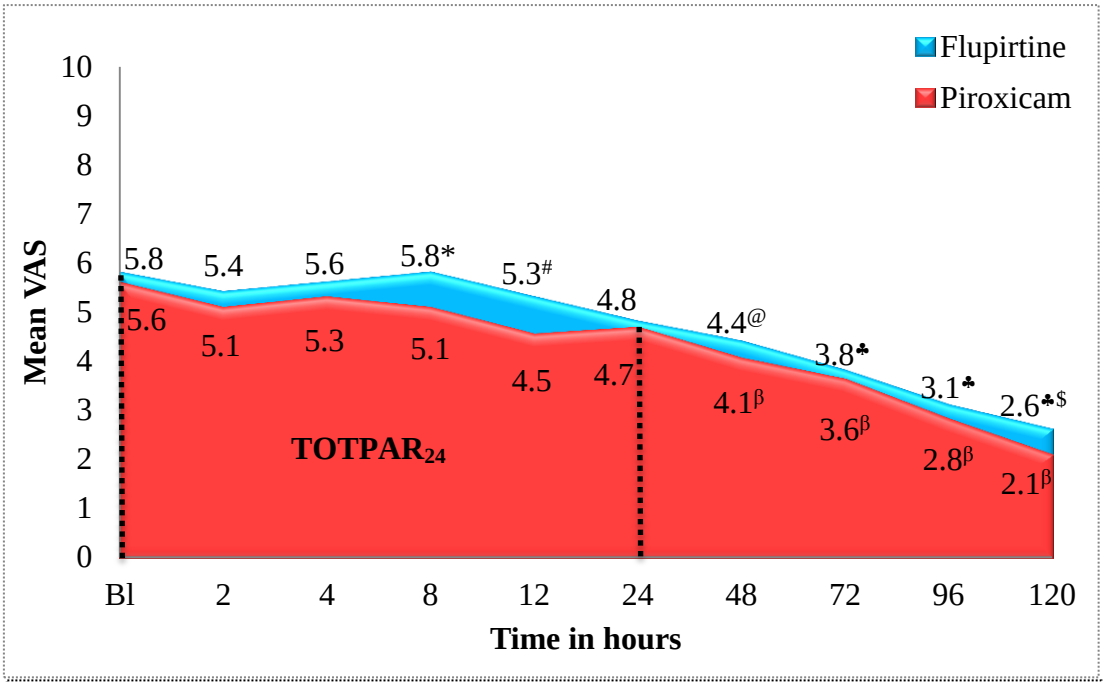

Figure 24: Areas under curve for flupirtine and piroxicam

Bl-Baseline

$^{@}p = 0.006$, $^{\clubsuit}p = 0.0001$, Comparison between baseline and Group F

$^{\beta}p = 0.0001$, Comparison between baseline and Group P

*p = 0.028 at 8 hours

$^{\#}p = 0.032$ at 12 hours

$^{\$}p = 0.021$ at 120 hours

} Intergroup comparison

The area under the curve for postoperative pain in patients receiving two different medications (Figure 24), was calculated by trapezoid rule which showed that the pain intensity expressed as $TOTPAR_{24}$, for the first 24 hours was lesser with piroxicam (116.38) than flupirtine (127.8) and a similar observation was noted there after upto 120 hours (piroxicam 332.64 and flupirtine 360).

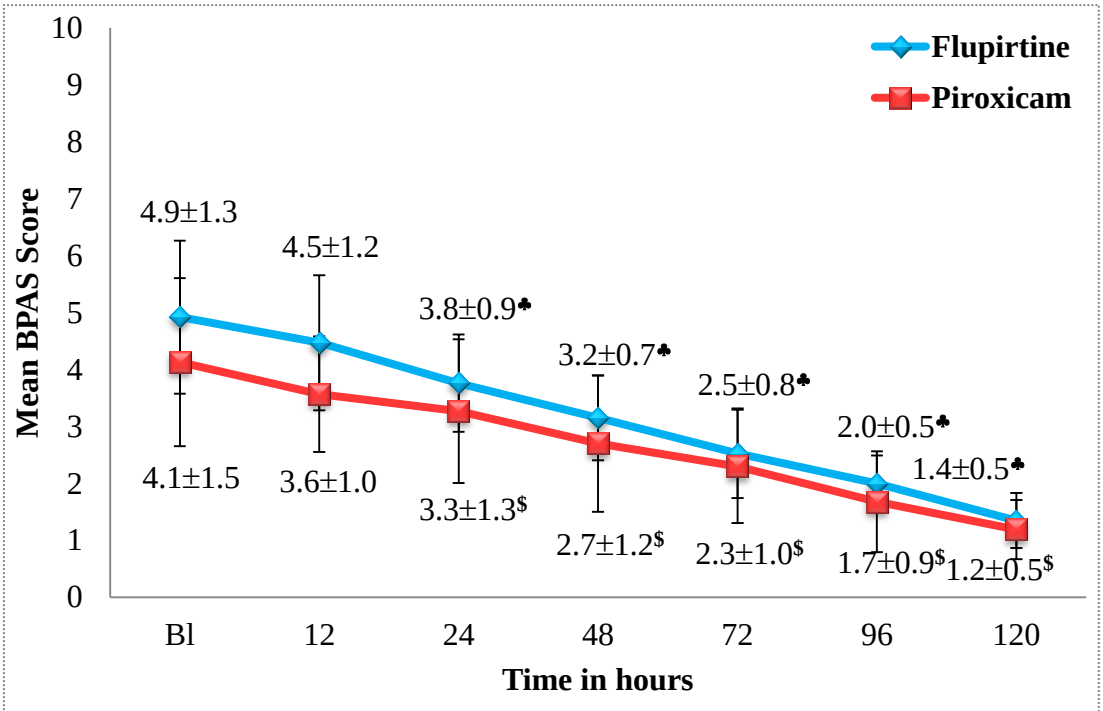

Figure 25: Comparison of mean BPAS scores within the groups

Bl-Baseline

♣p = 0.0001, Comparison between baseline and Group F

$p = 0.0001, Comparison between baseline and Group P

A decrease in mean BPAS scores was observed in both the groups (Figure 25) and was statistically significant within the group at all-time intervals of assessment after 24 hours postoperatively, as compared to baseline. At baseline only 23/71 of the patients could be assessed for FAS, of which 65.2% and 34.8% had moderate to severe limitation of activity in Groups F and P respectively (Table 6). In Group F, 6% patients and Group P, 27% had no limitation of activity at 72 hours and this improvement was observed in 59% and 54% of patients at 120 hours.

Table 6: Comparison of mean functional activity scores between two groups

Time Interval (hours)	Group	A (%)	B (%)	C (%)	NA (%)
Baseline	F	0	5 (14.7)	10 (29.4)	19 (55.9)
	P	0	5 (13.5)	3(8.1)	29 (78.4)
12	F	0	16 (47.1)	18 (52.9)	0
	P	1(2.7)	19 (51.4)	17 (45.9)	0
24	F	0	24 (70.6)	10 (29.4)	0
	P	3(8.1)	23 (62.2)	11 (29.7)	0
48	F	0	32 (94.1)	2(5.9)	0
	P	5 (13.5)	28 (75.7)	4 (10.8)	0
72	F	2(5.9)	31 (91.2)	1(2.9)	0
	P	10 (27.0)	27 (73.0)	0	0
96	F	11 (32.4)	22 (64.7)	1(2.9)	0
	P	16 (43.2)	21 (56.8)	0	0
120	F	20 (58.8)	13 (38.2)	1(2.9)	0
	P	20 (54.1)	17 (45.9)	0	0

A - No limitation B - Moderate limitation

C - Severe limitation NA - Could not assess

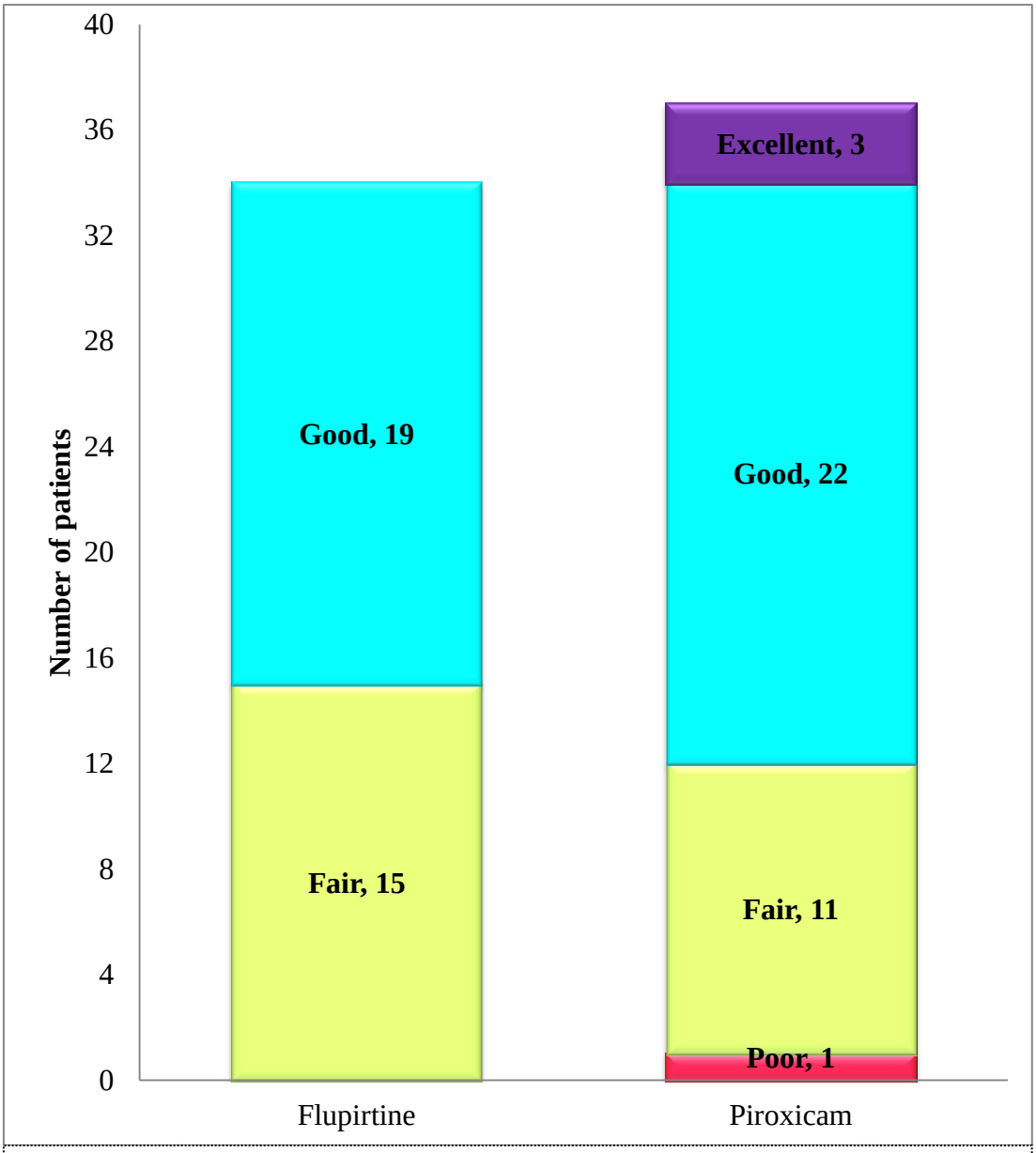

Figure 26: Patient satisfaction score in both the groups at end of 24 hours

In 55.9% patients of Group F and 59.5% of Group P the satisfaction score was 'Good' (Figure 26) and it was comparable (p = 0.698). The rescue analgesic tramadol was required by 18 and 22 patients in Group F and P respectively and it was insignificant between the groups (p = 0.58). Most patients (62.5%) in both the groups required one to two doses of the medication over the study period of five days and there was no significant difference in the number of doses between the groups (p = 0.365).

The most common adverse effect was dyspepsia which was observed in one patient receiving flupirtine and in three patients on piroxicam which was not statistically significant ($p = 0.4$). The effect of the study drugs on pulse, blood pressure and respiratory rate were assessed at different time intervals. There was no significant difference in these vital parameters within or between the groups.

Discussion

DISCUSSION

Pain management in post-surgical patients has been a major concern over the last few decades.[57] It is one of the important aspects to be considered because it is closely related to good clinical outcome. Orthopaedic procedures can cause severe intraoperative and postoperative pain which is indicative of tissue damage and is usually a major clinical problem occurring in 62 to 65% of patients.[28,58] Thus effective pain management is needed for recovery of range of movements, muscle strength for ambulation, rapid rehabilitation, shorter hospital stay and to improve the quality of life of patients.[59]

In our study majority were male patients with mean age of 35±10 years. Only the patients undergoing lower limb surgeries were recruited as the sensitivity of pain differs among different bones. The distribution of type of surgeries between the groups was comparable and predominant was implant placements (Figure 23). The mean duration of surgery was similar in patients receiving either medication. At baseline the mean VAS score was comparable between the two groups. The reduction in pain was significant at all points of time following 48 hours treatment as compared to baseline in both the groups (Table 5). This observation partly correlates with the findings of another study[60] indicating that though both the study drugs have a slight delay in onset, they have a longer duration of analgesia. Flupirtine used as pre-emptive analgesic in laparoscopic cholecystectomy surgery had provided adequate pain relief postoperatively in a study conducted by Yadav et al (2015)[61] and in post-abdominal hysterectomy study conducted by Thapa et al.[62] the above studies indicate that pre-emptive use of flupirtine could provide immediate postoperative pain

relief, hence administering this drug pre-emptively followed by postoperative dosing may be a better method for postoperative analgesia in orthopaedic surgeries.

In patients who received piroxicam, reduction in pain was significant at 8, 12 and 120 hours post operatively compared to flupirtine (Table 5). This suggests that patients receiving piroxicam had better analgesic effect compared to flupirtine. The $TOTPAR_{24}$ which is a measure of continuous pain relief also showed that piroxicam was better in relieving pain (Figure 24). However a study conducted by Yadav et al (2014) proved flupirtine to provide better analgesia than diclofenac[38] and that by Naser et al showed equal efficacy of flupirtine and ibuprofen in terms of analgesia when used in gynaecological surgeries. Similar studies by Attri et al, Ahuja et al, which compared flupirtine to other NSAIDs also revealed no significant difference between the medications in reducing postoperative pain.[5,60,63] These studies were conducted on patients undergoing gynaecological and other abdominal surgeries unlike the current study which was carried out in limb surgeries. The extensiveness and increased sensitivity of osteoid tissues tend to result in severe postoperative pain following surgeries involving the bone. Thereby the current study which assessed the efficacy of drugs on pain showed piroxicam to provide better analgesia than flupirtine.

The objective behavioural pain assessment scale (Figure 25) showed a reduction with both medications which reflects pain relief but another study has shown reduction in VAS score at an earlier point of time compared to BPAS score.[64] Improvement in the FAS reflects improvement in the range of movements in the operated limb. Majority of patients who had moderate to severe limitation of activity

at baseline improved over the first 96 hours (Table 6) and this was earlier in patients receiving piroxicam.

Patient satisfaction score at the end of 24 hours was good in 56% and 60% in flupirtine and piroxicam group (Figure 26). There was no significant difference in their satisfaction score which indicates that patients were contended with the medication they received. A study comparing similar drugs however showed flupirtine to have superior satisfaction score.[63] In our study the requirement of rescue analgesic was similar with both the medications, which was similar to another study.[63] In this study, the adverse effects were dyspepsia and dizziness. Dyspepsia was the only adverse effect in piroxicam group and is due to inhibition of protective effect of prostaglandin on gastric mucosa. Dizziness that occurred in a patient who received flupirtine could be attributed to the hypotension, which is a common side effect with flupirtine due to its effect on the K_v7 channels in vascular smooth muscle.[4] The study drugs showed no effect on the vital parameters such as pulse rate, blood pressure and respiratory rate.

The findings of our study imply that pain relief was similar with both the drugs but the onset was earlier with piroxicam. In individuals with history or risk of dyspepsia, flupirtine can be preferred.

Conclusion

CONCLUSION

- Most individuals undergoing orthopaedic surgeries were in their third decade and majority were male patients
- Implant placement surgeries were the predominant category of surgeries that were performed
- Patients received either flupirtine or piroxicam
- Mean VAS score reduced significantly after 48 hours in patients of both the groups and there was statistical significant pain relief in piroxicam group as compared to flupirtine group at 8, 12 and 120 hours
- $TOTPAR_{24}$, a measure of continuous pain relief also showed that piroxicam was better in relieving pain
- Behavioural pain assessment scale scores indicated pain relief following 24 hours of treatment with both the drugs
- Functional activity score improved earlier with piroxicam and majority of them had pain free movements
- Patient satisfaction score was similar in both the groups indicating that patients were contended with either of the analgesic received
- Most patients required only one to two doses of the rescue analgesic over a period of five days indicating the efficacy of both study medications
- The adverse effects were less in this study and the most common was dyspepsia
- Flupirtine and piroxicam reduced pain effectively but onset of pain relief was earlier with piroxicam

Summary

SUMMARY

Pain has been the most common problem encountered in the immediate postoperative period. Effective control of this pain has become essential as it helps in providing early mobilization, better recovery and cost-effective hospital stay. The existing medications used to relieve pain are NSAIDs, opioids, local anaesthetics, gabapentinoids, antiepileptics and steroids. Piroxicam, an oxicam derived NSAID, inhibits prostaglandin mediated pain and inflammation. Flupirtine, belongs to K_V7 potassium channel openers, exerting its action by exhibiting indirect antagonism on NMDA receptors of glutamate.

A total of 76 patients undergoing lower limb surgeries were recruited in this study. Following surgery all the patients received single dose of injection tramadol 100 mg intravenously. They were randomized to receive either capsule flupirtine 100 mg or tablet piroxicam 20 mg orally six hours after surgery and twice daily for the next five days. Seventy one patients completed the study. Intensity of pain was measured using VAS score at baseline, 2, 4, 8, 12, 24, 48, 72, 96 and 120 hours. $TOTPAR_{24}$ score for the first 24 hours and PSS at the end of 24 hours were assessed. The objective evaluation of pain was done using BPAS and FAS at 12, 24, 48, 72, 96 and 120 hours. Patients were administered injection tramadol 100 mg intravenously as rescue medication if VAS score was greater than three. Adverse effects for both the drugs were monitored and causality assessed.

Most individuals undergoing orthopaedic surgeries were in their third decade and majority were male patients. Implant placement were the predominant category of surgeries that were performed (46.1%). There was reduction in VAS score over time in patients of both the group and was significant at 48 hours and onwards

compared to baseline. Piroxicam reduced pain significantly compared to flupirtine at 8, 12 and 120 hours. The area under the curve for postoperative pain for the first 24 hours was lesser with piroxicam (116.38) than flupirtine (127.8). A decrease in mean BPAS scores was observed within the groups at all-time intervals after 24 hours postoperatively. In Group F, 6% patients and Group P, 27% had no limitation of activity at 72 hours and this improvement was observed in 59% and 54% of patients at 120 hours. In 55.9% patients of Group F and 59.5% of Group P the satisfaction score was 'Good'. The rescue analgesic tramadol was required by 18 and 22 patients in Group F and P respectively. In both the groups, 62.5% required one to two doses of the rescue medication during the study period. The most common adverse effect was dyspepsia observed in one patient receiving flupirtine and in three patients on piroxicam. Thus, flupirtine and piroxicam reduced pain effectively in patients following lower limb surgery but onset of pain relief was earlier with piroxicam.

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Annexures

PROFORMA

Serial No: Date:

OP No: IP 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:

10. Systemic examination:

CVS: RS:
PA: CNS:

11. Local examination:

12. Diagnosis:

13. Date of Surgery:

14. Time of start of Surgery: 15. Duration of Surgery:

16. Time of end of Surgery: 17. Duration of Anaesthesia:

18. Analgesics used from admission to shifting of patient to surgery:

19. Analgesics used in preoperative room:

20. Analgesics used intraoperatively:

21. Drugs used for anaesthesia:

22. Analgesics given in recovery room and the time of administration:

23. Time of start of oral feeds:

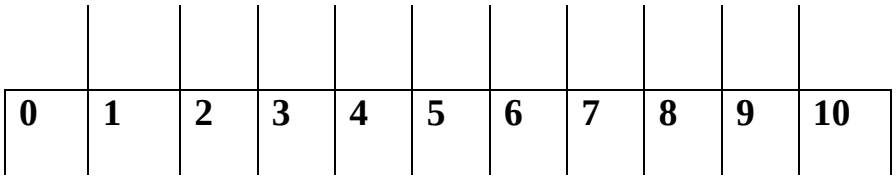
24. Time when study drugs given orally:
Flupirtine: Piroxicam:

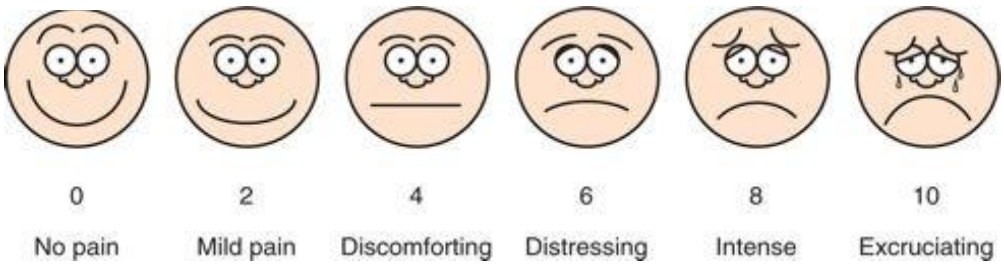
POSTOPERATIVE VITAL PARAMETERS

	Pulse	BP	RR
Baseline (Recovery room)			
2h			
4h			
8h			
12h			
24h			
48h			
72h			
96h			
120h			

METHODS FOR ASSESSMENT OF PAIN

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.

VAS	Baseline	2 h	4 h	8 h	12 h	24 h	48 h	72 h	96 h	120 h
Pain intensity										

BEHAVIOURAL PAIN ASSESSMENT SCALE

For patients unable to provide a self-report of pain: scored 0-10 clinical observation

BPAS	Baseline	12h	24h	48h	72h	96h	120h
Face							
Restlessness							
Muscle tone							
Vocalization							
Consolability							
Total score							

Instruction:

1. Observe behaviours and rate each of the five measurement categories (0, 1 or 2) according to the descriptions provided
2. Add these ratings together
3. Document the total pain score out of 10

FUNCTIONAL ACTIVITY SCORE (FAS)

	Baseline	12h	24h	48h	72h	96h	120h
FAS							

Instruction:

Patients who have received a spinal anaesthesia for their surgical procedure will have some extent of motor blockade. Functional activity scoring should be done after return of motor function.

Exclusion:

Any pre-existing condition that the patient may already have restriction for chosen activity/task.

ANY ADDITIONAL POST OPERATIVE ANALGESIA EFFECT (RESCUE MEDICATION)

Additional postoperative analgesia use		Total amount of analgesic used
No. of doses	Timing of drug administration	

PATIENT'S ASSESSMENT OF THE ANALGESIC USED (PATIENT SATISFACTION SCORE)

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

Patient satisfaction score	24h
Poor(1)	
Fair(2)	
Good(3)	
Excellent(4)	

SIDE EFFECTS OF PIROXICAM

	Baseline	2h	4h	8h	12h	24h	48h	72h	96h	120h
Flatulence										
Gastritis										
Skin rash										
Nausea										
Vomiting										
Dizziness										
Diarrhoea										
Hemorrhage										
Fatigue										
Others										

SIDE EFFECTS OF FLUPIRTINE

	Baseline	2h	4h	8h	12h	24h	48h	72h	96h	120h
Dizziness										
Headache										
Drowsiness										
Blurred vision										
Pruritus										
Dry mouth										
Nausea										
Vomiting										
Heart burn										
Gastric fullness										
Muscle tremor										
Disturbed sleep										
Fatigue										
Others										

Master Chart