COMPARISON OF EFFICACY AND SAFETY OF INTRAMUSCULAR PIROXICAM AND TRAMADOL FOR POST-OPERATIVE PAIN IN PATIENTS UNDERGOING CESAREAN DELIVERY

BY

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Dissertation submitted to the

Sri Devaraj Urs Academy of Higher Education and Research,

Tamaka, Kolar, Karnataka

In partial fulfillment of the requirements for the degree of

DOCTOR OF MEDICINE
IN
PHARMACOLOGY

Under the guidance of

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April 2014

Sri Devaraj Urs Academy of Higher Education and Research
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Declaration by the candidate

I hereby declare that this dissertation entitled **"COMPARISON OF EFFICACY AND SAFETY OF INTRAMUSCULAR PIROXICAM AND TRAMADOL FOR POST OPERATIVE PAIN IN PATIENTS UNDERGOING CESAREAN DELIVERY"** 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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ACKNOWLEDGEMENT

The writing of this dissertation has been one of the most significant challenges I have ever had to face. Without the support, patience and guidance of few kind hearted people, this study would have not been completed. It is to them that I owe my deepest gratitude.

I express my deep sincere gratitude to the ALMIGHTY GOD for the Blessings HE had bestowed upon me to do this work and my Life.

It gives me immense pleasure to express my deep sense of gratitude and sincere thanks to my guide, Dr BHUVANA K, Assosiate professor, Department of Pharmacology, Sri Devaraj Urs Medical College, Tamaka, Kolar. It is she who accepted the responsibility to oversee this thesis in mid – course and guided it to a successful completion by her patience, constant support and advice.

In this context, I owe my profound gratitude and heartfelt thanks to my Professor and initial guide Dr. KUMAR TN for his encouragement, guidance and support. And my continued reverence and acknowledgement to my former guide, Dr GIRISH M BENGALORKAR who undertook my partially completed dissertation work and motivated me to progress in this work despite his many other academic and professional commitments.

I am immensely pleased to place on record my deepest gratitude and reverence to Dr. Sarala N, Professor & HOD, Department of Pharmacology, Sri Devaraj Urs Medical College, Tamaka, Kolar. Her valuable suggestions and advice benefited in the completion and success of this study. Her endless passion in teaching is an inspiration to become a good teacher in future. I am gratefully indebted for her support.

I convey my deepest regards and earnest gratitude to my co – guide and Professor, Department of Obstetrics and Gynaecology, Dr M NARAYANASWAMY, for his support and advice and in preparing and completing this dissertation.

I thank Dr. NAGESH RAJU G, former Professor, Department of Pharmacology, Sri Devaraj Urs Medical College, Tamaka, Kolar, for his support and brilliant suggestions to my queries which helped me to progress my dissertation work.

I also thank Dr SMITHA RAI, Dr. MEENAKSHI LELLA, Dr JAYAKUMAR K and DR. ASHA B, Assistant professors in Department of Pharmacology for their encouragement and support.

I thank my colleagues Dr DHARMISTHA PATEL and Dr NANDISH C who were helping me out at every level in completing my dissertation. I thank Dr Revathi Ramesh, Dr CHETAN KUMAR G, Dr DHEEPAN NAYAGAM B, Dr GANASHREE P, Dr VARADARAJU Y, Dr ASHWITHA SHRUTI DASS, the postgraduate colleagues and my senior postgraduates Dr BALAMURALI K, Dr HARISH S and Dr VIDHYALAKSHMI C P in the Department of Pharmacology for their valuable feedback and support and I am also thankful to all the post graduates in the department of Obstetrics and Gynaecology for their constant support in case collection. I thank all the non teaching staff of Department of Pharmacology for helping out in carrying out this dissertation. And I express my sincere gratitude to all the subjects for providing me the opportunity to carry out this study.

I am infinitely obliged to my father Mr THIPPESWAMY C, my mother Mrs. SANNAMMA TV who supported me in all my work and decisions and also to my brother HARSHA T for his constant support and co – operation in my work. And I am very grateful to my husband Dr PRADEEP KUMAR CN without whom this would have been hard to complete. His moral support and constant patience gave me an immense energy in completing this work.

Date:

Place: Kolar Dr. TEJASHREE T

Dedicated

with

Reverence to my parents

List of abbreviations

NSAIDs	–	Non Steroidal Anti – inlammatory Drugs
VR1	–	Vanilloid Receptor 1
VRL1	–	Vanilloid Receptor Like 1
CGRP	–	Calcitonin Gene Related Peptide
5 – HT	–	5-Hydroxytryptamine
DMPP	–	Descending Modulatory Pain Pathways
TRPV1	–	Transient Receptor Potential Vanilloid 1
NMDA	–	N-methyl D-aspartate
PCA	–	Patient Controlled Analgesia
VAS	–	Visual Analogue Scale
MPQ	–	McGill Pain Questionnaire
PAG	–	Periaqueductal gray
COX	–	Cyclooxygenase
TENS	–	Transcutaneous Electrical Nerve Stimulation
COPD	-	Chronic Obstructive Pulmonary Disease

Abstract

Background and Objectives:

Post operative pain is an unavoidable sequel of major surgery which adversely affects the quality of life of patients and their care givers. Adequate management of pain is necessary for the good clinical outcome. Post caesarean section pain has to be managed effectively and rapidly to facilitate early ambulation and infant care. Both NSAIDs and opioids are used for pain relief. But, the use of opioids is associated with adverse effects which affects both the mother and the child.

Objectives of this study are:

1. To study the efficacy and safety profile of piroxicam and tramadol in post cesarean section pain
2. To assess the total amount of rescue analgesic required in the first 24 hours after surgery
3. To assess the patient's degree of satisfaction with regard to pain relief.

Materials and Methods:

Primigravidae undergoing elective cesarean section were randomly allocated to receive either piroxicam 20mg or tramadol 100mg intramuscularly, immediately after recovery from anaesthesia. Pain was assessed by Visual Analogue Scale (VAS) and side-effects were noted at baseline, 2, 4, 8, 12 and 24 hours post-operatively. Rescue analgesic butorphanol 2mg was administered intramuscularly if VAS was more than 4. Patient's satisfaction score was assessed at 12hours post operatively.

Interpretation and Results:

The mean age in piroxicam and tramadol groups was 22.03 ± 2.0 and 23.32 ± 3.43 years respectively. Significant reduction in pain was observed at 2, 4, 8, 12 and 24 hours in both the groups ($p<0.001$). Pain relief was significant at 2, 4 and 8 hours in piroxicam group compared to tramadol. Twenty-one patients in tramadol group received rescue analgesic butorphanol and 12 in piroxicam group. Sedation and nausea was significantly higher in tramadol group ($p<0.001$). 46.66% of patients graded their satisfaction score as good and 15% as excellent in piroxicam group. Intramuscular piroxicam 20mg showed reduction in post cesarean section pain for 24 hours with minimal side-effects compared to tramadol.

Key words: Post caesarean section pain, piroxicam, tramadol.

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Introduction

Introduction

Pain serves as an important biological function by signalling presence of damage or disease within the body. Post-operative pain is an inevitable consequence of major surgery, resulting from surgical trauma and handling of tissues. [1]

The inadequate relief of postoperative pain has adverse physiological effects that can contribute to significant morbidity and mortality, resulting in the delay of patient recovery and return to daily activities. [2]

Despite advances in post-operative pain management, post-operative pain relief and satisfaction are still inadequate in some patients because of individual variability and side effects of analgesic drugs or techniques. [3] Post caesarean section pain is usually relieved by opioids and NSAIDs.

Caesarean delivery patients have even more compelling reasons to achieve optimal postoperative pain relief than other surgical patients. They are at a higher risk for thromboembolic events, which may be precipitated by immobility from inadequate pain control or excessive sedation from opioids. It also impairs breastfeeding and bonding. Reduction of post caesarean section pain poses an additional challenge that the drug used should be safe during lactation. Systemic opioid administration provides adequate post-operative pain relief, but are known to cause significant side effects such as respiratory depression, nausea, vomiting and constipation. [4]

Tramadol, a synthetic opioid of the aminocyclohexanol group is a centrally acting analgesic with opioid & non-opioid modes of action which act synergistically. It has been shown to provide effective analgesia after both intramuscular and

intravenous route in post-operative pain. But, the use of tramadol has been associated with nausea, vomiting, sedation and sweating.[1,5]

An oxicam derivative, piroxicam which, despite being effective is also devoid of the unwanted effects of tramadol mentioned above, notably nausea, vomiting and sedation. [6]

But, there is a paucity of comparative studies between piroxicam and tramadol in post caesarean section pain among primigravida in India. Hence this study has been undertaken to compare the efficacy and safety of these drugs in the management of post caesarean section pain. Both the drugs have been reported to be safe during lactation and hence the choice, even though more recent analgesics are available whose safety remains a concern.

Objectives

Objectives of the study

1. To study the efficacy of piroxicam and tramadol in the management of post cesarean section pain
2. To study the safety profile of piroxicam and tramadol in the management of post caesarean section pain
3. To assess the total amount of rescue analgesic required in the first 24hrs after surgery
4. To assess the patient's degree of satisfaction with regard to relief of pain

Review of Literature

Review of literature

HISTORICAL BACKGROUND

Pain is the oldest medical problem and the universal physical suffering of mankind. Leeches were the mainstay in conventional 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.

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. Hunt O, a famous surgeon in Chinese medical history used this method for carrying out operations on various organs.[7]

European physicians judiciously used of opium to relieve pain after 1680, laudanum, the mixture of opium in sherry introduced by Thomas Sydenham . The opium poppy was cultivated as early as 3400 BC in Mesopotamia. The term opium refers to a mixture of alkaloids from the poppy seed.[8]

Early 1800s Morphine was first separated from opium by European chemists, and was found soon after in the United States, where it began to take the place of opium in patented pain medicines.

In1874 the cannabis plant, from which marijuana is made, became a well-regarded headache remedy by prominent physicians. In1898, Heroin the newest opium derivative, was first produced commercially by Germany's Bayer Company.

British scientist Michael Farady discovered that an electric current can produce a magnetic field and viseversa was also true. This observation served as the basis for neurostimulation. French scientist G. Gaiffe constructed an electrical nerve stimulating device called the Gaiffe TENS unit, which had all of the basic components of a modern neurostimulation device. But its low electrical output

(3 milliamperes) made it ineffective for neurostimulation.[7] Neurosurgeon C. Norman Shealy was the first surgeon to begin implanting neurostimulators in humans for pain relief. By 1970, six patients had undergone this treatment.

In 1980s the use of opioids administered directly to the spinal column via epidurals emerged as a treatment for chronic pain. In1991 the first prototype of a radio-frequency (RF) spinal cord stimulation system was developed for the relief of chronic neuropathic pain. Later in 1997 IntraDiscal Electrothermic Therapy (IDET) was introduced as an investigative treatment for chronic low back pain. This procedure involves killing of nerve fibers by heating a catheter positioned inside the spinal disc.

In 2002 the U.S. department of health & human services reported that narcotic analgesics were involved in 16% of total drug abuse-related emergency room visits. Therefore, the use of these drugs has been largely restricted for severe illness.

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 newest advancement in neuromodulation devices for the treatment of pain. In 2008 St. Jude introduces the Eon Mini TM neurostimulator, the world's smallest, longest-lasting rechargeable neurostimulator to treat chronic pain of the trunk or limbs and pain from failed back surgery.[7,9]

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.[10]

Pain was called by Sherrington, "the physical adjunct of an imperative protective reflex". Painful stimuli initiate potent withdrawal and avoidance responses. The response to pain can be highly variable among persons as well as in the same person at different times.[11]

Pain has been classified into two major types: fast pain and slow pain. Fast pain is felt within about 0.1 second after a pain stimulus is applied, whereas slow pain begins only after 1 second or more and then increases slowly over many seconds and sometimes even minutes. Fast pain is also described by many alternative names, such as sharp pain, pricking pain, acute pain, and electric pain. This type of pain is felt when a needle is stuck into the skin, when the skin is cut with a knife, or when it is acutely burned. Slow pain also goes by many names, such as slow burning pain, aching pain, throbbing pain, nauseous pain, and chronic pain. This type of pain is usually associated with tissue destruction.[12]

The term nociception is derived from noci (Latin for harm or injury), is used to describe the neural response only to traumatic or noxious stimuli. And the receptors which initiate pain are called nociceptors.

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 the periosteum, the arterial walls, the joint surfaces, and the falx and tentorium in the cranial vault.

Mechanical nociceptors respond to strong pressure (e.g., from a sharp object). Thermal nociceptors are activated by skin temperatures above 45 °C or by severe cold. Chemically sensitive nociceptors respond to various agents like bradykinin, histamine, high acidity, and environmental irritants. Polymodal nociceptors respond to combinations of these stimuli.

Vanillins are group of compounds, including capsaicin, that cause pain. The VR1 receptors respond not only to capsaicin but also to protons and to temperatures above 43 °C. VRL-1, which responds to temperatures above 50°C but not to capsaicin, has been isolated from C fibers. VR1 has a PIP_2 binding site, and when the amount of PIP_2 bound is decreased, the sensitivity of the receptors is increased.[13]

Acute pain: Acute pain typically has a sudden onset and recedes during the healing process. Acute pain can be considered as "good pain" as it serves an important protective mechanism. The pain is usually 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.

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. It has a dull, aching quality and is less well – localized.

Visceral pain: The visceral 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 and changes in blood pressure and heart rate.[13]

Referred pain: It can be visceral or parietal, 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.[14]

Chronic pain: Chronic pain is a prolonged pain, persisting beyond the expected normal healing time. This period can vary from 1 to 6 months. Chronic pain may be nociceptive, neuropathic or mixed. It can be continuous or intermittent. It is 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, including nonsteroidal anti-inflammatory drugs (NSAIDs) and opiates. It can result from nerve injury (neuropathic pain) including diabetic neuropathy, toxin-induced nerve damage, and ischemia.

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 successfully for relief of many chronic pain syndromes such as neuropathic pain, low back pain and fibromyalgia. These drugs block the reuptake of neurotransmitters such as epinephrine and norepinephrine, thereby altering neurotransmission along pain pathways. [11]

Post-operative pain

Post-operative pain is a type of acute pain, is a complex response to tissue trauma during surgery. It is one of the main postoperative adverse outcome causing distress to patients, prolonging hospital stay after surgery. Patients with moderate to severe pain

during post-operative period and patients who have undergone with risk of nerve damage are more likely to develop chronic pain.

Factors affecting the severity of post-operative pain

Type of surgery - (1) Size of the wound, amount of tissue damage

(2) Muscle cutting or splitting incision

(3)Technique, delicacy of dissection and retraction, type of stitch.

Site of surgery - (1)Movement of damaged tissues (e.g. chest and upper abdominal surgery)

(2)edema in a confined space (e.g. total knee replacement).

Patient factors - (1) Age, sex, medical condition and emotional state

(2) Other sources of distress: nausea, sleeplessness

(3) Cultural background - Attitudes to illness, treatment and pain.

Advantages of effective treatment

1. Physiological: Attenuating the stress response and reducing the sympathetic stimulation.

2. Clinical: Effective analgesia promotes patient co-operation with physiotherapy, improved respiratory function, earlier feeding, better mobilization with reduced risk of pressure sores and deep vein thrombosis. There will be improvement in respiratory, cardiovascular and the overall outcome. Early and aggressive treatment of acute pain may prevent the development of chronic postoperative pain.

3. Organizational: Reduction in post-operative complications and improved mobility. Earlier discharge results in cost savings.

Reasons for failure

Post-operative pain can be treated effectively with appropriate combinations of local anaesthetic, opioids, non-steroidal anti-inflammatory drugs (NSAID). Sub-optimal use of conventional drugs is the commonest cause of failure of analgesia that may lead to complications.[15]

Mechanism of post-operative pain

Pain after surgery is a compilation of several unpleasant sensory, emotional, and mental experiences, associated with autonomic, endocrine-metabolic, physiological, and behavioural responses. Surgical procedures causes damage to skin and various other tissues. Application of thermal and chemical stimuli to wound and often prolonged traction and manipulation of somatic and visceral structures also contribute to damage and destruction of tissues.

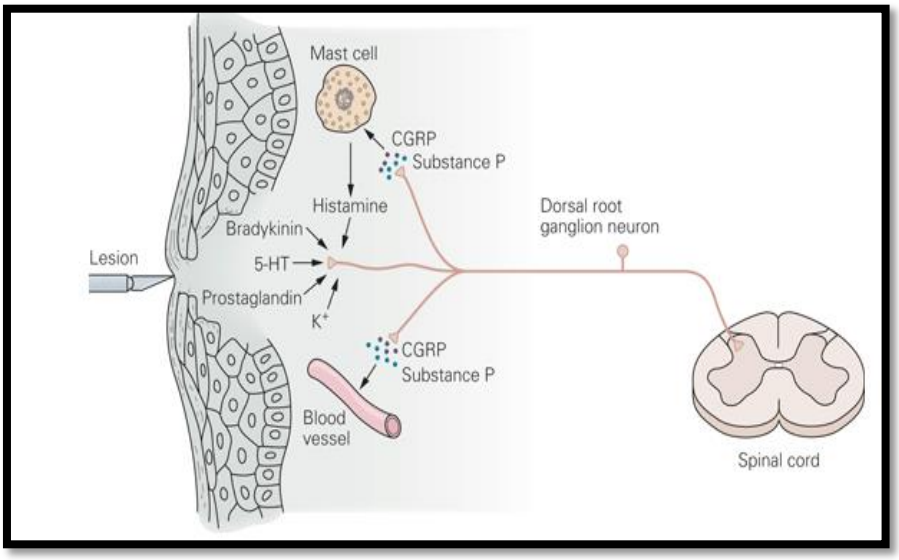


Fig: 1 Diagrammatic representation of action of chemical mediators[16]

In response to tissue injury, chemical mediators can sensitize and activate nociceptors. These factors 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 activates nociceptors. Substance P causes plasma extravasation and CGRP dilates blood vessels. The resulting edema causes additional release of bradykinin. Serotonin (5-HT) is released from platelets and activates nociceptors.[11]

Modulation of post-operative pain

Nociceptive pain is the key feature of acute post-operative pain. Modulation of nociceptive transmission occurs at multiple (peripheral, spinal, supraspinal) levels. Multiple complex pathways are involved which are referred to as the descending modulatory pain pathways (DMPP) and these can lead to either an increase in the transmission of pain impulses (excitatory) or a decrease in transmission (inhibition).

Peripheral modulation

It refers to increased pain perception to a given stimulus after an initial thermal or mechnical injury. Transient receptor potential family (especially TRPV1, heat and capsaicin sensitive) and tetrodotoxin-resistant sodium channel are the important receptors involved in the transduction of a pain signal. Many chemicals cause peripheral sensitization via these receptors.

Bradykinin is a 9-amino acid peptide chain formed by proteolytic cleavage of its kininogen precursor, high-molecular-weight kininogen, increased with noxious stimulation. It activates G protein coupled receptors (BK2) which then activates protein kinase C. This increases activity at the ion channel TRPV1. Also sensitises TRPV1 receptors through a protein kinase C independent manner, which is thought to

be caused by release of prostaglandins from the TRPV1 receptor. Bradykinin also contributes to vasodilation and increased vascular permeability of the injury site.

Prostaglandins are autocrine and paracrine lipid mediators that act upon neurons to sensitize them. They are formed by the action of cyclooxygenase on arachidonic acid. Prostaglandins, especially PGE2 and PGI (via their receptors EP1 and IP respectively) are thought to activate protein kinases C and A. They can both increase activity at the TRPV1 and Nav1 receptors respectively. Hence nociception transmission is enhanced. PGE2 is also be involved in the enhancement of activity at the primary afferents in the spinal cord.

Substance P is an important neuropeptide in primary afferents, especially in C fibers. It is released by sensory nerve endings locally by noxious stimuli and also via the axon reflex. It activates the neurokinin-1 receptor. It causes increased vascular permeability, vasodilatation and increased synthesis of prostaglandins. In addition calcitonin gene related peptide is another co-transmitter released together with substance P with similar actions.

Neurotrophic factors such as fibroblasts and mast cells are over expressed in tissue injury, promoting thermal sensitivity. Nerve growth factor sensitize nociceptors to substance P and other noxious stimuli. They also exert long term gene expression changes in nerve cells.

Histamine released by activation of mast cells causes smooth muscle contraction, vasodilation and thus encourages immune cells to reach the injury site. Serotonin is another important mediator released from mast cells and platelets. Serotonin (5-HT), is an algogen capable of directly (via ion channels) or indirectly (via protein phosphorylation) activating nociceptive afferent fibers.

All the above mediators take variable time frames to occur. Hence, after an initial period of injury, pain becomes worse with further stimuli, even innocuous ones. This hyperalgesia and allodynia due to various chemical mediators with one facilitating the other, to cause peripheral sensitization.[17]

Central modulation

Central sensitization 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." N-methyl D-aspartate (NMDA) receptor plays a key role in this process. NMDA activation induces calcium entry into sensory neurons in the dorsal horn induces activation of nitric oxide (NO) synthase, leading to the synthesis of NO. NO 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 sensitization. Repeated or prolonged input from C-nociceptors or damaged nerves causes a longer-lasting increase in dorsal horn neuron excitability and responsiveness.

Central sensitization is associated with a reduction in central inhibition, less recruitment of responses from neurons that normally respond to low intensity stimuli (altered neural connections). Clinically, these changes may manifest as: 1) an increased response to a noxious stimulus (hyperalgesia), 2) a painful response to a normally innocuous stimulus (allodynia), 3) prolonged pain after a transient stimulus (persistent pain), and 4) the spread of pain to uninjured tissue (referred pain).

Inhibition

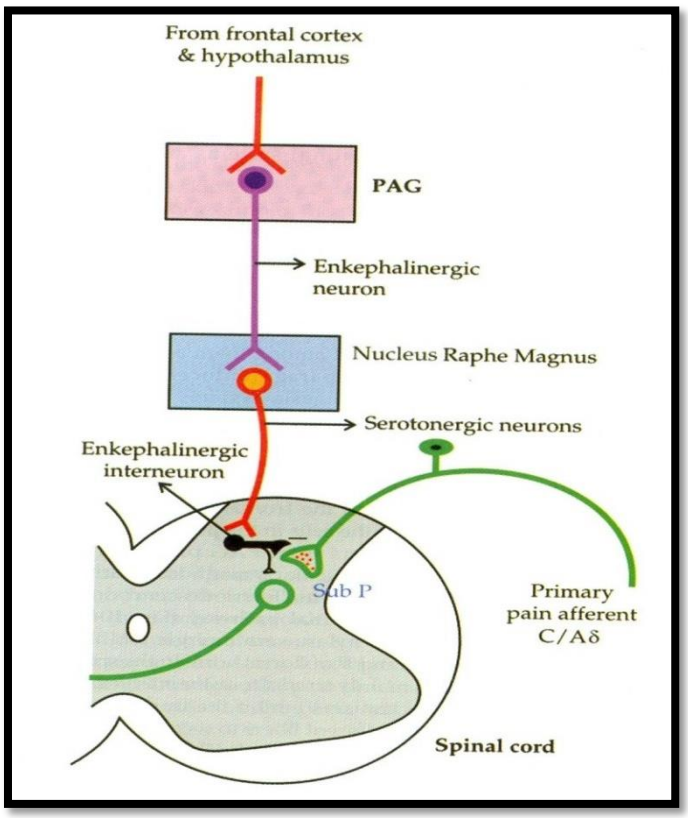


Fig: 2 Central inhibition

At supra spinal level: The periaqueductal gray and periventricular areas of the mesencephalon and upper pons send signals to the raphe magnus nucleus and the nucleus reticularis paragigantocellularis. From these nuclei, second-order signals are transmitted down the dorsolateral columns in the spinal cord to a pain inhibitory complex located in the dorsal horns of the spinal cord. At this point, the analgesia signals can block the pain before it is relayed to the brain.

At spinal level: The enkephalin is believed to cause both presynaptic and postsynaptic inhibition of incoming type C and type Aδ pain fibers where they synapse in the dorsal horns. Thus it can block pain signals at the initial entry point to the spinal cord.[13]

Gate control theory

This was proposed by Ronald Melzack and Patrick Wall during the early 1960s, with the idea that the perception of physical pain is not a direct result of activation of nociceptors, but instead it is modulated by a neurological "gate" that either blocks pain signals or allows them to continue on to the brain. The "gate" in the spinal cord operates by differentiating between the types of fibers carrying pain signals. Stimulation of large diameter fibres inhibits the transmission of pain thus closing the gate, whereas when smaller fibres are stimulated, the gate is opened. When gate is closed, signals from small diameter pain fibres do not excite the dorsal horn transmission neurons. It is often used to explain phantom or chronic pain.

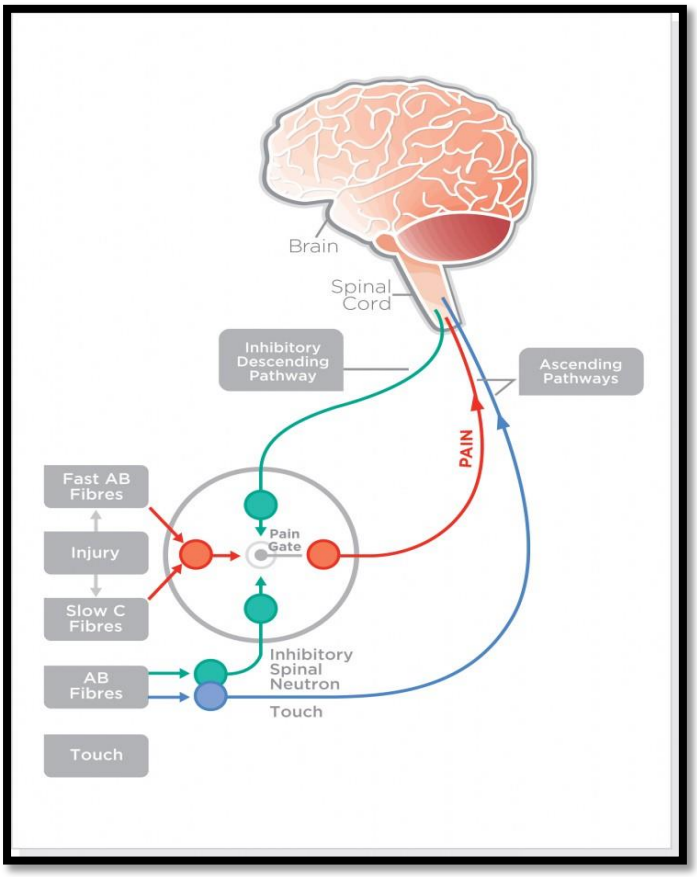


Fig: 3 The Gate control theory of pain[18]

Pathways involved in transmission of post-operative pain

There are two separate pathways for transmitting pain signals into the central nervous system. The two pathways mainly correspond to the two types of pain—an acute / fast pain pathway and a chronic / slow pain pathway. 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 6 and 30 m/sec. The 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 fibers at velocities between 0.5 and 2 m/sec. The Aδ and C fibers are involved in the transmission of pain impulses through the peripheral nerves. Spinal cord gray matter is divided into 10 lamina. The first six laminae which make up the dorsal horn receive all the afferent neural activity and represents the principal site of modulation of pain by ascending and descending neural pathways.

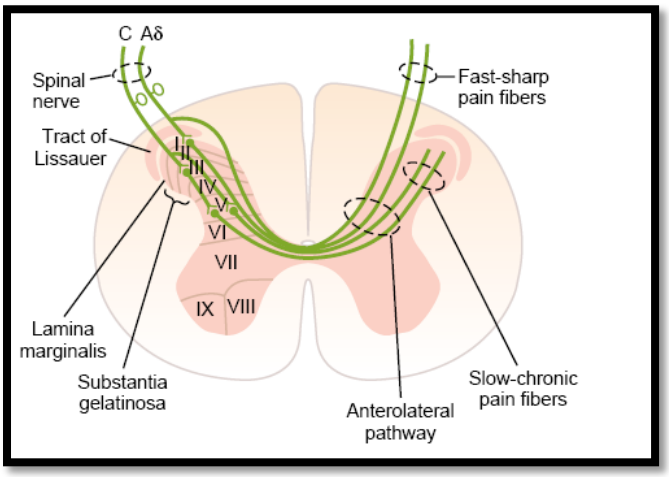


Fig: 4 Transmission of fast and slow pain fibres through the spinal cord[12]

The two ascending pathways are the neospinothalamic tract and the paleospinothalamic tract. [12] Neospinothalamic tract is the main pathway for transmission of acute post-operative pain.

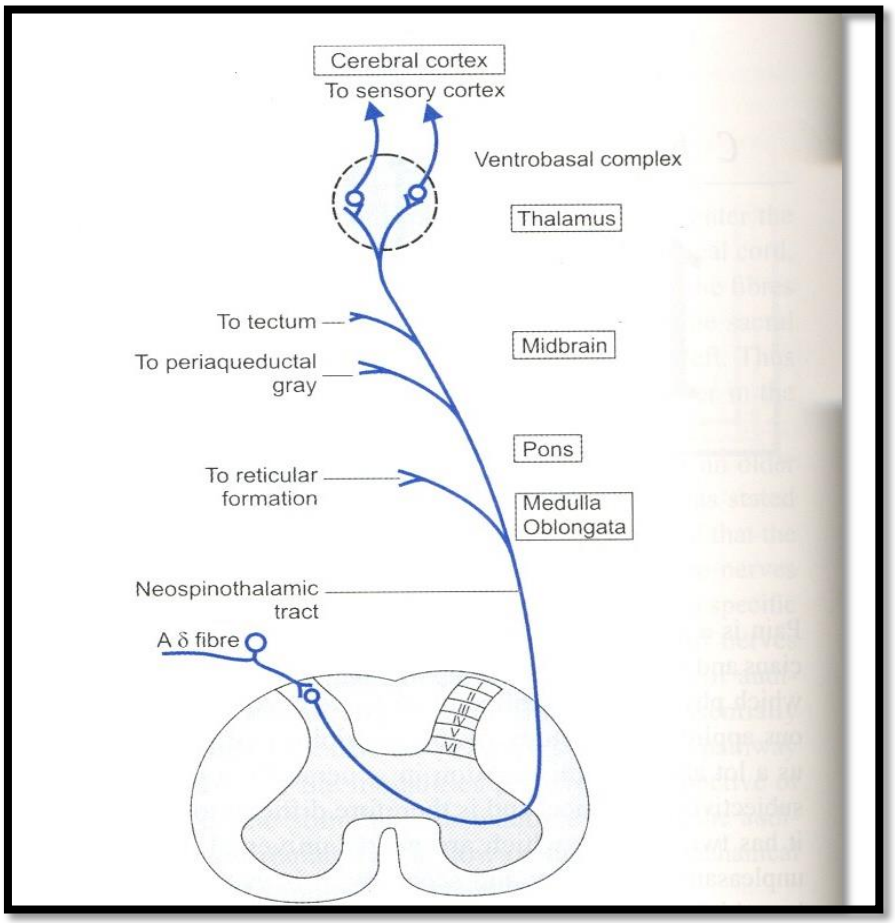


Fig: 5 Neospinothalamic tract[12]

The fast type Aδ pain fibers transmit mainly mechanical and acute thermal pain. They terminat in lamina I (lamina marginalis) of the dorsal horns and there 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. 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.[12]

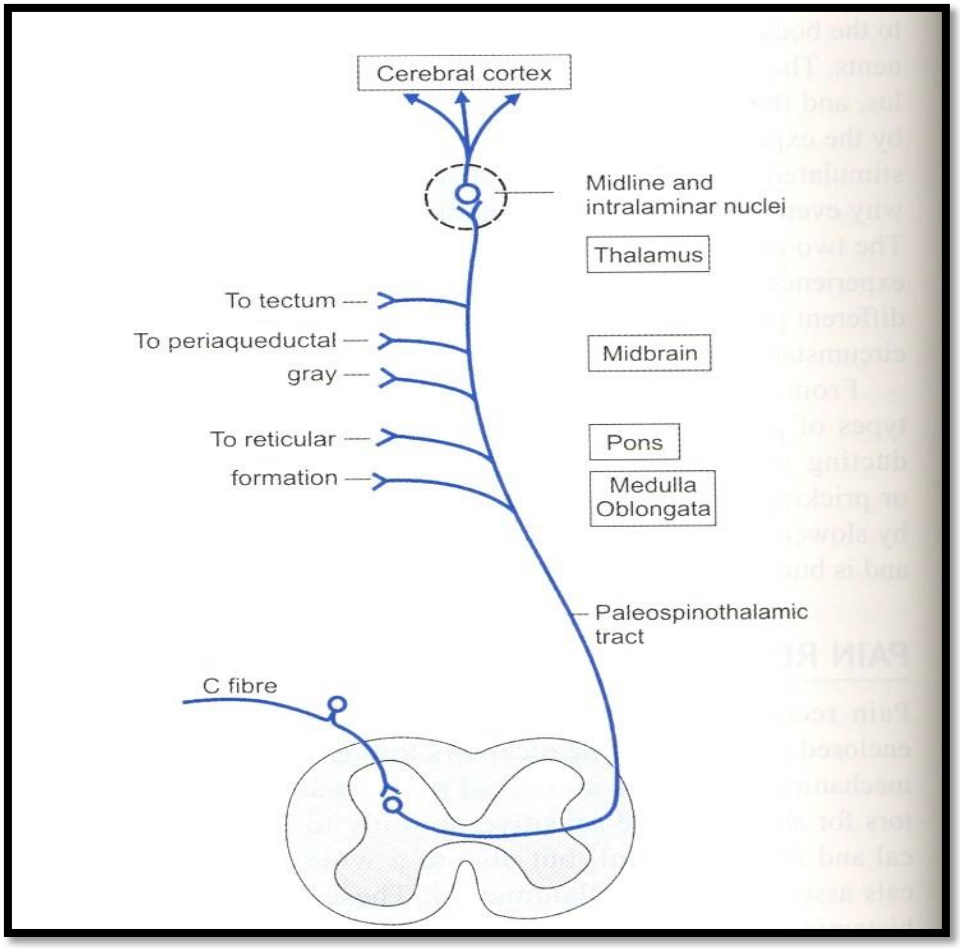


Fig: 6 Paleospinothalamic tract[12]

Patients with moderate to severe pain during post-operative 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 fiber 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 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.[12]

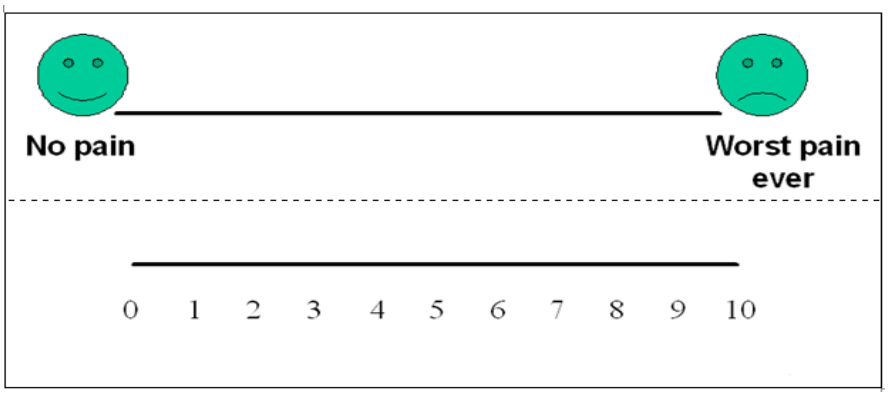
Assessment of pain

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 Assessment Scales[19,20]

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.

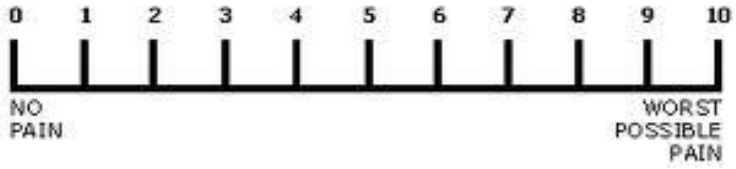
1. **Visual analogue scale (VAS)**



The most common and traditional method for assessment of pain is visual analogue score from 0 to 10, with zero being no pain and ten being the worst pain. A visual analogue scale (VAS) 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 it from discrete scales such as the numerical rating scale. This makes visual analogue scale superior metrical to discrete scales, thus a wider range of statistical methods can be applied to the measurements.

2. **Numerical rating scale**



The Numeric Rating Scale is a simple reporting instrument that can help to quantify a patient's subjective pain. The Numeric Rating Scale is administered by asking the patient to verbally estimate his or her pain on a scale of 0 to 10, with 0 representing no pain and 10 representing the worst possible pain

3. **Faces rating scale**

This rating scale is recommended for children ages 3 and older. Ask the child to choose the face that best describes his or her own pain, and note the appropriate number.

4. **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.

5. Behavioural rating scale

The behavioural 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 behaviours (restlessness, tense muscles, frowning/grimacing, patient sounds from none-severe). Obtain a pain score based on the highest behaviour observed.

6. Functional activity scale

This is an activity-related score. Ask your patient to perform an activity related to their painful area (for example, deep breathe and cough for thoracic injury or movement of the affected leg for lower limb pain).

Observe your patient during the chosen activity and score 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

7. CHEOPS scoring - paediatrics

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.

It involves 6 parameters: minimum score is 4 and maximum score is13.

Modes of analgesia

Pre-emptive analgesia

It is a antinociceptive treatment that prevents the establishment of altered central processing, which amplifies post-operative pain. It is based on the observation that if afferent pain signals are prevented from reaching the central nociceptive neurons by preinjury administration of analgesia, sensitization of the central neurons will not take place or will be reduced.

Advantages - Reduces acute perioperative pain arising from surgical wounds.

- Decreases the dose of analgesics post - operatively.
- Prophylaxis against pathologic chronic pain states.
- Amputees have been found less likely to experience phantom limb pain.[21]

Pre-emptive analgesia aims to prevent these changes by –

- Blocking transmission to the spinal cord (local anaesthetics)
- Preventing 'wind-up' (NMDA antagonists)
- Modifying pain processes within the spinal cord and brain (opioids)

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 which produce additive or synergistic analgesia used for the control of post-operative pain. The benefits of this approach are – it reduces the total dose of analgesia required in the post-operative period, improved pain relief, less adverse effects, enable patient for early discharge from the hospital and decreased cost.[2]

Patient controlled analgesia (PCA)

Patient-controlled analgesia encompasses a variety of techniques that provide effective postoperative pain relief without systemic exposure to opioids. Using PCA, patients control the application of pre-programmed doses of local anesthetics (ropivacaine or bupivacaine) 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 common drug used in a dose of 1 – 1.5 mg with a lock out period of five to ten minutes. It can be administered through intravenous, subcutaneous and epidural routes.

Post-operative pain management

Pharmacological measures

Opioid analgesics

Opioids acts as agonists on stereospecific opioids receptors (μ, δ and κ) at presynatic and postsynaptic sites within the CNS and in the peripheral tissues. Opioids mimic the actions of endogenous ligands by binding to opioid receptors, resulting in the activation of pain – modulating system.

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 1 and 2, which convert arachidonic acid to prostaglandins, responsible for both peripheral and central sensitization.

Non opioids – non NSAID

Flupirtine is neither an opioid nor a NSAID produces analgesic action through blockade of N – methyl – D – aspartate receptor by activation of K^+ channels. It also has muscle relaxant, neuroprotective and antiparkinsonian property. It is devoid of adverse effects of opioids and NSAIDs because of its unique mechanism of action. It is used in musculoskeletal pain, post-operative pain, neurogenic pain, cancer pain and fibromyalgia.[22]

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, gabapetin, pregabalin, dexmedetomidine, clonidine, neostigmine

Local anaesthetics

A local anesthetic is a drug that causes reversible local anesthesia 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 allow patients to undergo surgical and dental procedures with reduced pain and distress. In many situations, such as cesarean section, it is safer and therefore superior to general anaesthesia. Use of local anaesthetics preemptively reduces the dose of general anaesthesia and thus the adverse effects of general anaesthetics.

Local anaesthetics in use are lignocaine, bupivacaine, ropivacaine, tetracaine, prilocaine.

TRPV1antagonists

TRPV1 is expressed on small myelinated 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 grey and cortex. Activation of TRPV1 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 TRPV1 channels by chemicals but not by other painful stimuli like heat.[23]

Non – pharmacological measures

Transcutaneous electrical nerve stimulation (TENS) applied with a strong, subnoxious intensity and adequate frequency in the wound area reduce analgesic consumption in the post-operative period.

Accupuncture is another non – pharmacological means which is helpful in acute pain management in the post-operative period.[13]

Table 1- Complications of post-operative pain[13]

Functional Domain Stress	Responses to Pain	Examples of Clinical Manifestations
Endocrine/metabolic	Altered release of multiple hormones (e.g., ACTH, cortisol, catecholamines, insulin) with associated metabolic disturbances	Weight loss Fever Increased respiratory and heart rate Shock
Cardiovascular	Increased heart rate Increased vascular resistance Increased blood pressure Increased myocardial oxygen demand	Unstable angina (chest pain) Myocardial infarction (heart attack) Deep vein thrombosis (blood clot)
Hypercoagulation	Decreased air flow due to involuntary (reflex muscle spasm) and voluntary ("splinting") mechanisms that limit respiratory effort	Atelectasis Pneumonia
Gastrointestinal	Decreased rate of gastric emptying, Decreased intestinal motility	Delayed gastric emptying, constipation anorexia, ileus
Musculoskeletal	Muscle spasm Impaired muscle mobility and function	Immobility Weakness Fatigue
Immune	Impaired immune function	Infection
Genitourinary	Abnormal release of hormones that affect urine output, fluid volume, and electrolyte balance	Decreased urine output Hypertension (fluid retention) Electrolyte disturbances

Quality of life

Inadequate control of pain interferes with the patient ability to carry out daily activities (e.g., work, relationships, hobbies, sex) and also has adverse psychological consequences. Patients with inadequately managed pain may experience anxiety, fear, anger, depression, or cognitive dysfunction, and family members report varying levels of helplessness, frustration. These consequences are likely to occur in patients with chronic pain.[13]

Introduction to opioids

Opium is a dark brown resinous material obtained from poppy capsules called papaver somniferum. Serturner, a German pharmacist first isolated the active principle of opium in 1806 and named it morphine after the Greek God of dreams – Morpheus. The term opioid denotes all naturally occurring, semisynthetic and synthetic drugs which have morphine like action (relief from pain and depression of CNS). Opioids have long been used to treat acute pain (such as post-operative pain). They have also been found to alleviate the severe, chronic, disabling pain of terminal conditions such as cancer and degenerative condition such as rheumatoid arthritis.[9]

Opioids acts through specific opioids receptors – μ, κ and δ. The opioids receptors are members of G protein coupled receptor family signals via a second messenger cyclic adenosine monophosphate or an ion channel.

Opioid receptors

Table 2 - Classification of opioid receptors and their actions [24]

Receptor sub types	Mu (μ)	Kappa (κ)	Delta (δ)
Actions	Supraspinal (μ_1) and spinal(μ_2) analgesia, respiratory depression, sedation, euphoria, miosis, reduced gastrointestinal motility, physical dependence	Supraapinal (κ_3)and spinal (κ_1) analgesia, respiratory depression, dysphoria, hallucinations, sedation, physical dependence, reduced gi motility	Spinal and affective component of supraspinal analgesia, respiratory depression, affective behavior, reinforcing actions, reduced gi motility.
Endogenous opioids peptide	Endorphin>Enkephaline>Dynorphine	Enkephaline>Endorphin &Dynorphine	Dynorphine>Endorphin & Enkephaline

Opioids exert its analgesic action at spinal and supraspinal levels.

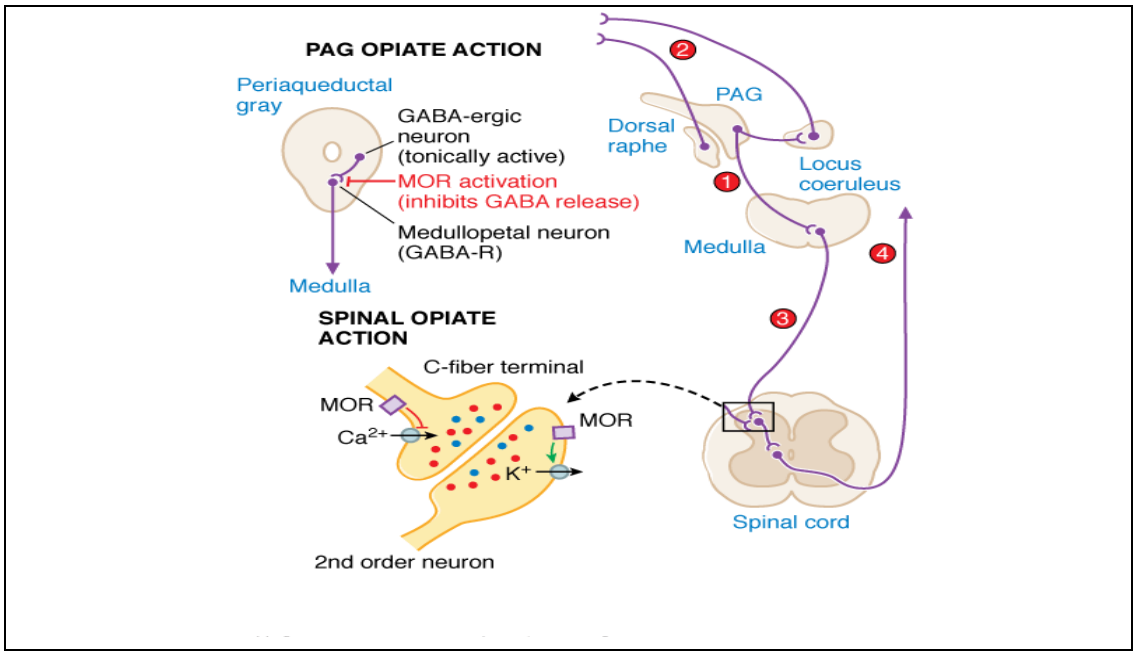


Fig: 7 Spinal and supraspinal actions of opioids[25]

Spinal action: The primary afferent synapse with the second order neuron, where pre and post synaptic opiate receptors are coupled with ca++ and k+ channels respectively. Activation of μ opioids receptors (MOR) presynaptically, blocks the opening of voltage sensitive ca++ channels which inhibits the production of excitatory neurotransmitter at C – fiber terminal and the pain impuse carrying through ascending neuron is ceased. MOR activation postsynaptically enhances opening of k+ channels, leading to hyperpolarization, thereby suppressing the evoked excitation of the second order neuron.

Supra spinal action: The periaqueductal matter (PAG) situated in the mid – brain play an important role in the descending modulation of pain. Stimulation of PAG by μ – opioid agonists inhibits the release of GABA and therefore activates enkephalin releasing neurons that project to the raphe nuclei where serotonin is released. The released serotonin descends to the dorsal horn of the spinal cord causing excitation of the inhibitory interneurons, these will inhibit the release of excitatory

neurotransmitter from Aδ and C fibers thereby inhibiting the activation of second order neurons which carry pain impulse to the thalamus. [25]

Opioid induced side effects include sedation, nausea, vomiting, respiratory depression and constipation .Less common side effects include confusion, urinary retention, dizziness and myoclonus.[25]

Most commonly used opioids in post-operative pain management are morphine, fentanyl, tramadol, tapentadol, butorphanol, buprenorphine, pethidine.

Morphine is the prototype and is the gold standard to which all other opioids are compared. Plasma half-life is 2hours but its analgesic duration is 4 – 5 hours. It undergoes hepatic glucuronidation to morphine – 6 – glucuronide which is a active metabolite and contributes to its analgesic action and also for its side effects like drowsiness, nausea, vomiting, respiratory depression.

Hydromorphone is a semisynthetic opioid, 4 – 5 times more potent than morphine. Its bioavailability via subcutaneous route is 78%, and therefore is the ideal drug for long term subcutaneous administration in the opioid – tolerant patient. The active metabolites are dihydromorphine and dihydroisomorphine.

Fentanyl, a synthetic opioid, 80 times more potent than morphine. It is extensively metabolized in the liver and therefore suitable for patients with renal failure. Sufentanil, alfentanil and remifentanil are analogues of fentanyl. Sufentanil is 1000 times more potent than morphine. It is highly lipophilic and has shorter elimination half-life. The high intrinsic potency of sufentanil makes it an excellent choice for epidural analgesia in opioid dependent patients. Alfentanil is 10 times more potent than morphine. Remifentanil is an ultrashort acting synthetic opioid. It gets rapidly degraded by tissues and plasma esterases. Its t1/2 is 10 – 20 minutes. Rapid

clearance and lack of accumulation makes it a desirable opioid in the operative setting.

Meperidine is a synthetic μ opioid agonist. It is biotransformed in the liver to normeperidine, a potentially neurotoxic metabolite with a t1/2 of 12 – 16 hours. Repetitive dosing can cause accumulation of normeperidine, which may precipitate tremulousness, myoclonus and seizures.

Buprenorphine is a potent semisynthetic opioid derived from thebaine. It is a mixed agonist, antagonist and partial μ receptor agonist with an analgesic potency 25 – 30 times greater than morphine. Its half-life for dissociation from the receptor is 166 minutes compared to 7 minutes for fentanyl. Therefore on epidural administration there will be very little progression to cephalad portion and less chance of respiratory depression. It is an excellent alternative for the treatment of acute pain in the patient who cannot tolerate morphine secondary to allergy or other sensitivity. It has a ceiling effect for respiratory depression but not for analgesia.

Butorphanol is a κ agonist and μ antagonist opioid. It is best suited for relief of acute pain and because of its potential for antagonizing μ receptor agonists, should not be used in combination with other opioids.

Tramadol is synthetic codeine analogue. It has dual mode of action that is it acts as μ receptor agonist and inhibits uptake of norepinephrine and serotonin. It has less respiratory depression as compared to morphine. The primary O – demethylated metabolite of tramadol is 2- 4 times as potent as the parent drug and is suitable for acute pain.

Tapentadol is structurally and mechanistically similar to tramadol. It has a mild opioid activity and possess monoamine reuptake inhibitor activity. Similar to tramadol, in its action, efficacy and side effects.

Pharmacology of tramadol

Introduction

Tramadol is a centrally acting analgesic. It is a synthetic 4 – phenyl- piperdine analogue of codeine. It has both opiate agonist activity and monoamine reuptake inhibition that contribute to its analgesic efficacy used in treating moderate to severe pain. It is a racemic mixture of 2 enantiomers, each one displaying different affinities for various receptors. The action of these two enantiomers is both complementary and synergistic and results in the analgesic effect of tramadol.[26]

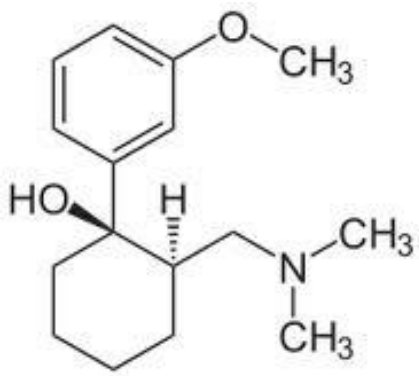
History

The German pharmaceutical company named Grunenthal GmbH decided to fight against the pain that was being suffered by millions of patients all over the world. Grunenthal GmbH was founded in 1946 in German and it has been owned by a family (The Wirtz) since then. Their first objective was to produce medicines for the penniless German inhabitants after the Second World War. To manufacture their products they used medicinal herbs they cultivated on their leased land. In 1948, the company experienced an important event, Grunenthal brought the first penicillin medication to the market.

In 1962, tramadol was discovered and Tramal (tramadol) development started. After 15 years of uninterrupted investigation, Tramal was launched in 1977. This molecule revolutionized the painkiller market because it was different from other opioids as it has a dual mode of action. After the first tramadol release, other companies started to market this drug with a wide range of brand names and different pharmaceutical forms. It has been improved to offer patients faster and better pain

relief.[27] Tramadol has been available in other countries since 1977 and is now marketed in more than 100 countries worldwide. The Food and Drug Administration (FDA) approved tramadol in 1995.[28]

Structure and chemistry [26]



The chemical name is (±)cis-2-[(dimethylamino)methyl]1-(3-methoxyphenyl) cyclohexanol. Tramadol is a unique analgesic offering dose-dependent pain relief through its action at multiple sites. It consists of two enantiomers, both of which contribute to analgesic activity via different mechanisms. Tramadol and the metabolite O-desmethyltramadol are agonists at the opioid receptor. Tramadol also stimulates presynaptic release of serotonin and inhibits serotonin reuptake whereas tramadol inhibits norepinephrine reuptake-1. Thus, tramadol enhances inhibitory effects on pain transmission both by opioid and monoaminergic mechanisms.[26]

Pharmacokinetics

Tramadol is rapidly and almost completely absorbed after oral administration. However, its mean absolute bioavailability is only 65–70% due to the first-pass hepatic metabolism. Following a single 100 mg oral dose, plasma Cmax of approximately 300 ng/mL is reached within 1-3 hrs.

Tramadol is distributed in the body, with a mean distribution half-life of 1.7 hrs. The high volume of distribution of 306 litres after oral administration indicates its high tissue affinity. The plasma protein binding of this drug is 20%.[29]

The bioavailability of tramadol hydrochloride after intramuscular injection administration is nearly 100%, the mean peak serum concentration is achieved after 45 minutes. Tramadol hydrochloride has a linear pharmacokinetic profile within the therapeutic dosage range.

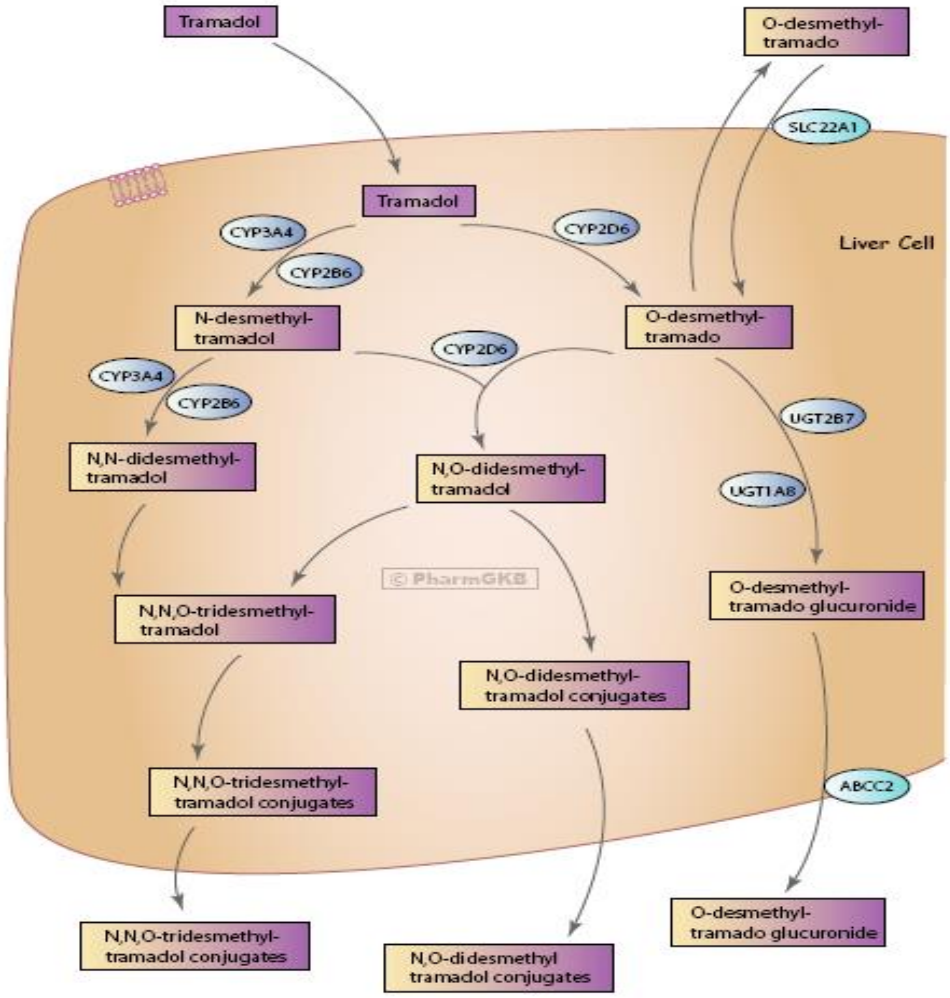


Fig: 8 Metabolism of tramadol[30]

Tramadol is extensively metabolized in the liver by O and N-demethylation and by conjugation reactions to form glucuronides and sulfates. Elimination of

tramadol and its metabolites is predominantly via the kidneys. The O-desmethyled tramadol(M1) is catalysed by cytochrome P450 (CYP) 2D6. The N-desmethyltramadol (M2) is catalysed by CYP2B6 and CYP3A4. M1 and M2 may then be further metabolized to secondary metabolites N, N-didesmethyltramadol (M3) and N,O-didesmethyltramadol (M5), and then to N, N,O-tridesmethyltramadol (M3). In the phase II metabolism, O-desmethyltramadol is inactivated by glucuronidation in the liver via UGT2B7 and UGT1A8. Among all its metabolites, only O-desmethyltramadol (M1) and to a lesser extent N,O-didesmethyltramadol (M5), are pharmacologically active.

O-desmethyltramadol (M1) has a significantly higher affinity (2 to 4 times) for opioid receptors than the parent drug and is more potent in producing analgesia.[24] Tramadol hydrochloride has a linear pharmacokinetic profile within the therapeutic dosage range.

Tramadol hydrochloride and its metabolites are excreted mainly in the urine. The elimination half-life is 5 to 7 hours, but is prolonged in impaired hepatic and renal function. Tramadol hydrochloride crosses the blood-brain and placental barrier. Small amounts are excreted unchanged in breast milk.[30]

Mechanism of action

Tramadol is a centrally acting analgesic with dual mode of action comprising both μ opioid and monoaminergic agonism. In-vivo and in-vitro studies suggest that the analgesic activity is independently mediated by each of the enantiomers of tramadol and the metabolite O – demethyl tramadol (M1) contribute to its analgesic action.[31]

Tramadol has been shown to exhibit only low affinity for opioid receptors and like morphine, binds more selectively to μ receptors than to κ or δ opioid receptors.

The analgesic action of tramadol is only partially inhibited (less than 30%) by the opioid antagonist nalaxone suggesting the existence of another mechanism of action. Tramadol exert its analgesic effect through activation of this central inhibitory monoaminergic pathway by inhibiting norepinephrine and serotonin reuptake thus attenuating the dorsal horn exitability.[32]

Pharmacodynamics

Analgesic effects

The analgesic effect of tramadol is due to synergistic activity of the racemate with further contribution from M1 metabolite. The peak effect occurs 1- 4 hours after oral drug administration and analgesia persists for 3-6 hours. Hepatic demethylation of tramadol by the liver enzyme cytochrome P450 (CYP) 2D6, sparteine-oxygenase play a major role in mediating the analgesic effect of this agent. Since ~8% of Caucasians are deficient in CYP2D6 (poor metabolisers), tramadol may have reduced analgesic effects in these patients.[33]

Respiratory effect

Opioid analgesics are generally associated with respiratory depression, mediated through a decrease in sensitivity of the respiratory centre to CO2 which results in a decrease in respiratory rate and tidal volume. Tramadol, unlike other opioids , is unlikely to produce clinically relevant respiratory depression at the recommended dosage. However, respiratory depression may occur if the recommended dosage is considerably exceeded.[34]

Cardiovascular system

Tramadol does not have clinically relevant effects on heart rate or blood pressure in adults and children. A case series study showed that none of the patients had serious cardiovascular effects on tramadol overdose.[35]

Gastrointestinal system

Tramadol causes slight increase in gastric emptying and colonic transit time. It also induces nausea and vomiting which is due its monoaminergic inhibition property. The incidence of constipation is very less compared to other opioids.[36]

Central nervous system

Tramadol produces CNS effects like dizziness, sedation, headache, euphoria, CNS stimulation (tremor, agitation, anxiety, hallucination), dysphoria and seizures. Incidence of seizures is less than 1% and is linked with predisposition such as, epilepsy, alcohol / drug withdrawal or antidepressant therapy. Tramadol is known to possess anticonvulsant effect mediated by kappa-receptors.[37]

Antidepressant effect

Antidepressant effect is based on monoaminergic reuptake inhibition.[38]

Immunomodulatory effects

Tramadol significantly depress T lymphocyte function at analgesic doses, but does not modify the activity of natural killer cells, which mediate cytotoxic effect against tumour cells and are important in immune defence against viral infection.[39] Another study demonstrated immunostimulatory properties of tramadol. In contrast to Morphine, tramadol increased natural killer cell activity in normal non-operated rats and was able to prevent surgery-induced suppression of natural killer cell activity.[40]

Uses

1.Treatment of moderate to severe post-operative pain.[37]

2. Treatment of chronic pain.[41]

3. Diabetic neuropathy – Relieves pain by acting as a central analgesic.[42,43]

4. Post herpetic neuralgia.[44,45]

5. Acute opioid withdrawal management.[46]

6. Obsessive compulsive disorder.[47]

Adverse effects

Tramadol produces fewer adverse effects similar to other opioids like nausea, vomiting, dizziness, dry mouth, sedation and headache which are dose dependent. Minimum effective dose has to be started during the initial days of treatment to improve the tolerability.

Respiratory depression is less than with equianalgesic dose of morphine and the degree of constipation is less than that seen after equivalent doses of codeine. It can cause seizures and exacerbate seizures in patients with predisposing factors.[25]

Less common adverse effects are ataxia, dilation of pupils, numbness of limbs, tremulousness and dysphoria. The majority of adverse effects appeared to be attributable to inhibition of monoamine reuptake rather than opioid effects.

Drug interactions

Tramadol is extensively metabolised in the liver via CYP3A4 and CYP2D6 enzymes and thus, drugs acting on these enzymes may affect the pharmacokinetic properties of tramadol. Concomitant administration of tramadol with carbamazepine, an inducer of hepatic enzymes, resulted in 50% reduction in tramadol t1⁄2, through induction of the metabolism of tramadol

The risk of seizures is increased if tramadol is used with other drugs that have the potential to lower the seizure threshold tricyclicantidepressants, SSRIs, MAO inhibitors, doxepin, nefazodone, clozapine, cyclosporine, pethidine, fentanyl, propofol.

Serotonin syndrome can occur at high doses when used along with other drugs that raise serotonin concentrations which includes TCA's, SSRI's, MAO inhibitors.

Anticoagulant - warfarin effect is prolonged when given along with tramadol. The symptoms appear after 3 –5 days of starting of oral tramadol. The warfarin dose should be reduced by 25- 30% with repeat measurement of the INR in patients who are starting tramadol therapy.

The preoperative use of ondansetron has been noted to reduce the postoperative analgesic efficacy of tramadol.[37]

Dosage and administration

Tramadol is available as tablet, capsule, suppository, ampoule for IM/IV for moderate to severe pain. It can also be given by infusion or as a part of a patient controlled analgesia system. Tramadol hydrochloride can be given orally as a modified – release preparation once or twice daily.

A dose of 50 – 100mg given 4 – 6 hours by intramuscular or intravenous injection over 2 – 3 minutes. For the treatment of post-operative pain, the initial doses 100mg followed by 50mg every 10 – 20 minutes if necessary to a maximum of 250mg in the first hour. Rectal doses by suppository are 100mg up to 4 times daily.[37]

Introduction to Non-Steroidal Anti-Inflammatory Drugs

Non-steroidal anti-inflammatory drugs are the most commonly used drugs because of their anti-inflammatory, analgesic and antipyretic effects. The therapeutic benefit is mediated through inhibition of cyclooxygenase (COX) enzymes 1 and 2, which convert arachidonic acid to prostaglandins. COX 1 is the constitutive enzyme that produces prostaglandins, which are important for “house keeping” functions such as gastric protection and hemostatis. COX 2 is the inducible, involved in synthesis prostaglandins that mediate pain, inflammation, fever and carcinogenesis.[48]

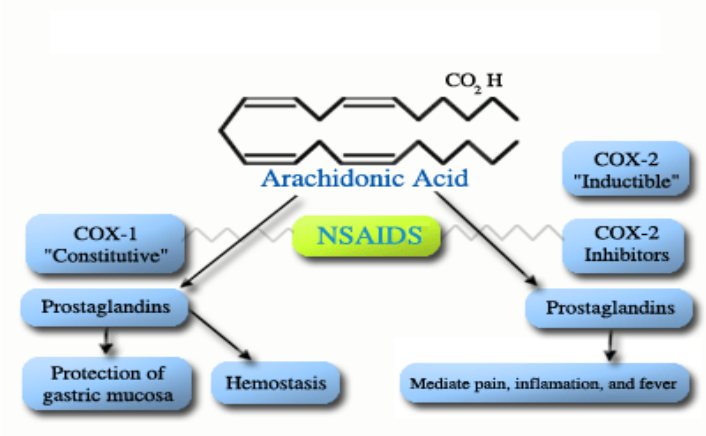


Fig: 9 Mechanism of action of NSAIDs

PGE2 and PGI2 are the key mediators of both peripheral and central pain sensitization. Peripherally prostaglandins (especially PGE2) contribute to hyperalgesia by sensitizing nociceptors via its receptors, EP_1 and EP_4—causes phosphorylation of transient receptor potential V_1 and other ion channels on nociceptors and increases their terminal membrane excitability. Centrally, prostaglandins enhance pain transmission at the level of dorsal horn by (1) increasing the release of substance P and glutamate from the first order neurons (2) increasing the sensitivity of second order neurons and (3) inhibiting the release of neurotransmitters from the descending pain modulating pathways.[49-51]

NSAIDs are effective in the treatment of postoperative pain. Although the efficacy is much less than the opioids, NSAIDs lack the unwanted effects of opiates like nausea, vomiting, sedation, respiratory depression and the potential for development of physical dependence. Coadministration of NSAIDs can reduce the opioids dose needed for sufficient pain control and thus reduce the adverse effects of opioids.

Most commonly used NSAIDs for post-operative pain are diclofenac, ketorolac, piroxicam, lornoxicam, selective COX2 inhibitors like etoricoxib and parecoxib.

Advantages of NSAIDs

- Decrease sensitization of peripheral nociceptors
- Attenuation of inflammatory response
- Absence of dependence or addiction potential
- Absence of respiratory depression
- Less nausea and vomiting
- Less dose variability compared to opioids
- Absence of cognitive impairment

Side effects

- Platelet dysfunction may lead to operative site bleeding
- Gastrointestinal ulceration and bleeding
- Renal tubular dysfunction
- Allergic reaction

Pharmacology of piroxicam

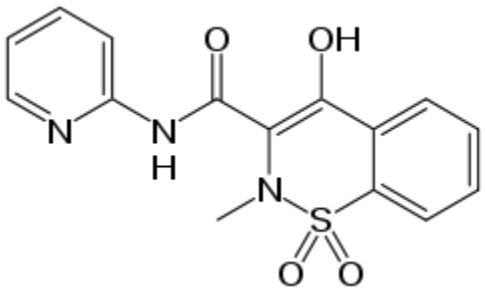
Introduction

Piroxicam, an oxicam class of non-steroidal anti-inflammatory agents, has a long half-life of approximately 50 hours and is highly bound to plasma proteins. The long half-life may allow improved compliance through once daily dosing.[52]

It is well established for the treatment of rheumatoid arthritis and osteoarthritis. Also used in post-operative pain, musculoskeletal disorders and dysmenorrhoea.[53]

The FDA approved piroxicam in April 6, 1982 for rheumatoid arthritis, osteoarthritis. Unlabelled use for ankylosing spondylitis, menstrual cramps, juvenile rheumatoid arthritis.[54]

Structure and chemistry [53]



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

Pharmacokinetics

Absorption

Piroxicam is well absorbed from gastrointestinal tract. Peak concentration attained about 2 hours after oral administration. A second peak is observed between 6

and 10 hours which is 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 after oral, rectal, intramuscular and intravenous administration, signifying nearly complete oral absorption. Because of its long elimination half – life, plasma concentrations of piroxicam vary less between consecutive doses than those of other non – steroidal anti-inflammatory drugs.[51]

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 tissue. Piroxicam is 99% bound to plasma proteins.[55] Concentration of piroxicam in breast milk is 1% of maternal plasma.[56]

Metabolism

Piroxicam is metabolized in the liver by hydroxylation and conjugation with glucuronic acid. Metabolites of piroxicam have no anti – inflammatory activity and are inactive.[55]

Elimination

2 – 5% of piroxicam is excreted unchanged in the urine. The elimination half – life of piroxicam is 30 - 60 hours.[53]

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 post-operative pain by decreasing the nociceptive transmission to the brain.

Pharmacodynamics[53]

Analgesic activity

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

Antipyretic activity

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

Antiinflammatory activity

NSAIDs 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 more potent than naproxen and 14 times more potent than phenylbutazone. Oral piroxicam suppresses both primary and secondary lesions of adjuvant arthritis in control rats. Topical and rectally administered piroxicam is equipotent with 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 20mg or fenbufen 600mg, microbleeding was less with fenbufen than with piroxicam.[57]

Effect on prostaglandin synthesis

Piroxicam decreases plasma concentration of PGE1 and PGF2α in rheumatoid arthritis patients. Also suppress the synthesis of metabolic regulatory factors in

conditioned medium derived from synovial cultural containing significant cartilage cell catabolic – inducing activity.

Uses

- Rheumatoid arthritis
- Osteoarthritis
- Ankylosing spondylitis
- Acute gout
- Post-operative pain
- Mesothelioma[57]
- Complex regional pain syndrome[58]

Adverse effects

Gastro intestinal effects

Local irritation is about 13%, peptic ulceration and gastrointestinal haemorrhage is 0.15% and increases upto 7% at higher doses. Skin rash and pruritis is 0.8%.

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.

Dosage and administration

The initial adult dosage in rheumatoid arthritis, osteoarthritis and ankylosing spondylitis is oral 20 mg daily as a single dose. Daily maintenance doses may vary between 10-30mg. In acute musculoskeletal conditions, an initial dose of 40 mg daily

for 2 days followed by 20mg daily for 2 weeks. In acute gout 40 mg daily for 5 – 7 days. In post operative pain 20mg daily intramuscularly. 40mg daily recommended for prolonged operations as in orthopaedic surgeries.

Piroxicam as dispersible tablets used in children above 6 years.

Topical gel in a concentration of 0.5% for local painful inflammatory conditions, applied three or four times daily.[37]

Materials & methods

Materials and Methods

This prospective study was conducted by departments of Pharmacology and Obstetrics and Gynecology on the patients admitted to the department of Obstetrics and Gynecology in R. L. Jalappa Hospital & Research Centre attached to Sri Devaraj Urs Medical College, Tamaka, Kolar. The study was done from January 2012 to December 2013. Protocol designed for 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. A total of 120 primigravidae women were recruited into the study and were randomly divided into two groups. It was an open label study.

Inclusion Criteria

1. Women aged between 20 – 35 years.
2. Primigravidae women admitted for elective caesarean section under spinal anaesthesia

Exclusion Criteria

1. Patients diagnosed with pre-eclampsia or eclampsia
2. History of peptic ulcer, gastrointestinal bleeding
3. History of asthma, Chronic Obstructive Pulmonary Disease (COPD)
4. Patients with renal or hepatic dysfunction and hemorrhagic disorders
5. History of hypersensitivity to the piroxicam or tramadol

Names, age, occupation, address, educational status, hospital number of women were recorded at the time of recruitment into the study. History of smoking, alcohol, drug abuse, diabetes mellitus, hypertension, bronchial asthma and family

history of bronchial asthma and COPD were recorded. 120 women who were recruited were randomly divided into two groups of 60 women each. Group 1 received single dose of injection piroxicam 20mg and group 2 injection tramadol hydrochloride 100mg intramuscularly immediately after recovery from anaesthesia.

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 – 4), moderate (5 – 8), and severe (9 – 10)[6, 59] . It was explained and administered at baseline (before administration of the drugs) 2, 4, 8, 12 and 24 hours post operatively. Rescue analgesic, injection butorphanol 2mg was administered intramuscularly to patients if VAS score was more than 4 during post-operative period.

Pulse rate, blood pressure and respiratory rate were monitored immediately after recovery from anaesthesia 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.[60] Sedation was assessed at baseline, two and four hours post operatively. Patients were assessed for any adverse effects. Patient's satisfaction was assessed at the end of 12 hours on a four point scale in which score 1 as poor, 2 fair, 3 good and 4 excellent.[61]

Statistical methods

To detect the mean difference in VAS score at the end of 2 hours of 2.9 with a standard deviation for both the groups of 3.2, α error of 0.05 with 90% power and 10% dropout rate using a two sided, two sample‘t’ test, the sample size required in each group was 30 using a two sided, two sample‘t’ test.

Descriptive data were expressed as mean ± standard deviation and analysed using descriptive statistics. Continuous data post treatment changes compared to baseline was analysed by paired Student t – test and between the groups by unpaired t test. The intragroup analysis of the continuous data was done by applying repeated measure ANOVA and post hoc Bonferroni adjustment test. Categorical data was analysed by Chi – square test. p-value of 0.05 or less was considered statistically significant.

Results

Results

A total of 120 primigravidae undergoing elective caesarean section under spinal anaesthesia were included in the study to observe the effect of tramadol and piroxicam on post-operative pain and to assess the tolerability. They were randomized into groups 1 and 2 to receive injection piroxicam 20mg and injection tramadol hydrochloride 100mg respectively. Both the drugs were administered intramuscularly immediately after recovery from anaesthesia. All the patients completed the study protocol.

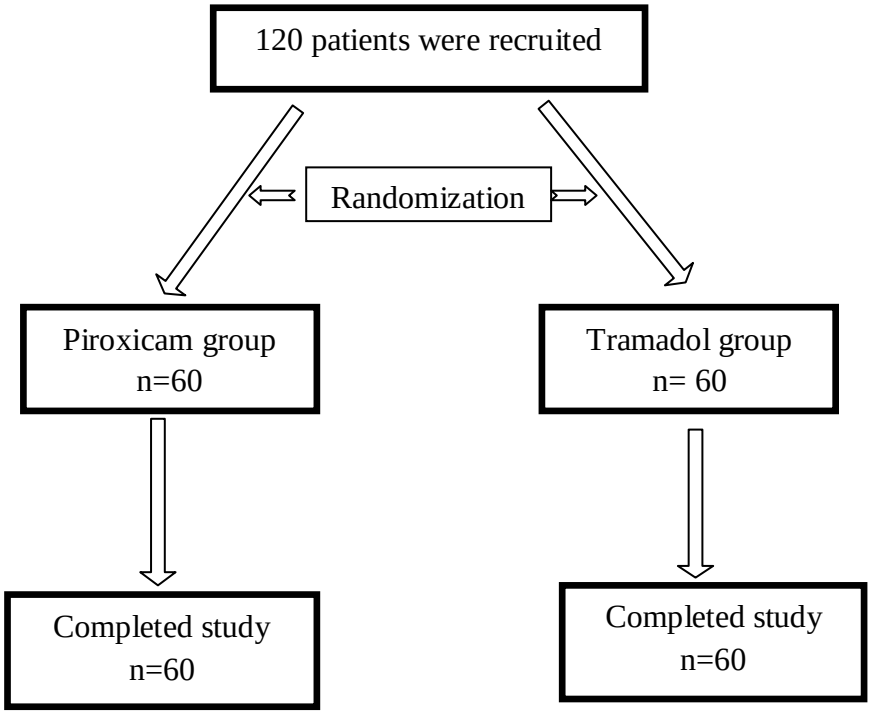


Fig 10: Flow chart representing recruitment of patients

Table 3 - Age distribution

Age in years	Group 1 Piroxicam No. of patients (%)	Group 2 Tramadol No. of patients (%)
20 – 25	47 (78.33)	57 (95)
26 – 30	11 (18.33)	03 (05)
31 – 35	02 (3.33)	0

Table 1 represents the age distribution in both the groups. Primigravidae in the age group of 20-25 years were more in both the treatment groups with 78.33% in piroxicam group and 95% in tramadol group. The mean age was 23.32 ± 3.437 and 22.03 ± 2.017 years in piroxicam and tramadol groups respectively.

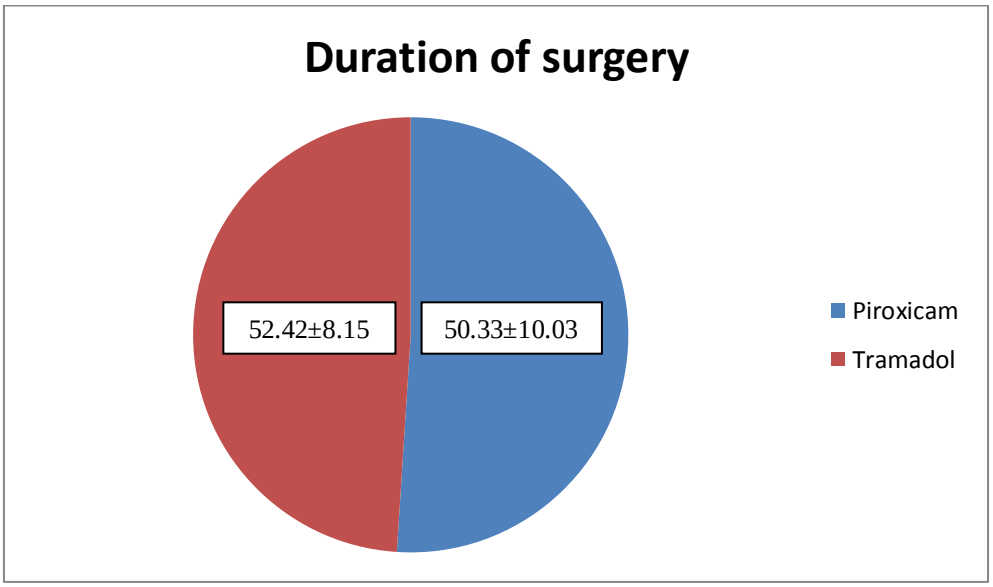


Fig 11: Duration of surgery (in min)

The mean duration of surgery was 52.42 ± 8.15 and 50.33 ± 10.03 minutes in piroxicam group and tramadol group respectively. Both the groups were comparable.

Table 4 - Graded Visual Analogue Scores in Piroxicam and Tramadol groups

Time intervals	No. of patients in group 1			No. of patients in group 2		
	Painless	**Mild (1 – 4)**	**Moderate (5 – 8)**	**Painless**	**Mild (1 – 4)**	**Moderate (5 – 8)**
Baseline	-	-	60	-	01	59
2 hrs	-	55	05	-	60	-
4 hrs	-	59	01	01	58	01
8 hrs	-	60	-	01	55	04
12 hrs	-	59	01	-	57	03
24 hrs	-	60	-	-	60	-

Table 4 represents the distribution of patients to painless, mild and moderate groups of visual analogue scale score. At baseline, number of patients in both the groups having moderate pain were more. After drug administration, most of the patients had only mild pain till the end of 24 hours. Seven and eight patients had moderate pain in piroxicam and tramadol groups respectively and these patients received rescue analgesic injection butorphanol intramuscularly. One patient did not experience pain at four and eight hours in tramadol group.

Table 5 - Mean VAS score in piroxicam group

VAS Score	**Baseline**	**2 hrs**	**4 hrs**	**8 hrs**	**12hrs**	**24hrs**
Piroxicam	6.65±0.82	2.68±0.79	1.67±0.72	1.58±0.62	2.58±1.38	2.78±0.71
p value		0.001	0.001	0.001	0.001	0.001

Table 3 represents the mean VAS score in piroxicam group. The reduction in VAS score was significant at each time point as compared to the baseline.

Table 6 - Mean VAS score in tramadol group

VAS Score	Baseline	2 hrs	4 hrs	8 hrs	12hrs	24hrs
Tramadol	6.35±0.89	3.03±0.63	2.02±1.03	2.22±1.34	2.65±1.40	2.95±0.72
p value		0.001	0.001	0.001	0.001	0.001

Table 4 represents the mean VAS score in tramadol group. Significant reduction in VAS score from baseline was observed at each time point when compared to the baseline.

Table 7 - Comparison of mean VAS scores

VAS Score	Baseline	2 hrs	4 hrs	8 hrs	12hrs	24hrs	#p value
Piroxicam	6.65 ± 0.82	2.68 ± 0.79	1.67 ± 0.72	1.58 ± 0.62	2.58 ± 1.38	2.78 ± 0.71	0.001
Tramadol	6.35 ± 0.89	3.03 ± 0.63	2.02 ± 1.03	2.22 ± 1.34	2.65 ± 1.40	2.95 ± 0.72	0.001
***p value**	0.059	0.009	0.034	0.001	0.793	0.207	

* - unpaired ‘t’ test # - repeated measure ANOVA

There was a significant reduction in mean VAS score at 2, 4, 8, 12 and 24 hours($p<0.001$) following treatment in both the groups. In piroxicam group, the post hoc bonferroni’s test showed significant reduction in VAS score for all combinations except at 2 and 24 hours, 4 and 8, 4 and 12 hours. In tramadol group, the post hoc test

showed a significant reduction in VAS score at 2, 4, 8, 12 and 24 hours ($p < 0.001$) and at all permutable combinations except for 2 and 24 hours, 4 and 8 hours, 8 and 12 hours.

At baseline, the mean VAS was comparable between the groups. After administration of the study drugs, the mean visual analogue score was significantly lower at 2, 4 and 8 hours in piroxicam group compared to tramadol group. At 12 and 24 hours the reduction in VAS score was statistically insignificant.

VAS score at 2, 4, 8, 12 and 24 hours can also be represented by area under curve for piroxicam and tramadol groups. It depicts the overall effect of piroxicam and tramadol on intensity of pain over a period of time than at a single isolated point of time in visual analogue scale.

The area under curve for both the groups (figures 12 and 13) was calculated by trapezoid method and the pain intensity from baseline to 24 hours was less in piroxicam group (4.56) compared to tramadol group (4.87).

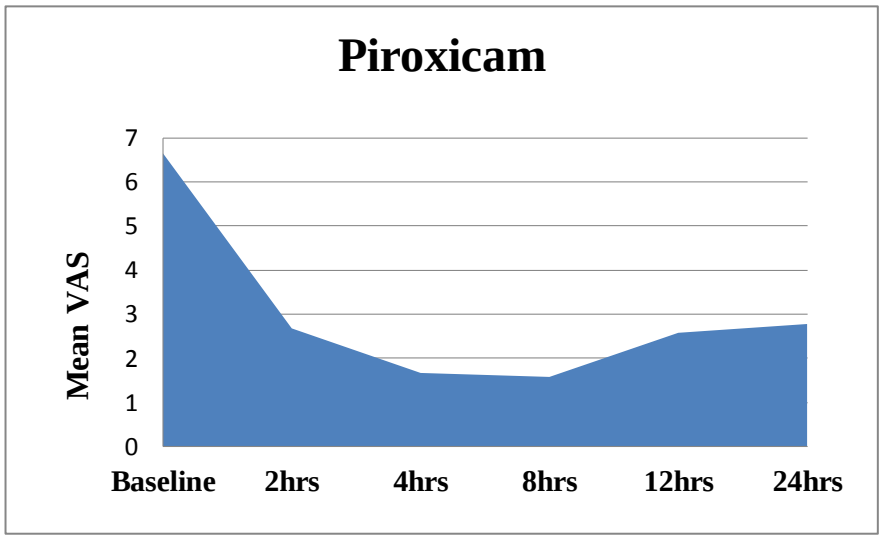


Fig 12: Area under curve for Piroxicam

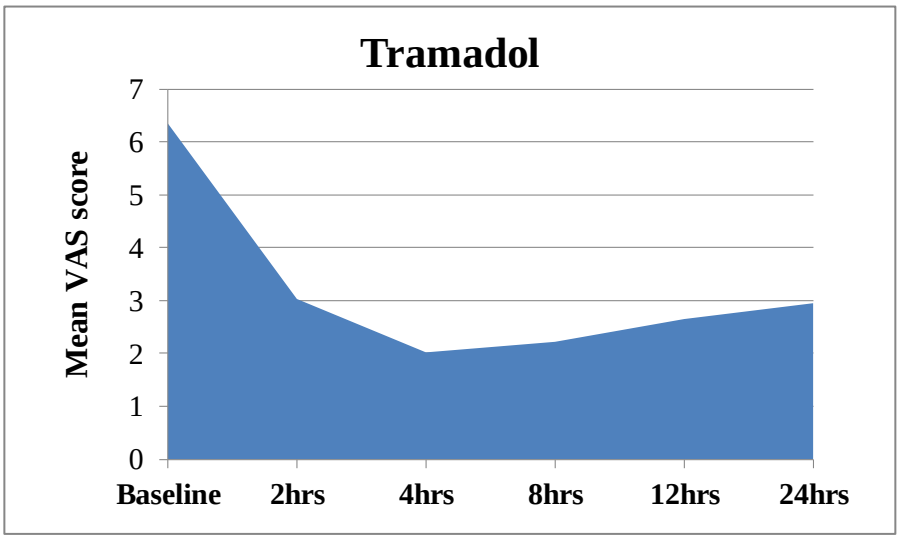


Fig 13: Area under curve for tramadol

Table 8 - Time of rescue analgesic

Time of rescue analgesic in hours	Number of patients (%) in Piroxicam group	Number of patients (%) in Tramadol group	p value
4	1 (1.67)	3 (5)	0.309
8	-	8 (13.33)	0.003
12	11 (18.33)	10 (16.67)	0.810

Rescue analgesic was required after four hours in both the groups. Eight patients in tramadol group received rescue analgesic after 8 hours while in piroxicam group none of them required. Eleven and ten patients in piroxicam and tramadol groups respectively received the rescue medication after 12 hours. The total amount of rescue analgesic required in piroxicam and tramadol group was 24mg and 42mg respectively.

The systolic and diastolic blood pressure (BP) was increased in both the groups up to 24 hours. There was a significant rise in diastolic BP up to 4 hours in piroxicam group compared to tramadol group ($p < 0.001$) and further rise was minimal up to 24 hours as shown in fig 14.

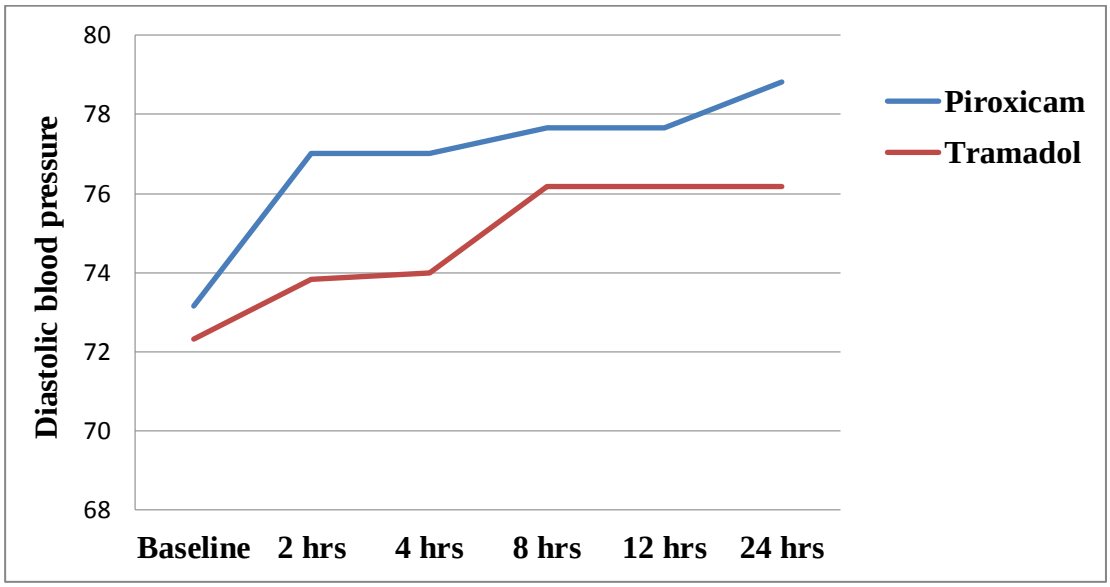


Fig 14: Diastolic blood pressure in both the groups

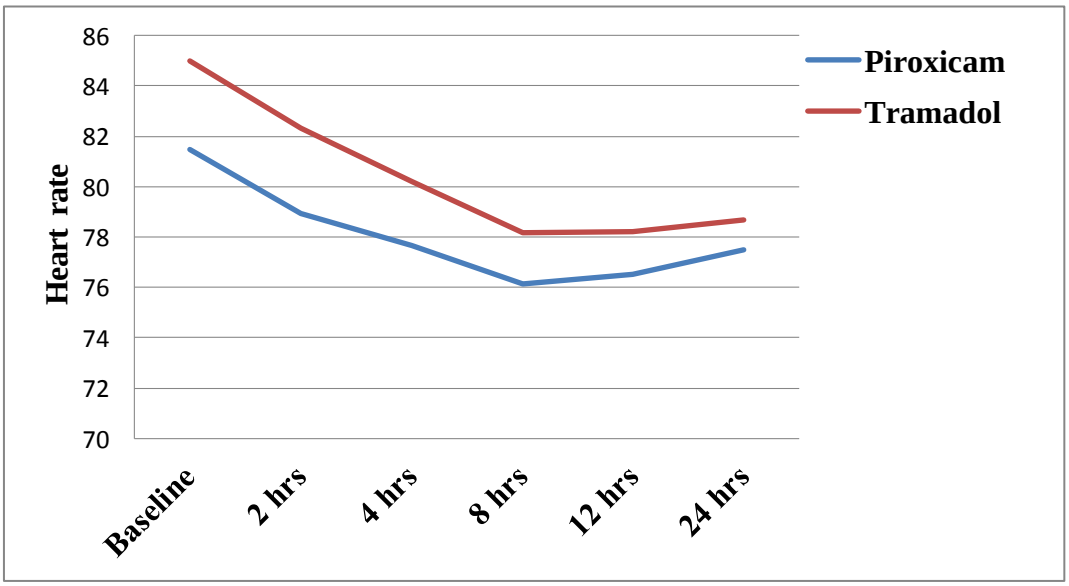


Fig 15: Heart rate in both the groups

Decrease in heart rate was observed in both the groups up to 8 hours and was maintained at the same rate up to 24 hours. The decrease was significant at all the assessed six intervals ($p < 0.001$).The respiratory rate decreased significantly in piroxicam group at 2, 4 and 24 hours compared to patients in tramadol group.

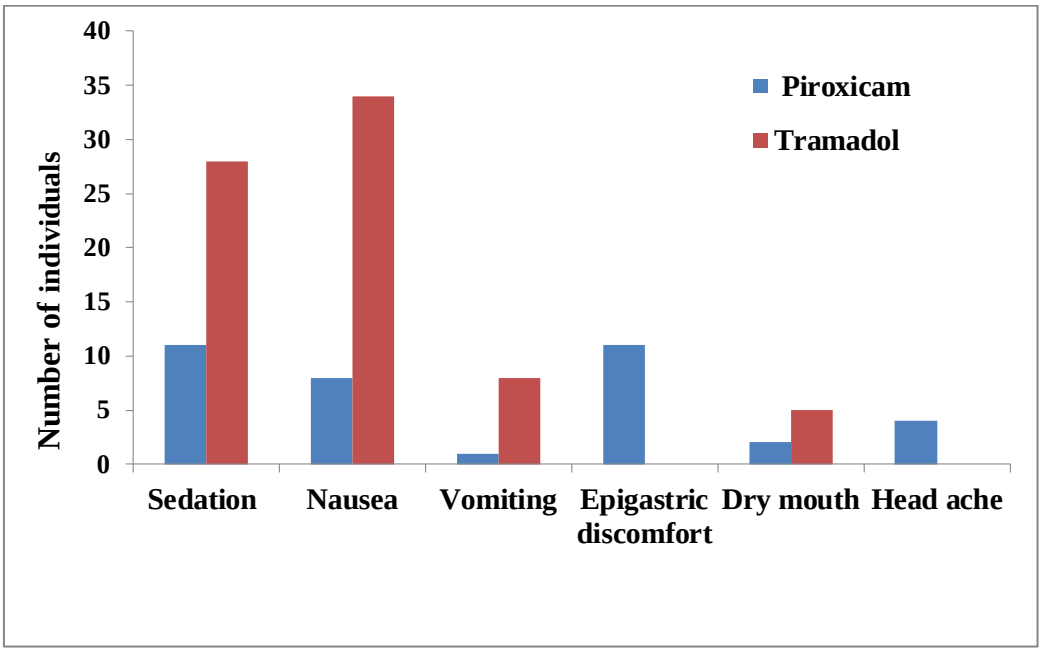


Fig 16: Adverse effects of the study drugs

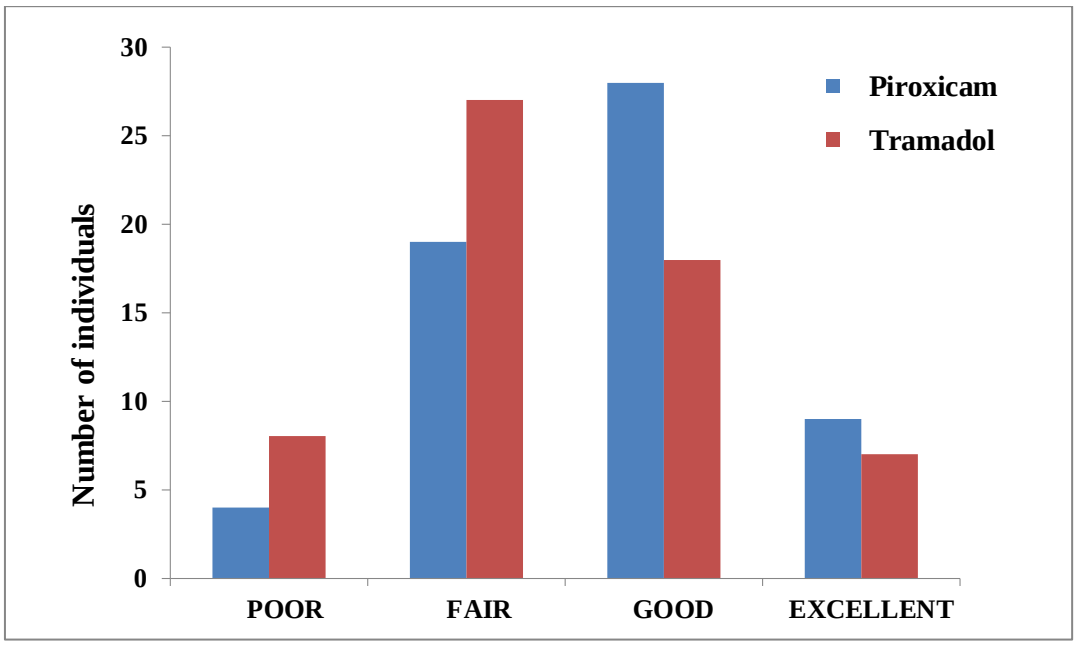


Fig 17: Patient satisfaction score (as above)

Figure 16 represents the adverse effects of both the study drugs. The adverse effects were well tolerated. The number of patients in the tramadol group having adverse effects was more compared to piroxicam group. Sedation and nausea was significantly higher in tramadol group ($p<0.001$ and $p=0.043$ respectively) whereas the epigastric discomfort and headache was observed to be significant in piroxicam group ($p<0.001$ and $p=0.042$ respectively).

At the end of 12 hours, 46.66% of patients graded their satisfaction score as good and 15% as excellent in piroxicam group whereas 30% as good and 11.66% as excellent in tramadol group.

Discussion

Discussion

Post-operative pain is indicative of tissue damage leading to immobilization of the patient, which favours wound healing. Though a useful symptom, it is usually a major clinical problem which is distressing and adversely affects the quality of life of patients and their care givers. It is one of the important aspects to be considered after surgery because it is closely related with good clinical outcome. Various factors contribute to effective postoperative pain management such as acute pain management team, patient education, regular staff training, use of balanced analgesia and regular pain assessment using specific assessment tools to meet the needs of the patient.[62] Post-operative pain is due to incisional damage to the skin and other tissues which liberates various chemical mediators and they sensitize the nociceptors. These nociceptors are involved in carrying impulses to brain. Thus effective management of pain is needed to improve the quality of life of patients, facilitate rapid recovery, reduce morbidity and allow early discharge from the hospital.[63]

Cesarean section is a major surgical procedure and post-cesarean section pain management is a challenge for all healthcare professionals to facilitate early ambulation and infant care including breast feeding, maternal infant bonding and also to prevent postoperative morbidity. Cesarean section differs from other major laparotomies because women are expected to recover expeditiously and to take care of their new-borns within a few hours following surgery. [62,64,65]

NSAIDs are preferred for post-operative pain unless there is a definite indication for an opioid.[66] Piroxicam is one of the NSAIDs of oxicam class used in

post-operative pain. It is a potent non-selective, reversible inhibitor of COX (cyclooxygenase) leading to inhibition of prostaglandin synthesis, which is responsible for pain and inflammation and it also inhibits the migration of leucocytes to the site of inflammation.[67]

Tramadol, a centrally acting opioid, is the most commonly used opioid for post-operative pain. The noceciptive action is mediated mainly by inhibition of serotonin and norepinephrine reuptake and weak agonistic action at μ_1 and μ_2 receptors. Therefore both opioid and monoaminergic mechanisms contribute to the analgesic effect of tramadol. But it is associated with side effects like nausea, vomiting, sedation and reduced seizure threshold.[68]

Women receiving opioids for pain relief become drowsy and sedated, thus restricting the postnatal care of their baby. In addition, there is associated risk of respiratory depression both in the mother and child. To overcome the above disadvantages with opioids, Non-steroidal anti-inflammatory drugs (NSAIDs) like oxicams and diclofenac are being widely used.

There is a paucity of comparative studies between piroxicam and tramadol in post caesarean section pain among primigravidae in India. Hence this study was carried out to compare the efficacy and safety of these drugs in the management of post caesarean section pain. Both the drugs have been reported to be safe during lactation and hence the choice, even though more recent analgesics are available whose safety remains a concern.

In our study primigravidae aged between 20 – 35 years were included. The age group is in accordance with other studies by Farshchi et al and Sunshine et al.[6,69] We choose to include only primigravidae since the intensity of pain differs in primi

and multigravidae. The mean duration of surgery was 52.42 ± 8.156 and 50.33 ± 10.03 minutes in piroxicam and tramadol groups respectively.

At baseline the mean VAS was comparable between the two groups. In both the groups the reduction in pain was significant at all points of time when compared to baseline. This observation correlates with the findings of Farshchi et al indicating both the study drugs have longer duration of analgesic effect for postoperative pain.

In piroxicam group, pain relief was significant at 2, 4 and 8 hours post operatively compared to tramadol group. But in a similar study conducted by Farshchi et al there was no significant difference between the groups at any point of time in reducing post operative pain. The mean VAS score at 12 hours in our study was 2.58±1.38 in piroxicam group which is less (3.3±0.4) compared to the finding by Farshchi et al and similarly the mean VAS score was less in our study in tramadol group (2.65±1.4 Vs 3.4±0.7). These observations suggest that pain relief was better at 12 hours in our study. The mean VAS scores of piroxicam and tramadol groups at 24 hours remained approximately same as at 12 hours as shown in Table no. 7 in our study but it had reduced to 1.1±0.4 and 1.3±0.5 respectively in a study by Farshchi et al. This suggests that patients receiving piroxicam had better analgesic efficacy in postoperative pain compared to tramadol. The reduction in pain was persisting up to 12 hours and was maintained till 24 hours. This coincides with the weaning effect of the drugs after 12 hours and analgesic effect lasting for 24 hours.

Roelofse et al used piroxicam and tenoxicam to compare their analgesic efficacy in patients undergoing oral surgery. Tenoxicam or piroxicam 40mg was administered 30 minutes prior to surgery and 20mg post-operatively for seven days. Single daily dose of piroxicam administered orally had reduced postoperative pain

effectively, which implies that one dose of piroxicam per day is effective for 24 hours which has been observed in our study also.[70]

Sayyid et al showed that, epidural tramadol 100mg was effective in providing adequate post-operative analgesia after cesarean delivery. The mean VAS score at 24 hours in control, tramadol 100mg and tramadol 200mg was 2.56±0.8, 0.91±0.84 and 1.12±0.4 respectively. The reduction in pain was significant in tramadol 100mg and 200mg compared to control but, there was no significant difference between two doses. The reduction in VAS score at the end of 24 hours as compared to our study as shown in Table no. 6 is higher probably due to epidural route of administration and since the drug is delivered in close proximity to the receptors in spinal cord or nerves exiting the spinal cord producing profound analgesia.[71,72]

Yu-yan et al showed that at the end of 24 hours the mean VAS score with epidural tramadol 100mg for post cesarean section pain was 2.24±0.76 which was similar to our study where the VAS was 2.95±0.72.[73]

Lanzetta et al showed that intramuscular tramadol had more pronounced analgesic effect than intramuscular ketorolac in orthopaedic post operative pain and was well tolerated. After 2 hours, 52.5% of the patients who had received tramadol experienced pain relief whereas in our study all patients had mild pain and at 4 hours 3.34% of them were completely relieved of pain.[74]

In our study, the area under curve for both the groups denotes that patients experience with pain at each time point from baseline to 24 hours. The piroxicam group patients had less encounter with pain compared to tramadol as shown in Figures 3 and 4.

In this study, 21 patients received the rescue analgesic butorphanol and 5% at the earliest (4hours) following administration of tramadol whereas only 12 patients received butorphanol and 1.67% at 4 hours after receiving piroxicam. In a similar study conducted by Farshchi et al, none of them received rescue medication for 24 hours post – operatively.

In other studies, the vital signs like blood pressure and heart rate were observed intra – operatively. As they are the important indicators of hemodynamic stability even during post operative period, which necessitated their monitoring post operatively for 24 hours in our study.

The diastolic blood pressure post operatively was reduced probably due to sympathetic blockade following spinal anaesthesia, as observed during intraoperative period but it began to increase in the postoperative period. In the present study, in both the groups, increase in the diastolic blood pressure was observed but was significant in piroxicam group compared to tramadol at all time points. This could be explained by the fact that it inhibits the cyclooxygenase enzyme causing inhibition of vasodilating prostaglandins leading to water retention and increased total peripheral resistance. It is also influenced by increased renal endothelin 1 synthesis by piroxicam.[75]

The heart rate was high immediately following recovery from anaesthesia which may be due to patient's agony with pain. Subsequently as the pain reduced gradually, heart rate returned towards normal and it was significant in piroxicam group indirectly reflecting that pain relief was better with piroxicam.

The adverse effects in both the groups were well tolerated. In this study, 11 and 28 patients reported sedation in piroxicam and tramadol groups

respectively whereas in Farshchi et al, it was 22 and 35 patients in piroxicam and tramadol groups respectively. Nausea was significantly higher in tramadol group which is similar to findings in our study. This may interfere with feeding and infant care. These adverse effects due to tramadol can be explained by the serotonin and norepinephrine reuptake inhibition. Epigastric discomfort was more in piroxicam group due to inhibition of protective effect of prostaglandin on gastric mucosa mediated by COX inhibition but it did not warrant any need for medication. Eight patients complained of vomiting in tramadol group whereas in Sayyid et al none of the patients had vomiting which is an added advantage when epidural route is chosen.

In a study by Sunshine et al, dizziness was the most common adverse effect reported with 150 mg tramadol whereas none of the patients in our study reported this adverse effect.[69] Tramadol had markedly less clinically significant respiratory depressant action and other side effects like nausea, vomiting, dizziness, drowsiness were less than morphine which is also observed in our study.[34]

The patient's satisfaction was assessed by 'Patient satisfaction score'. At the end of 12 hours, 46.66% and 15% graded their satisfaction score as good and excellent respectively in piroxicam group whereas in tramadol group it was 30% and 11.66% respectively indicating that patients were contented with the use of piroxicam.

Conclusion

Conclusion

- 86.67% of primigravidae undergoing elective cesarean section were in the age group of 20 – 25 years.
- The VAS score in piroxicam and tramadol groups showed significant improvement at 2, 4, 8, 12 and 24 hours compared to their baseline ($p<0.001$)
- Pain relief was significant with piroxicam (1.58±0.62) compared to tramadol (2.22±1.34) up to eight hours postoperatively.
- Area under curve which represented the effect of drugs for a period of 24 hours showed intensity of pain was less with piroxicam (4.56) compared to tramadol (4.87).
- Patients receiving piroxicam required less rescue analgesics compared to tramadol.
- The diastolic blood pressure increased significantly up to 4 hours in both the groups and was stabilized thereafter.
- In piroxicam group, the reduction in pain was associated with significant decrease in heart rate and respiratory rate ($p < 0.001$)
- Sedation and nausea was significantly higher in tramadol group.
- 15% and 46.66% of patients graded their satisfaction for pain relief with piroxicam as excellent and good respectively as compared to tramadol (11.66% and 30%) .
- Intramuscular injection of piroxicam can be used as an alternative to tramadol for treating acute pain following cesarean section as it is devoid of central depressive effects of opioids.

Summary

Summary

Post-cesarean section pain is a type of acute pain initiated due to the stimulation of nociceptors through tissue trauma during surgery. Effective post cesarean section pain management facilitates early ambulation and infant care. NSAIDs and opioids are the commonly used analgesics for pain relief after surgery.

A prospective study was conducted on 120 primigravidae undergoing elective cesarean section to study the analgesic effect of piroxicam and tramadol. They were randomised to receive either injection piroxicam 20mg or tramadol 100mg intramuscularly immediately after recovery from anaesthesia. Pain was assessed by Visual Analogue Scale (VAS) and side-effects were noted at baseline, 2, 4, 8, 12 and 24 hours post-operatively. Rescue analgesic butorphanol 2mg was administered intramuscularly if VAS was more than 4. Patient's satisfaction score was assessed at 12hours post operatively.

Majority (86.67%) of women were in the age group of 20 – 25 years. Baseline VAS scores were comparable between the groups ($p = 0.06$). The VAS score reduced significantly at each interval from baseline in both the groups. The reduction in VAS score was statistically significant in piroxicam group at 2, 4 and 8 hours compared to tramadol group ($p<0.001$). The intensity of pain was less in piroxicam group (4.56) compared to tramadol group (4.87) for a period of 24 hours as depicted by area under the curve (AUC) for both the drugs. 12 patients in piroxicam group and 21 patients in tramadol group received rescue analgesic.

The altered hemodynamics as a result of spinal anaesthesia and postoperative pain were improved significantly by piroxicam. The adverse effects like sedation and nausea was observed with tramadol and epigastric discomfort with piroxicam. At the end of 12 hours, 15% of patients expressed satisfaction to pain relief as excellent in piroxicam group and 12% in tramadol group. Thus, intramuscular injection of piroxicam effectively reduces post – cesarean section pain for 24 hours with less adverse effects like sedation and nausea as compared to tramadol.

Bibliography

References

1. Banerjee M, Bhaumik DJ, Ghosh AK. A comparative study of oral tramadol and ibuprofen in postoperative pain in operations of lower abdomen. J Indian Med Assoc 2011; 109:619-22.

2. Macres SM, Moore PG, Fishman SM. Acute pain management. In: Barash PG, Cullen BF, Stoelting RK, Cahalan MK, Stock MC, editors. Clinical anaesthesia. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2009. p. 1473 – 504.

3. Dolin SJ, Cashman JN, Bland JM. Effectiveness of acute postoperative pain management: Evidence from published data. Br J Anaesth 2002; 89: 409-23.

4. Sinatra RS, Lodge K, Sibert K, Chung KS, Chung JH, Parker A et al. A comparison of morphine, meperidine and oxymorphone as utilized in patient-controlled analgesia following caesarean delivery. Anesthesiology 1989; 70: 585 – 90.

5.Khandave SS, Sawant SV, Joshi SS, Bansal YK, Kadam SS. Comparative bioequivalence studies of tramadol hydrochloride sustained- release 200mg tablets. Drug des. Dev. Ther 2010; 4: 367 – 74.

6.Farshchi A, Ghiasi G. Comparison the analgesic effects of single dose administration of tramadol or piroxicam on postoperative pain after caesarean delivery. Acta Med Iran 2010; 48:148-53.

7. Newyork spine and wellness center [Internet]. 2013. [cited 2013 feb 10]. Available from:
http://www.nyspineandwellness.com/education_printouts/historyofpain.pdf

8. Trescot AM, Datta S, Lee M, Hansen H. Opioid Pharmacology.Pain Physician 2008;11:S133-53.

9. The world of chronic pain [Internet].2013. [cited 2013 feb 16]. Available from : http://painworld.org/pain-history.htm

10. Chaturvedi S, Chaturvedi A. Post operative pain and its management. Indian journal of critical care medicine 2007;11: 204 – 11.

11. Ganong WF, editor. Review of medical physiology. 23rd ed. United states: McGraw Hill; 2005. p. 167 – 72.

12. Guyton AC, Hall JE, editors. Text book of medical physiology. 12th ed. Philadelphia: Elsevier saunders; 2006. p. 598 – 609.

13. Berry PH, Chapman CR, Covington EC, Dahl JL, Katz JA, Miaskowski C, editors. Pain:Current Understanding of Assessment, Management,and Treatments [Internet]. 2001. [cited 2013 feb 11]. Available from : http://www.npcnow.org/App_Themes/Public/pdf/Issues/pub_related_research/pub_quality_care/Pain-Current-Understanding-of-Assessment-Management-and-Treatments.pdf

14. Patel NB. Guide to pain management in low – resource settings [Internet]. 2010. [cited 2013 feb 11]. Available from : http://www.iasppain.org/AM/Template.cfm?Section=Home&Template=/CM/ContentDisplay.cfm&ContentID=121 62

15. Kirwan T. Post operative pain [Internet]. United Kingdom: Cambridge university press 2005. [cited 2013 feb 4]. Available from: http://www.fk.unair.ac.id/pdfiles/ebook/Core%20Topics%20in%20Pain.pdf#page=175

16. Chemical mediators.[Cited feb 26].Available from: https://www.google.co.in/search?q=chemical+mediators+of+inflammation&source=lnms&tbm=isch&sa=X&ei=FZBbUpTiGsParAfY7oHQAw&ved=0CAcQ_AUoAQ&biw=1092&bih=485&dpr=1#q=chemical%20mediators&tbm=isch

17. Woo A. Molecular Mechanisms of Peripheral Sensitisation, Physiological Pain and Clinical Pain [Internet] .2008. [cited 2013 feb 11]. Available from : http://www.frca.co.uk/article.aspx?articleid=101039

18. Gate control theory of pain.[image on the internet]. [Cited Mar 2]. Available from: http://www.google.co.in/image/141609/350wm/C0078654-Gate_control_theory_of_pain,_artwork-SPL.jpg&w=271&h=350&ei=upJbUrzpPIWMkwXTpYGwDQ&zoom=1&ved=1t:3588,r:20,s:0,i:147&iact=rc&page=2&tbnh=197&tbnw=144&start=9&ndsp=13&tx=58&ty=143

19. Williamson A. Pain: a review of three commonly used pain rating scales . Journal of Clinical Nursing 2005; 14: 798–804.

20. Pain assessment scales [Internet]. 2003. [cited 2013 Mar 13]. Available from : http://www.painedu.org/downloads/nipc/pain_assessment_scales.pdf

21. Ready LB. Acute perioperative pain. In:Cucchiara RF, Miller ED, Reves JD, Roizen MF, Savarese JJ, editors. Anaesthesia. 5th ed. Philadelphia : Churchill livingstone; 2000. p. 2323 – 54.

22. Popovici F**,** Dorostkar M**,** Boehm S. The non-opioid analgesic flupirtine is a modulator of $GABA_A$ receptors involved in pain sensation. BMC Pharmacology 2008; 8: A14.

23. Bevan S, Hothi S, Hughes G, James IF, Rang HP, Shah K et al. Capsazepine: a competitive antagonist of the sensory neurone excitant capsaicin. Br J Pharmacol 1992; 107:544-52.

24. Davis MP, Pasternak GW. Opioid receptors and opioids pharmacodynamics. [Internet].2005. [cited 2013 Mar 11]. Available from : http://fds.oup.com/www.oup.com/pdf/13/9780199236640_chapter1.pdf

25. Kronsky AM, Vincenti F, Bennet WM. Opioids, Analgesia, and Pain Management. In: Brunton LL, Chabner BA, Kollmann BC. editors. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 12th ed. New York; McGraw-Hill: 201. p. 1405-32.

26. Dayer P, Desmeules J, Collart L. Pharmacology of tramadol. Drugs 1997; 53 Suppl 2:18 – 24.

27. Tramadol Abuse Help [internet] .2013. [cited 2013 feb 13]. Available from: http://www.tramadolabusehelp.com/wordpress/history-of-tramadol

28. Ridgway D. Analgesics for Acute Pain Meeting the United States Food and Drug Administration's Requirements for Proof of Efficacy. Clin J Pain 2004; 20:123 – 32.

29. Ardakani YH,Rouini MR. Pharmacokinetic study of tramadol and its three metabolites in plasma, saliva and urine. DARU J Pham Sci 2009;17: 245 – 55.

30. Gong L. Pathway: Tramadol pharmacokinetics [Internet]. 2013. [cited 2013 feb 18]. Avialable from : http://www.pharmgkb.org/pathway/PA165946349

31. Lintz W, Beier H, Gerloff J. Bioavailability of tramadol after i.m. injection in comparison to i.v. infusion. Int J Clin Pharmacol Ther. 1999; 37: 175-83.

32. Desmeules JA, Piguet V, Collart L, Dayer P. Contribution of monoaminergic modulation to the analgesic effect of tramadol. Br J Clin Pharmacol 1996; 41: 7-12.

33. Sinatra RS, Jahr JS, Watkins – Pitchford JM. The essence of analgesia and analgesics [Internet]. United Kingdom:2011. [cited 2013 feb 16]. Available from: http://books.google.co.in/books

34. Houmes RM, Voets MA, Verkaaik A, Erdmann W and Lachmann B. Efficacy and Safety of Tramadol Versus Morphine for Moderate and Severe Postoperative Pain With Special Regard to Respiratory Depression. Anesth Analg 1992; 74: 51- 4.

35. Spiller HA, Gorman SE, Villalobos D, Benson BE, Ruskosky DR, Stancavage MM et al. Prospective Multicenter Evaluation of Tramadol Exposure. J Toxicol Clin Toxicol1997; 35: 361-4.

36. Wilder- Smith CH, Bettiga A. The analgesic tramadol has minimal effect on gastrointestinal motor function. Br J Clin Phormocol 1997; 43: 7 1-75.

37. Sweetman SC. Martindale The complete drug reference. 33rd ed. London; Pharmaceutical Press: 2002.

38. Yalcin, Ipek, Aksu, Fazileʾ Bodard, Sylvie. Antidepressant - like effect of tramadol in the unpredictable chronic mild stress procedure : possible involvement of the noradrenergic system. Behav Pharmacol 2007;18: 623-31

39. Tsai YC, Won SJ. Effects of tramadol on T lymphocyte proliferation and natural killer cell activity in rats with sciatic constriction injury. Pain 2001; 92: 63 – 69.

40. Sacerdote P, Bianchi M, Gaspani L, Manfredi B, Maucione A, Terno G et al. The Effects of Tramadol and Morphine on Immune Responses and Pain After Surgery in Cancer Patients. Anesth analg 2000; 90: 1411– 14.

41. Schnitzer TJ, Gray WL, Paster RZ, Kamin M. Efficacy of tramadol in treatment of chronic low back pain. J Rheumatol 2000; 27: 772-78.

42.Harati Y, Gooch C ,Swenson M, Edelman SV, Greene D Raskin P, et al Double-blind randomized trial of tramadol for the treatment of the pain of diabetic neuropathy. Neurology 1998; 50: 1842 - 46.

43.Harati Y, Gooch C ,Swenson M, Edelman SV, Greene D Raskin P, et al .Maintenance of the long-term effectiveness of tramadol in treatment of the pain of diabetic neuropathy. J Diabet Complications 2000; 14: 65–70.

44. Boureau F, Legallicier P, Kabir-Ahmadi M. Tramadol in post-herpetic neuralgia: a randomized, double-blind, placebo-controlled trial. Pain 2003; 104: 323–31.

45. Wu CL , Raja SN. An Update on the Treatment of Postherpetic Neuralgia. J Pain 2008; 9: S19-30.

46. Sobey PW , Theodore V. Parran J ,Scott F, Grey, Christopher L, Adelman, Yu J. The Use of Tramadol for Acute Heroin Withdrawal. J Addict Dis 2003; 22:13 – 25.

47. Goldsmith TD, Shapira NA, Keck PE. Rapid Remission of OCD With Tramadol Hydrochloride. Am J Psychiatry 1999; 156: 660a-661.

48. Ramsay MAE. Acute postoperative pain management. BUMC proceedings 2000; 13: 244–47.

49. Moriyama T, Higashi T, Togashi K, Iida T, Segi E, Sugimoto Y et al. Sensitization of TRPV1 by EP1 and IP reveals peripheral nociceptive mechanism of prostaglandins [Internet]. 2005. [cited 2013 feb 12]. Available from: http://www.molecularpain.com/content/1/1/3

50. Taiwo YO, Levine JD. Prostaglandins Inhibit Endogenous Pain Control Mechanisms by blocking transmission at spinal noradrenergic synapses. J Neurosci 1988 ; 8:1348-349

51. Nicol OD, Klingberg DK, Vasko MR. Prostaglandin E, Increases Calcium Conductance and Stimulates Release of Substance P in Avian Sensory Neurons. J Neurosci 1992 ; 12:1917- 927

52. Rudy AC,Figueroa NL,Hall SD,Brater DC. The pharmacokinetics of piroxicam in elderly persons with and without renal impairment. Br J clin Pharmac 1994; 37: 1-5

53. Brogden RN, Heel RC, Speight TM, Avery GS. Piroxicam A reappraisal of its pharmacology and therapeutic efficacy. Drug 1984; 28: 292 – 323.

54. Prescription drugs overview. 2011. [cited 2013 feb 12]. Available from: http://www.healthystock.net/drugs/piroxicam.shtml

55. Ostensen M. Piroxicam in human breast milk. Eur J Clin Pharmacol 1983; 25: 829 – 30.

56. Collins AJ, Notarianni LJ. The acute action of fenbufen and piroxicam on the gastric mucosa as measured by gastric microbleeding. J Int Med Res. 1984;12:179-83.

57. Spugnini EP, Crispi S, Scarabello A, Caruso G, Citro G, Baldi A. Piroxicam and intracavitary platinum-based chemotherapy for the treatment of advanced mesothelioma in pets: preliminary observations. J Exp Clin Cancer Res 2008; 27 – 6.

58. Kalita J, Vajpayee A, Misra UK. Comparison of prednisolone with piroxicam in complex regional pain syndrome following stroke: a randomized controlled trial. Q J Med 2006; 99: 89–95.

59. Hassan W, Inam M, Satar A, Arif M. Postoperative analgesia with tramadol in orthopedic surgery: Continuous infusion versus repetitive bolus administration. J Surg Pak 2012; 17: 147 – 50.

60. Hashmi ZA, Bashir G, Shah SA Tramadol hydrochloride in postoperative analgesia: clinical comparison with diclofenac sodium. Gomal J Med Sci 2004; 2: 47 – 9.

61. Lee SY, Lee WH, Lee EH, Han KC, Ko YK. The Effects of Paracetamol, Ketorolac, and Paracetamol Plus Morphine on Pain Control after Thyroidectomy. Korean J Pain 2010; 23: 124-30.

62. Layzell M. Current interventions and approaches to postoperative pain management. Br J Nurs 2008; 17: 414 – 19.

63. Andres JD, Fischer HBJ, Ivani G, Mogensen T, Narchi P, Singelyn FJ, Stienstram R. Postoperative Pain Management –Good Clinical Practice General recommendations and principles for successful pain management.p 3-5.

64. McDonnell JG, Curley G, Carney J, Benton A, Costello J, Maharaj CH, et al. The analgesic efficacy of transverses abdominis plane block after cesarean delivery: a randomized controlled trial. Anesth Analg 2008; 106(1): 186-91

65. Jakobi P, Weiner Z, Solt I, Alpert I, Itskovitz-Eldor J, Zimmer EZ. Oral analgesia in the treatment of postcesarean pain. Eur J Obstet Gynecol Reprod Biol 2000; 93 :61-4.

66. Thompson C. Post operative pain.The virtual anaesthesia textbook [Internet]. 2000 [cited 2011 Feb 7]. Available from: http://www.virtual-anaesthesia-textbook.com/vat/pain.html.

67.Moghimipour E, Dabbagh MA, zarif F. Characterization and in vitro evaluation of piroxicam suppositories. Asian J Pharm Clin Res 2009; 2: 92 – 8.

68. Zwaveling J, Bubbers S, Meurs AHJV, Schoemakes RC, Heel IRDV, Vermeij P, Burggraaf J. Pharmacokinetics of rectal tramadol in postoperative paediatric patients. Br J Anaesth 2004; 93: 224 – 7.

69. Sunshine A, Olson NZ, Zighelboim I, DeCastro A, Minn FL. Analgesic oral efficacv of tramadolhydrochloride in posioperative pain. Clin Pharmacol Ther 1992;51 :740 – 6.

70. Roelofse JA, Swart LC, Stander IA. An observer-blind randomised parallel group study comparing the efficacy and tolerability of tenoxicam and piroxicam in the treatment of post-operative pain after oral surgery. J Dent Assoc S Afr. 1996; 51: 707-11.

71. Sayyid SS, Maroun AM, Sleiman D, Sfeir M, Baraka A. Epidural tramadol for post operative pain after cesarean section. Can J Anesth 1999; 46: 731-35.

72. Torske KE Dyson DH . Epidural analgesia and anesthesia. Vet Clin North Am Small Anim Pract 2000; 30: 859 – 74.

73. Yu-yan N, Shao-qiang H, Wei-yi L. Comparison of intravenous flurbiprofen axetil and epidural tramadol for postoperative pain after cesarean section. Drugs 1993; 46: 313 – 40.

74. Lanzetta A, Vizzardi M, Letizia G, Umberto Martorana U, Sanfilippo A, Osti L, Cervelli C et al. Intramuscular tramadol versus ketorolac in patients with orthopedic and traumatologic postoperative pain: a comparative multicenter trial. Curr Therap Res 1998; 59: 39–47.

75. Frishman WH. Effects of nonsteroidal anti-inflammatory drug therapy on blood pressure and peripheral edema. Am J cardiol 2002; 89: 18 – 25.

Annexures

Proforma

OP No: Date:

Serial No:

1. Name –
2. Age –
3. Occupation –
4.
5. Educational status –
6. Address with phone no. –
7. Date of admission –
8. Time of start of surgery
9. Time of end of surgery
10. Duration of surgery
11. Family history of asthma, COPD –
12. Personal history – Smoking/ alcohol/ drug abuse/ diabetes mellitus/ hypertension/ bronchial asthma
13. General physical examination

    Per abdomen –

    Cardiovascular system –

    Respiratory system –

    Central nervous system –

14. **Additional post operative analgesia - (Rescue medication)**

Additional post operative analgesia use					Total amount of analgesic used	Duration of analgesia (min)
Drug	Dose mg	Route	No. of doses	Time of drug administration		
Butorphanol	2	IM				

15. **Side effects**

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

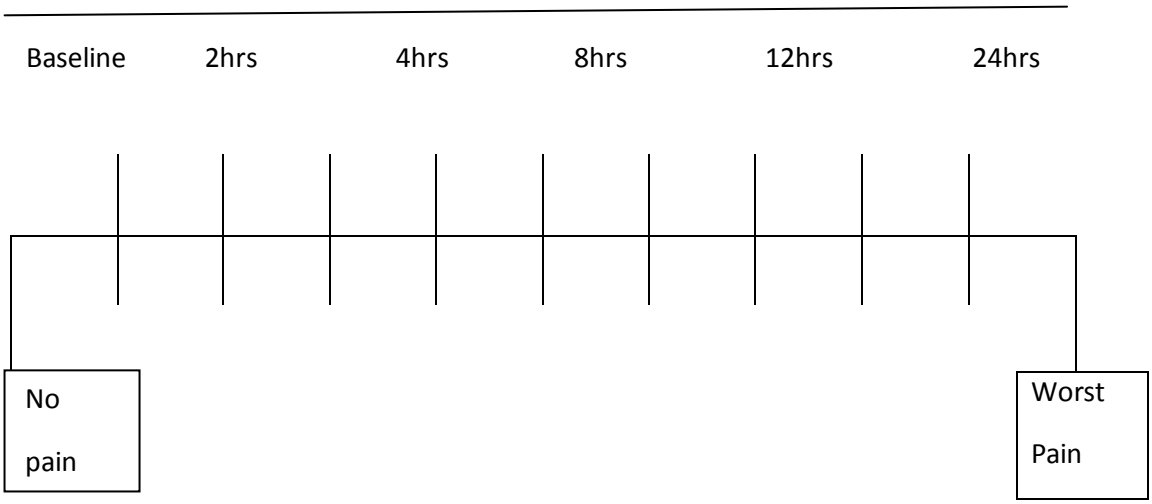
16. **Post – operative parameters**

	Heart rate	Blood pressure	Respiratory rate
Baseline			
2hours			
4hours			
8hours			
12hours			
24hours			

ROUTINE LABORATORY ANALYSIS REPORT

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

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 Score [6,59]

Painless = 0

Mild = 1 – 4

Moderate = 5 – 8

Severe = 9 – 10

Sedation score[69]

Alert = 0

Sedated = 1

Drowsy = 2

Asleep = 3

Comatose = 4

Patient's assessment of the analgesic used (patient satisfaction score)[61]

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

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

Key to master chart

- Sl no. – Serial number
- DOS – Duration of surgery
- VAS – Visual Analogue Scale
- BL – Baseline
- h – Hours
- SS – Sedation Score
- Buto – Butorphanol
- Side – effects

✓ 1 – Nausea

✓ 2 – Vomiting

✓ 3 – Headache

✓ 4 – Epigastric discomfort

✓ 5 – Dry mouth

- BP – Blood pressure
- Sys – Systolic
- Dia – Diastolic
- PSS – Patient's Satisfaction Score
- P – Poor
- F – Fair
- G – Good
- E - Excellent

Sl no.	Name	Piroxicam	Age	DOS	VAS Score						Sedation score			Buto	Side - effects						Heart rate						BPBaseline		BP2h		BP4h		BP8h		BP12h		BP24h		Respiratory rate						PSS			
					BL	2h	4h	8h	12h	24h	BL	2h	4h		BL	2h	4h	8h	12h	24h	BL	2h	4h	8h	12h	24h	Sys	Dia	Sys	Dia	Sys	Dia	Sys	Dia	Sys	Dia	Sys	Dia	BL	2h	4h	8h	12h	24h	P	F	G	E
1	Padma	327094	27	40	6	3	2	2	2	2	0	0	0	0	0						86	82	84	78	80	78	110	70	110	70	110	70	120	70	120	70	120	80	18	16	14	14	12	14			1	
2	Suma	321953	22	50	6	2	2	1	2	3	0	0	0	0	0						82	78	78	76	80	80	130	80	120	80	120	80	120	80	120	80	120	80	20	16	14	14	14	16		1		
3	Roopa	799530	23	45	7	3	1	2	2	2	0	0	0	0	0			3	3		84	80	78	78	76	78	110	70	120	80	120	80	120	80	120	80	120	80	14	14	12	12	14	14		1		
4	Subhashini	800164	24	45	6	2	1	1	5	1	0	0	0	0	1						80	80	78	78	76	76	110	70	110	70	120	70	120	70	120	70	120	70	16	16	14	14	12	14	1			
5	Shadakhanum	800481	21	55	5	3	2	2	2	3	0	0	0	0	0						82	76	78	72	74	74	110	70	110	80	110	80	110	80	110	80	120	80	18	16	16	14	14	16			1	
6	Venkatalakshmi	799946	25	50	6	2	1	2	3	3	0	0	0	0	0						80	82	78	78	76	80	130	80	120	80	120	80	120	80	120	80	120	80	16	14	14	14	16	18		1		
7	Noorfatima	777001	20	45	6	3	2	2	2	3	0	0	0	0	0		1				82	78	78	76	80	80	110	70	110	80	110	80	110	80	110	80	120	80	18	16	16	14	14	16				1
8	Nasreen taj	807841	20	60	5	2	1	3	3	3	0	0	0	0	0						80	78	78	76	76	78	120	80	120	80	120	80	120	80	120	80	110	80	16	18	16	16	14	16			1	
9	Pavitra	832016	21	40	7	3	1	1	5	3	0	1	0	1	1						80	78	78	80	80	78	110	70	110	70	110	70	110	70	110	70	120	80	16	16	14	16	14	14		1		
10	Renuka	823181	20	65	6	3	2	2	3	4	0	0	0	0	0	1	5	4			78	76	76	74	76	76	120	80	120	80	120	80	120	80	120	80	120	80	18	16	14	14	16	14			1	
11	Roja	823557	22	50	6	3	2	3	3	4	0	0	0	0	0						84	80	78	78	76	78	110	70	120	80	120	80	120	80	120	80	120	80	14	14	12	12	14	16			1	
12	Mangala	824443	24	60	8	3	2	2	3	3	0	0	0	0	0						86	78	72	74	76	78	120	70	120	80	120	80	120	80	120	80	120	80	18	16	12	14	14	16			1	
13	Meenakshi	824540	23	50	7	3	2	2	3	3	1	0	0	1	0						80	84	78	74	76	78	130	80	120	80	120	80	120	80	120	80	120	80	16	18	14	12	12	14		1		
14	Anuradha	803031	20	45	7	2	2	2	5	3	0	0	0	0	1						82	76	78	72	72	74	110	70	110	80	110	80	110	80	110	80	120	80	18	16	16	14	14	16			1	
15	Asha	825528	22	70	6	3	2	2	3	3	0	0	0	0	0						82	78	78	76	80	80	120	70	120	80	120	80	120	80	120	80	120	80	20	16	14	14	14	16		1		
16	Sudha	825404	20	55	7	3	2	3	3	4	0	0	1	1	0						80	82	78	76	72	76	120	70	120	70	120	70	120	80	120	80	120	80	16	14	14	14	16	16	1			
17	Ahamadi	843568	22	45	6	3	1	1	2	3	0	0	0	0	0	3					84	80	78	78	76	78	110	70	120	80	120	80	120	80	120	80	120	80	14	14	12	12	14	14		1		
18	Chandrakala	854873	32	55	7	3	1	1	2	2	0	0	0	0	0	1			4		80	80	78	78	76	76	110	70	110	70	120	70	120	70	120	70	120	70	16	16	14	14	12	14			1	
19	Lakshmidevamma	855828	29	50	8	3	2	2	2	3	0	0	0	0	0						82	76	78	72	74	74	110	70	110	80	110	80	110	80	110	80	120	80	18	16	16	14	14	16				1
20	Shalini	856199	21	50	7	2	1	1	1	2	0	0	0	0	0			4			80	82	78	78	76	80	110	70	110	80	110	80	110	80	110	80	120	80	16	14	14	14	16	18				1
21	Manjula	856168	22	60	7	3	2	2	3	4	0	0	0	0	0						82	78	78	76	80	80	130	80	120	80	120	80	120	80	120	80	120	80	18	16	16	14	14	16	1			
22	Thareema	856951	20	40	8	3	1	1	5	3	0	0	1	1	1						80	78	78	76	76	78	120	80	120	80	120	80	120	80	120	80	110	80	16	18	16	16	14	16			1	
23	Muniyamma	858196	27	65	6	2	1	1	2	3	0	1	0	1	0				4		80	78	78	80	80	78	110	70	110	70	110	70	110	70	110	70	120	80	16	16	14	16	14	14		1		
24	Lakshmi	859419	20	50	5	2	2	2	2	3	1	0	0	1	0						78	76	76	74	76	76	120	80	120	80	120	80	120	80	120	80	120	80	18	16	14	14	16	14			1	
25	Bhagyamma	861393	30	60	6	3	2	1	2	3	0	0	0	0	0						80	78	78	80	80	78	110	70	110	70	110	70	110	70	110	70	120	80	16	16	14	16	14	14			1	
26	Sharada	861457	23	50	6	2	1	2	2	3	0	0	0	0	0			4			78	76	76	74	76	76	120	80	120	80	120	80	120	80	120	80	120	80	18	16	14	14	16	14		1		
27	Aruna	795325	22	45	7	3	3	2	6	2	0	0	0	0	1						84	80	78	78	76	78	110	70	120	80	120	80	120	80	120	80	120	80	14	14	12	12	14	16			1	
28	Pallavi	848933	31	55	8	3	2	2	5	2	0	0	0	0	1		3				86	78	72	74	76	78	120	70	120	80	120	80	120	80	120	80	120	80	18	16	12	14	14	16			1	
29	Bhavya	870518	22	55	7	2	2	1	2	3	0	0	0	0	0	1					80	84	78	74	76	78	130	80	120	80	120	80	120	80	120	80	120	80	16	18	14	12	12	14		1		
30	Ayeeha taj	870561	20	50	7	2	2	1	2	3	0	1	0	1	0		4				82	76	78	72	72	74	110	70	110	80	110	80	110	80	110	80	120	80	18	16	16	14	14	16			1	
31	Anitha	866554	28	45	6	2	2	2	2	2	1	0	0	1	0						82	78	78	76	80	80	120	70	120	80	120	80	120	80	120	80	120	80	20	16	14	14	14	16		1		
32	Mamatha	871808	25	60	7	2	1	1	1	3	0	0	1	1	0				4	4	80	82	78	76	72	76	120	70	120	70	120	70	120	80	120	80	120	80	16	14	14	14	16	16				1
33	Shoba	871815	20	40	7	3	1	2	2	3	0	0	0	0	0						82	78	78	76	80	80	130	80	120	80	120	80	120	80	120	80	120	80	20	16	14	14	14	16			1	
34	Divya	871765	20	65	6	2	1	2	3	4	0	0	0	0	0						84	80	78	78	76	78	110	70	120	80	120	80	120	80	120	80	120	80	14	14	12	12	14	14	1			
35	Prathiba	865635	23	50	6	3	2	1	1	3	0	0	0	0	0						80	80	78	78	76	76	110	70	110	70	120	70	120	70	120	70	120	70	16	16	14	14	12	14		1		
36	Sudharani	865961	24	60	7	2	2	1	1	2	0	0	0	0	0		3				82	78	78	76	80	80	130	80	120	80	120	80	120	80	120	80	120	80	20	16	14	14	14	16			1	
37	Sunaya	830988	20	50	7	2	1	1	2	2	0	1	0	1	0			4	4	4	84	80	78	78	76	78	110	70	120	80	120	80	120	80	120	80	120	80	14	14	12	12	14	14		1		
38	Sudha	867545	22	45	7	2	1	2	1	2	0	0	0	0	0						80	80	78	78	76	76	110	70	110	70	110	70	110	70	110	70	120	80	16	16	14	14	12	14			1	
39	Ramaza Begum	867901	20	70	8	3	5	1	2	2	0	0	0	1	1		4,5				82	76	78	72	74	74	120	80	120	80	120	80	120	80	120	80	120	70	18	16	16	14	14	16		1		
40	Saritha	802867	28	45	8	4	2	1	5	3	0	0	0	1	1	1,2					80	82	78	78	76	80	110	70	110	70	110	70	110	70	110	70	120	80	16	14	14	14	16	18			1	
41	Sowbhagya	868165	20	60	7	3	2	3	1	3	0	0	0	0	0						82	78	78	76	80	80	120	80	120	80	120	80	120	80	120	80	120	80	18	16	16	14	14	16			1	
42	Mamatha	868664	20	40	7	2	2	1	1	1	0	0	0	0	0						80	78	78	76	76	78	120	80	120	80	120	80	120	80	120	80	110	80	16	18	16	16	14	16				1
43	Ashwini	891929	24	45	6	2	1	1	2	3	0	0	0	0	0						84	80	78	78	76	78	110	70	120	80	120	80	120	80	120	80	120	80	16	14	14	14	16	18			1	
44	Radha	892040	22	55	5	2	2	2	1	2	0	0	0	0	0						80	80	78	78	76	76	120	70	120	80	120	80	120	80	120	80	120	80	18	16	16	14	14	16				1
45	Bharathi	892061	21	60	6	3	2	2	2	3	0	0	0	0	0						82	76	78	72	74	74	130	80	120	80	120	80	120	80	120	80	120	80	16	18	16	16	14	16		1		
46	Asha	892366	27	50	7	3	1	2	2	4	0	0	0	0	0	1					80	82	78	78	76	80	110	70	110	80	110	80	110	80	110	80	120	80	16	16	14	16	14	14		1		
47	Lavanya	882653	20	55	6	2	1	1	2	4	0	0	0	0	0						82	78	78	76	80	80	120	70	120	80	120	80	120	80	120	80	120	80	18	16	14	14	16	14			1	
48	Bharathi	892892	30	40	8	4	2	1	6	3	0	0	0	1	1						80	78	78	76	76	78	120	70	120	70	120	70	120	80	120	80	120	80	14	14	12	12	14	16			1	
49	Roja	893012	25	65	7	4	1	1	5	2	0	0	0	0	1	1					80	78	78	80	80	78	110	70	120	80	120	80	120	80	120	80	120	80	18	16	12	14	14	16		1		
50	Asharani	893350	22	60	7	2	2	2	2	3	0	0	0	0	0		4				78	76	76	74	76	76	110	70	110	70	120	70	120	70	120	70	120	70	16	18	14	12	12	14			1	
51	Amrin taj	893563	30	55	6	2	1	2	2	2	0	0	0	0	0						84	80	78	78	76	78	110	70	110	80	110	80	110	80	110	80	120	80	18	16	16	14	14	16				1
52	Shazia	893624	22	55	7	2	1	1	2	3	0	0	0	0	0						86	78	72	74	76	78	120	70	120	70	120	70	120	80	120	80	120	80	20	16	14	14	14	16		1		
53	Kavya	893426	21	60	7	4	1	1	5	2	0	0	0	0	1	1					80	84	78	74	76	78	110	70	110	70	120	70	120	70	120	70	120	70	16	14	14	14	16	16			1	
54	Nawziya	893322	27	45	6	2	1	1	2	4	0	0	0	0	0						82	76	78	72	72	74	120	80	120	80	120	80	120	80	120	80	110	80	14	14	12	12	14	14		1		
55	Anjanamma	893904	24	55	6	3	2	1	1	3	0	0	0	0	0						82	78	78	76	80	80	110	70	110	70	110	70	110	70	110	70	120	80	16	16	14	14	12	14				1
56	Amilamma	893891	22	40	7	2	2	2	2	3	0	0	0	0	0						80	82	78	76	72	76	120	80	120	80	120	80	120	80	120	80	120	80	18	16	16	14	14	16			1	
57	Vinodha	893342	24	60	6	3	1	1	5	2	0	0	0	0	1			4			84	80	78	78	76	78	110	70	110	70	110	70	110	70	110	70	120	80	16	14	14	14	16	18	1			
58	Mamatha	894053	21	45	7	2	1	1	1	2	0	0	0	0	0						80	80	78	78	76	76	120	80	120	80	120	80	120	80	120	80	120	80	18	16	16	14	14	16				1
59	Usha	894416	26	65	8	3	3	2	2	3	0	0	0	0	0						82	76	78	72	74	74	110	70	110	70	120	70	120	70	120	70	120	70	16	18	14	12	12	14			1	
60	Munirathnamma	894643	23	50	8	4	3	1	2	3	0	0	0	0	0						80	78	78	80	80	78	110	70	120	80	120	80	120	80	120	80	120	80	18	16	12	14	14	16			1	