COMPARATIVE STUDY OF EFFICACY AND SAFETY OF INTRAMUSCULAR ACECLOFENAC AND DICLOFENAC IN MANAGEMENT OF POSTOPERATIVE PAIN IN PATIENTS UNDERGOING COMPOSITE RESECTION FOR ORAL CANCER

BY

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Dissertation submitted to the
Sri Devaraj Urs Academy of Higher Education and Research,
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In partial fulfillment of the requirements for the degree of

DOCTOR OF MEDICINE
IN
PHARMACOLOGY

Under the guidance of

Dr. SARALA. N, MD

DEPARTMENT OF PHARMACOLOGY
SRI DEVARAJ URS MEDICAL COLLEGE, KOLAR

April 2016

DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation entitled **"COMPARATIVE STUDY OF EFFICACY AND SAFETY OF INTRAMUSCULAR ACECLOFENAC AND DICLOFENAC IN MANAGEMENT OF POSTOPERATIVE PAIN IN PATIENTS UNDERGOING COMPOSITE RESECTION FOR ORAL CANCER"** is a bonafide and genuine research work carried out by me under the direct guidance of **Dr. SARALA. N, MD** Professor and HOD, Department of Pharmacology, Sri Devaraj Urs Medical College, Tamaka, Kolar.

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Dedicated with

REVERENCE

to

My Parents

LIST OF ABBREVIATIONS

NSAIDs	Non Steroidal Anti-inflammatory Drugs
COX	Cyclooxygenase
IDET	Intra Discal Electrothermic Therapy
FLACC	Face Legs Activity Cry Consolability
VAS	Visual Analogue Scale
WHO	World Health Organisation
MPQ	Mcgill Pain Questionnaire
CHEOPS	Children Hospital of Eastern Ontario Pain Scale
PCA	Patient Controlled Analgesia
NMDA	N-Methyl D-Aspartate
TRPV1	Transient Receptor Potential Vanilloid 1
PG	Prostaglandin
COPD	Chronic Obstructive Pulmonary Disease
ANOVA	Analysis Of Variance

ABSTRACT

BACKGROUND:

Post-operative pain is inevitable following surgeries. Opioids and NSAIDs are most commonly used analgesics for post-operative pain management. Aceclofenac is a newer phenylacetic acid derivative. Being a predominant cyclooxygenase-2 (COX-2) inhibitor, it has better gastrointestinal tolerability than diclofenac.

OBJECTIVES:

1. To study the efficacy of aceclofenac and diclofenac in management of post-operative pain using Face legs activity cry consolability (FLACC) scale score and Visual analogue scale (VAS) score

2. To assess the total amount of rescue analgesic required

3. To monitor the adverse effects using WHO causality scale

4. To assess the patient's satisfaction score

MATERIALS AND METHODS:

Seventy six patients who underwent composite resection for oral cancer at R.L.Jalappa Hospital and Research Center from February 2014 to June 2015 were randomly assigned to receive either injection aceclofenac 150mg or diclofenac 75mg intramuscularly at 0, 12, 24, 36, 48, 60 and 72 hours post operatively. FLACC score was assessed at 2, 4, 8, 12 and 24hours and VAS score at 24, 36, 48, 60 and 72 hours.Rescue analgesic, tramadol 100mg (IV) was given if FLACC or VAS score was >3. Patient's satisfaction score was assessed at 48 and 72 hours

RESULTS:

There were 61 female patients and mean duration of surgery in aceclofenac and diclofenac groups were 450.00±116.00 and 416.84±130.63 minutes. Mean FLACC scores between the two groups was not significant. Patients receiving diclofenac had significant reduction in mean VAS score (p=0.005) at end of 72hours compared to 24 hours. Between groups there was no significant difference in mean VAS scores at any time interval. Amount of rescue analgesic required in both groups was similar (p=0.34). At 72 hours, 31.57% patients graded their satisfaction score as 'good' in aceclofenac and 34.21% in diclofenac groups. Nausea and dyspepsia were the common adverse effects seen in both groups.

CONCLUSION:

Aceclofenac and diclofenac were both effective in reducing postoperative pain following composite resection for oral cancer. In individuals with history or risk of gastritis or peptic ulcer, aceclofenac can be an alternative to diclofenac.

Key words: Oral cancer, aceclofenac, diclofenac

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Introduction

INTRODUCTION

Head and neck cancer accounts for 30-32% of all cancers in India, among them oral cancer is most common.[1] In patients undergoing oncology surgeries, estimating pain has become a subject of importance.[2] Post-operative pain management is a challenge because analgesics should provide effective pain relief without causing significant adverse effects, which may prolong hospitalization.[3]

Non steroidal anti inflammatory drugs (NSAIDs) are usually combined with opioids as this enables the reduction in the dose of opioids with improved analgesia and also reduction of opioid related adverse effects.[3] Diclofenac sodium is a potent, established and commonly prescribed drug for relief of pain. Being a nonselective inhibitor of cyclooxygenase, it is associated with adverse effects such as nausea, epigastric pain, peptic ulcer, maculopapular rash and fixed drug eruptions.[4]

Another approach for reducing post-operative pain is by the use of newer phenyl acetic acid derivative, aceclofenac. It has anti-inflammatory properties similar to those of diclofenac. Being a predominant cyclooxygenase-2(COX-2) inhibitor it has better gastrointestinal tolerability. It has lower incidence of myocardial infarction and atherosclerosis when compared to other selective COX-2 inhibitors.[5]

There is paucity of information regarding comparative studies between aceclofenac and diclofenac in post-operative pain management. Hence this present study was undertaken to compare the efficacy and safety of these drugs in post-operative pain in patients undergoing composite resection for oral cancer.

Aims

&

Objectives

AIMS AND OBJECTIVES

1. To study the efficacy of aceclofenac and diclofenac in management of post-operative pain using Face legs activity cry consolability (FLACC) scale score and Visual analogue scale (VAS) score
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Review Of Literature

REVIEW OF LITERATURE

Historical background of pain

Ever since humans have experienced pain, they have given explanations for its existence and tried to find soothing agents to reduce or cease the painful sensation. Primitive man perceived illness and pain as the work of evil spirits. Treatment consisted of extracting the intruding object or frightening away the spirits. Archaeologists have uncovered clay tablets dating back to 5,000 BC which mentions the cultivation and use of the opium poppy to bring joy and cease pain.[6]

Acupuncture, a method prevalent in China since 2700 B.C. consists of inserting metal needles at certain points of the skin to varying depths, to counteract pain and other symptoms. E.H.Hume described that Hunt O, a famous surgeon in Chinese medical history, born in 190 A.D had used acupuncture for carrying out surgeries on various organs.[7]

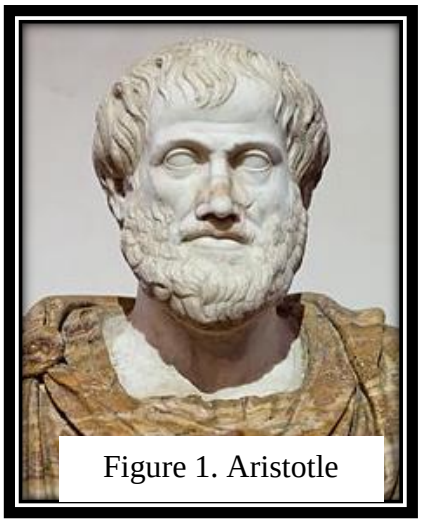


Figure 1. Aristotle

Aristotle (Figure 1) did not include a sense of pain when he enumerated the five senses. He saw pain and pleasure not as sensations but as emotions. Alternatively, Hippocrates believed that pain was caused by an imbalance in the vital fluids of a human. In Greece – Alcamaeon produced the idea that the brain and not the heart was the center for pain.[8] Benjamin Bell (1749–1806), surgeon to the Royal Infirmary, Edinburgh, described the use of a nerve compressor to reduce pain during amputations in his textbook dated 1796.

In 1804, Descartes (Figure 2) described in his book called "L Homme (Man)" that the conduction of sensation including pain was via delicate threads contained in the nerves which connected the tissue to the brain.[8] The new era of analgesia was initiated with Joseph

Figure 2. Portrait of Rene Descartes

Priestley's discovery of nitrous oxide. Charles Beu described that the functions of dorsal root are distinct from those of the ventral root and after 15 years, Johannes Muller developed this idea. The modern era of systemic analgesia began in 1806 when morphine was isolated by Sertuner and was frequently used intramuscularly as preoperative medication and for postoperative analgesic.[8]

In 1874 the cannabis plant from which marijuana was obtained became a well-regarded remedy for headache prescribed by treating physicians. In 1898, heroin the newest opium derivative was produced commercially by Germany Bayer Company. Significant advances were made in pain management during the 19th century.[9] Injection of dilute solutions of cocaine through the sacral hiatus into the epidural space was first described by Sicard in 1901, to treat patients suffering from severe sciatic pain. In 1912, Kappis described paravertebral somatic blocks pain relief during surgeries. In 1953 John J. Bonica developed an interest in pain management and published a seminal book - The Management of Pain, where therapy of pain was focused on nerve blocks. In 1970 neurostimulators, based on a theory that electric current can produce magnetic field was used for pain relief.[8]

In 1988, Brian Ready used Patient Controlled Analgesia (PCA) mode to provide safe and effective management of severe post-operative pain. In 1997 Intra Discal Electrothermic Therapy (IDET) was introduced to investigate chronic low backache. In 2004-05, the first rechargeable spinal cord stimulation systems became available in United States which represent the new advancement in neuromodulation devices for the treatment of pain. In 2008 St. Jude introduced smallest long lasting neurostimulator to treat failed back surgeries and chronic pain of trunk and limbs.[8, 9]

Definition and classification of pain

Pain is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage. Pain is always subjective. The term "nociception" is obtained from “noci” (Latin for harm or injury) and is used to describe the neural response only to traumatic or noxious stimuli.[10]

Pain is categorized as follows[11]

I) **Acute pain** -Typically appears suddenly and has a limited duration. It is frequently caused by damage to bone, muscle or organs and the onset is often accompanied by anxiety or emotional distress. It is considered as good pain as it serves an important protective mechanism. Acute pain stimulates sympathetic nervous system resulting in increased heart rate, respiratory rate, sweating, dilated pupils, restlessness and apprehension.

Acute pain can be divided into:

A) Somatic pain: Further classified as, superficial or deep

(a) 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.

(b) Deep somatic pain arises from muscles, tendons, joints or bones. It has a dull, aching quality and is not well-localized.

B) Visceral Pain

The visceral acute pain is due to a disease process or abnormal function of an internal organ or its covering. It is dull and diffuse in character and is associated with abnormal sympathetic or parasympathetic activity. Ischemia, chemical stimuli, spasm or over distension of hollow viscus are some of the causes for visceral pain.

C) Referred pain

The site of stimulus and area of referred pain is supplied by the same spinal segment . Hence the patients feel the pain in an area distant from the site of the stimulus.

II) Chronic pain- Lasts longer than acute pain and generally does not respond to medical treatment. Prolongs and persist beyond expected normal time. This period can vary from 1 to 6 months or longer. Chronic pain can be the result of damaged tissue, but very often is attributable to nerve damage.

Post operative pain

Post-operative pain is one of the most common adverse consequence following surgery and is a type of acute nociceptive pain. The pain, a patient experiences after surgery, is related to the extent of tissue damage and the site of surgery. Unrelieved pain after surgery can interfere with patients physical functioning and wellbeing which will in turn extend the duration of hospital stay. Effective pain control is important in order to prevent complications such as hypertension, myocardial ischemia, arrhythmias, respiratory impairment and poor wound healing.[12]

Pain receptors

The receptors of pain are present in the skin and other tissues, are all free nerve endings. They are widespread in the superficial layers of skin, periosteum, the arterial walls, the joint surfaces and the falx and tentorium in the cranial vault. Most other tissues are only supplied with pain endings.

Three type of stimuli which excite pain receptors in response to tissue injury are mechanical, thermal and chemical pain. Fast pain (Aδ fibres) which is felt within 0.1s is elicited by mechanical and thermal stimuli. Bradykinin, serotonin, histamine, prostaglandins,

acetylcholine are some of the chemicals exciting chemical type of pain (Figure 3). Slow pain (C fibres) which begins over seconds or even minutes is elicited by all three stimuli.[13]

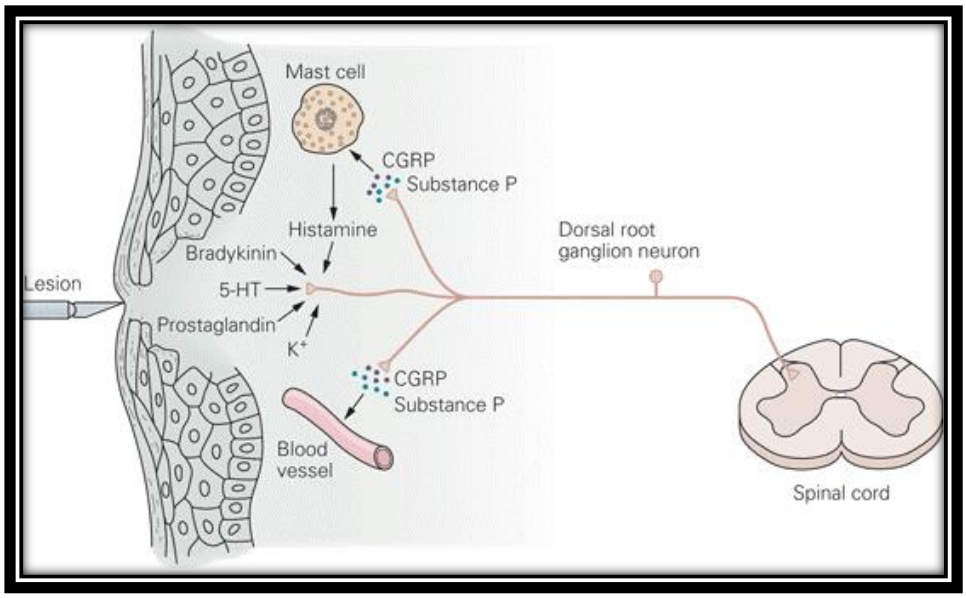


Figure 3.Chemical mediators of pain

Primary afferent fibers

- Aβ fibres are highly myelinated and of large diameter, therefore allowing rapid signal conduction. They have a low activation threshold and usually respond to touch and transmit non noxious stimuli.
- Aδ fibres are lightly myelinated and smaller in diameter, hence conduct more slowly than Aβ fibres. They carry fast pain and are responsible for the initial reflex response to acute pain.
- C fibres are the smallest type of primary afferent fibre which are unmyelinated, hence they demonstrate the slowest conduction.

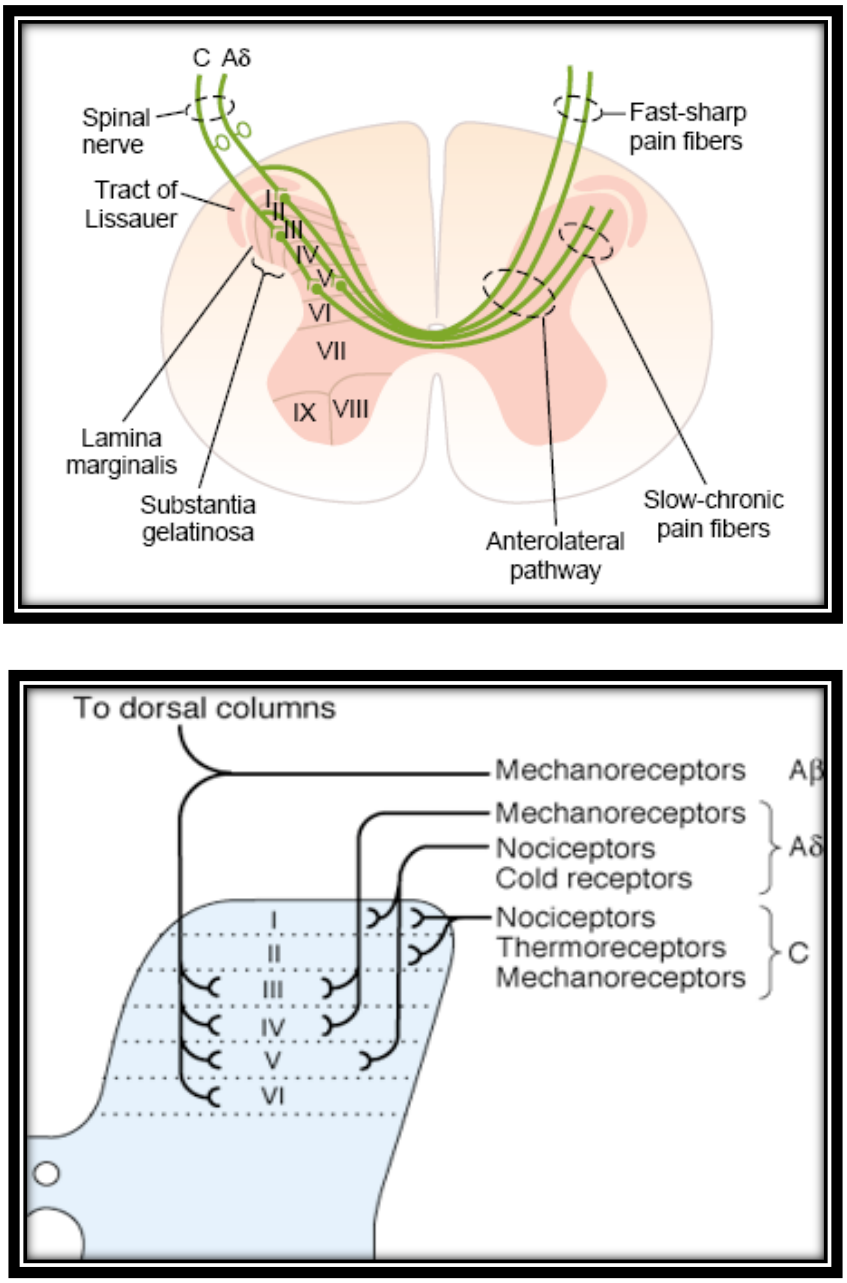


Figure 4. Transmission of fast and slow pain signals to the spinal cord

The fast (Aδ) and slow fibers (C), on entering the spinal cord terminate on relay neurons in the dorsal horns. Substance P and glutamate released in the dorsal horn, is a regulator of pain and channels pain impulses from the peripheral receptors to the central nervous system. Spinal cord grey matter is divided into 10 laminae called as Rexed laminae. The first six laminae which make up the dorsal horn receive all afferent neural activity and represent principal site of pain modulation (Figure 4).[14]

Dual pathways for transmission of pain signals into the CNS

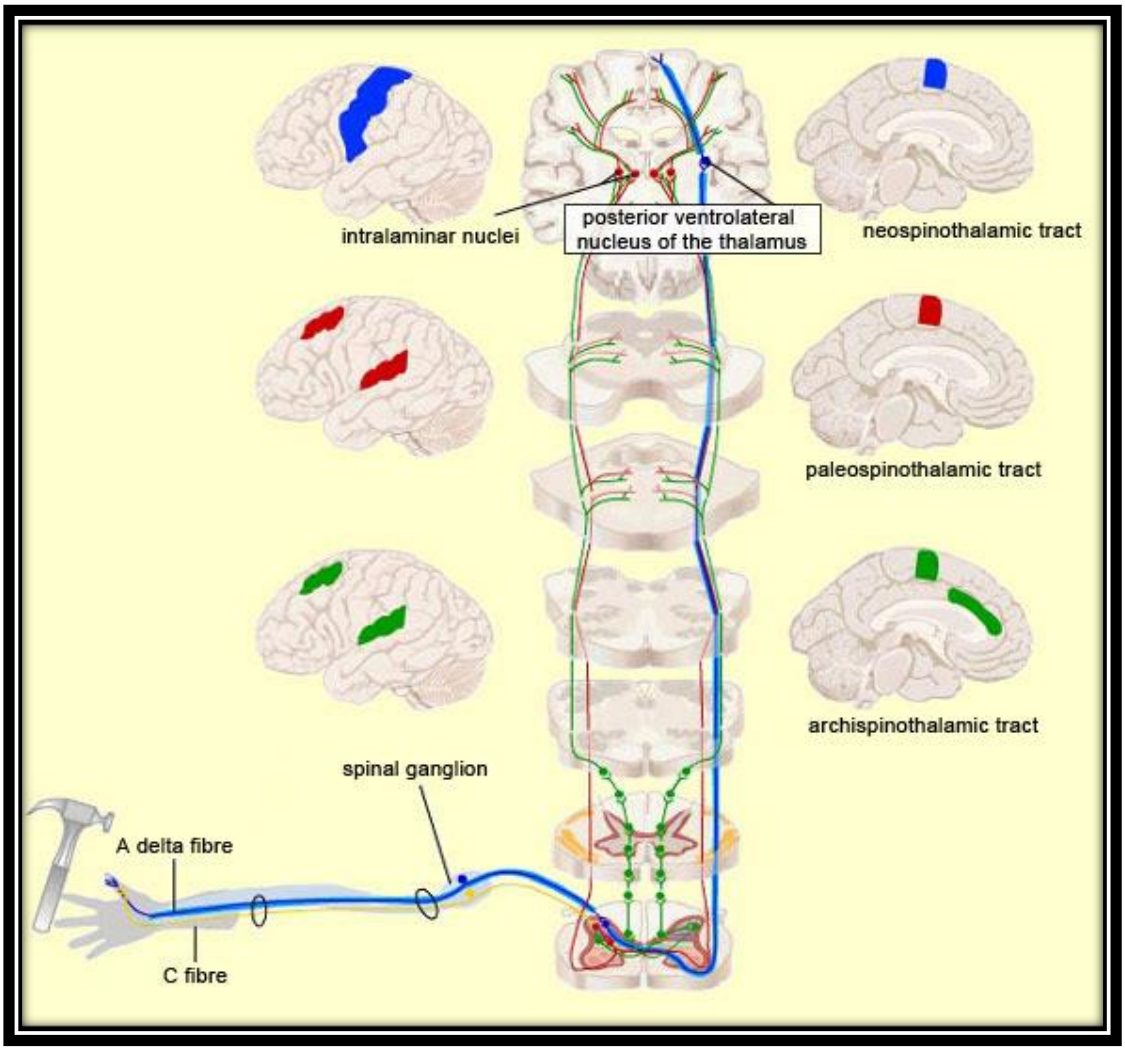


Figure 5. Neospinothalamic and paleospinothalamic tract

On entering the spinal cord pain signals take two pathways to the brain via,

1. Neospinothalamic tract[12]

This transmits fast pain (Aδ fibres) which mainly terminate in lamina 1(lamina marginalis) of the dorsal horn (Figure 4). They excite second order neurons of the tract. These give rise to long fibers that cross immediately to the opposite side of the cord over the anterior commissure and pass to the brain in the anterolateral column.

A few fibers of the tract terminate in the reticular areas of the brain stem but most pass to thalamus without interruption terminating in the venterobasal complex along with dorsal column medial leminiscal tract for tactile sensations. Some fibres also terminate in the posterior nuclear group of the thalamus. From these areas, signals are transmitted to the cortex (Figure 5).

2. Paleospinothalamic tract [12]

Slow chronic type of pain is carried by type C fibres in paleospinothalamic tract which terminate in lamina II and III of the dorsal horn (substantia gelatinosa) (Figure 4). Signals then pass through second order neurons within the dorsal horns before entering lamina V. The last neurons in the series give rise to long axons that join the fibers from fast pain pathway, passing first through the anterior commissure to the opposite side of the cord, then upward to the brain in anterolateral pathway. (Figure 5)

They terminate widely in the brain, only one tenth to one fourth of the fibers pass all the way to thalamus. Most terminate in one of the following three areas.

a) The reticular nuclei of medulla, pons and mesencephalon

b) The tectal area of mesencephalon

c) The periaqueductal gray region surrounding the aqueduct of sylvius

Theories of pain[15-17]

A) Specificity Theory

Specificity theory is one of the first modern theories for pain**.** It states that specific pain receptors transmit signals to "pain center" in the brain that produces the perception of pain. This theory also says that separate fibers do carry pain signals to the brain eventually.

However, the theory does not explain the psychological factors that influence perception of pain.

B) Pattern Theory

Above theory explains that pain signals are conveyed to the brain only when stimuli combine together to produce a specific combination or pattern. The theory neither postulates specialized receptors for pain nor does it see the brain as having control over the amount of pain experienced. Here, the brain is only observed as a message recipient.

C) Gate Control Theory

The Gate Control Theory was proposed in 1965 by Ronald Melzack and Patrick Wall. They suggested that there is a gate or control system in the substantia gelatinosa of dorsal horn of the spinal cord, which modulates the sensory information from primary afferent fibres before reaching the brain. The substantia gelatinosa controls whether the gate is open or closed. An open gate means that the small fibres (C) can carry signals to the brain where pain is perceived whereas stimulating large diameter fibres inhibits the transmission of pain thus closing the gate and no pain signal is sent to the brain (Figure 6).

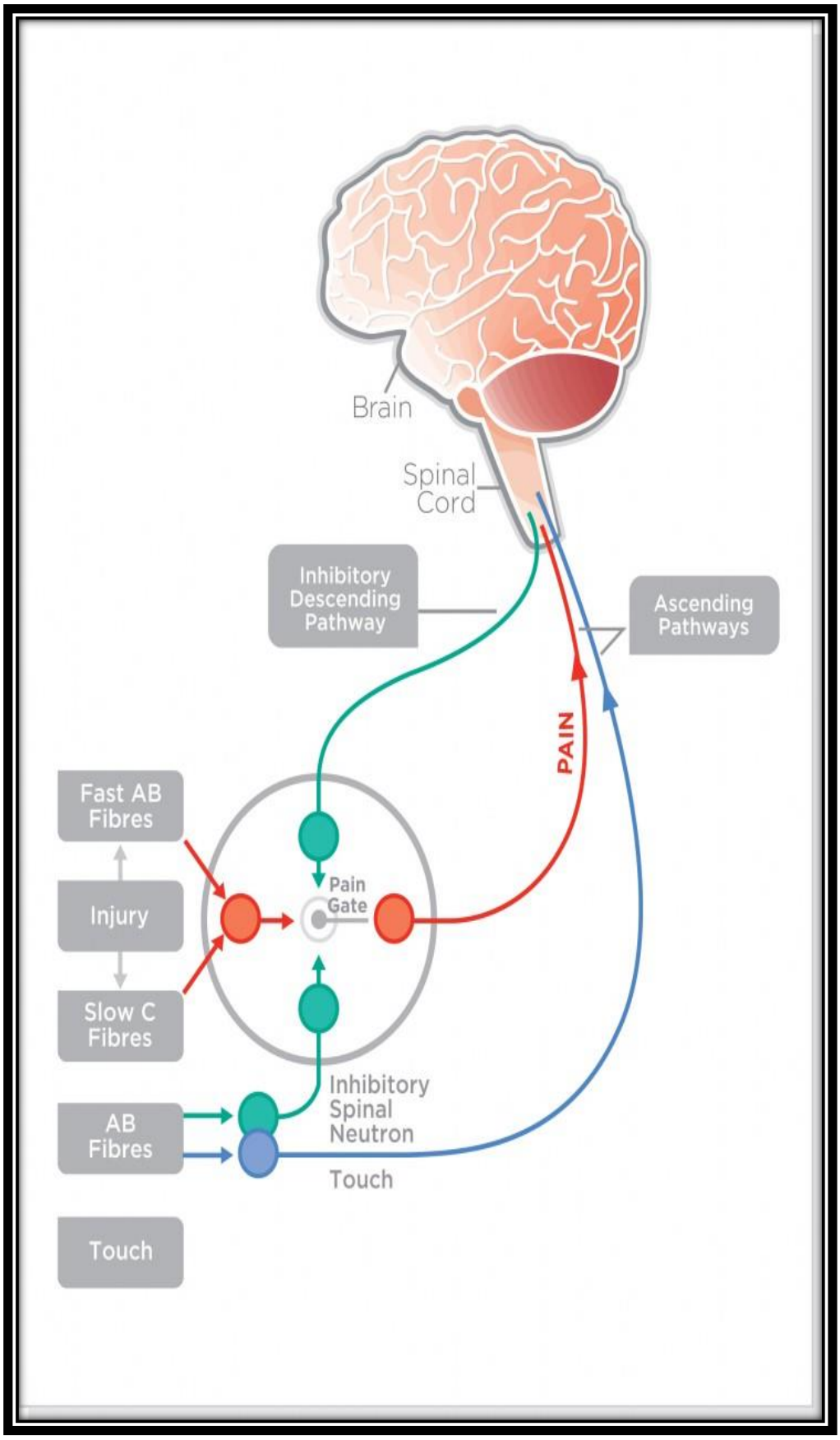


Figure 6. Gate control theory

Assessment of pain

Ideal pain management is carried out by assessing the pain experienced by the patient. It aims at assessing the intensity, duration and quality of pain. Pain assessments are done in the form of a scale which will help in deciding the choice and effectiveness of therapy.[18]

Pain assessment scale[19, 20]

1. Visual analogue scale

This is the most commonly used method of pain assessment at present. First described by Aitken is 1966. The patient makes a mark on a 10cm line, one end of which is marked as 'No pain' which is indicated by 0 and the other as 'The worst(excruciating) possible pain one can perceive' which is indicated by 10. Here patients are asked to indicate pain intensity on a scale of 0 to 10 (Figure 7).

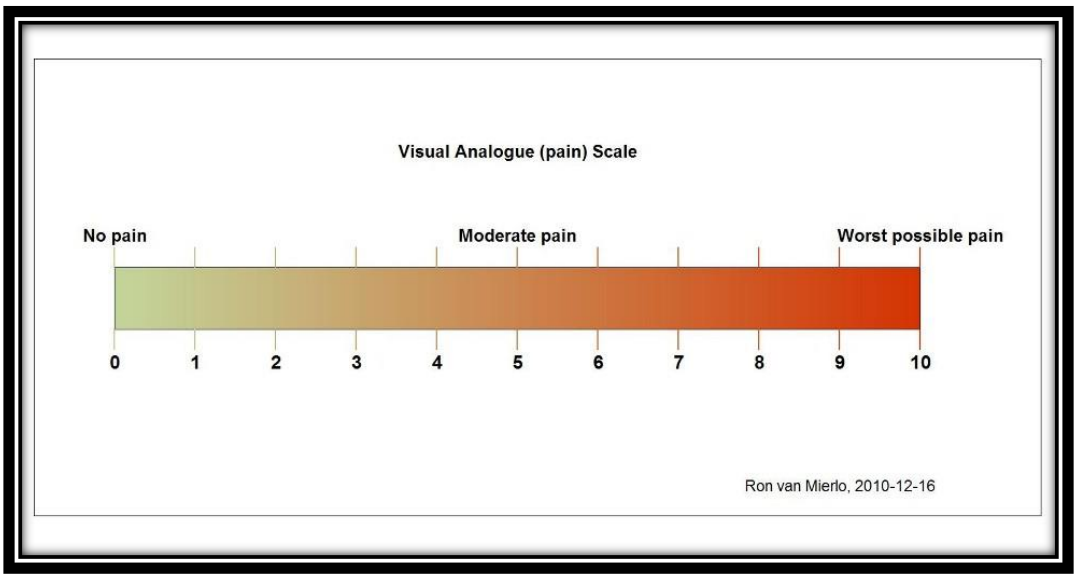


Figure 7. Visual Analogue Scale Score

2. Faces rating scale

Recommended for children above 3 years of age. Ask the child to choose the face that best describes his or her pain and note the appropriate number(Figure 8).

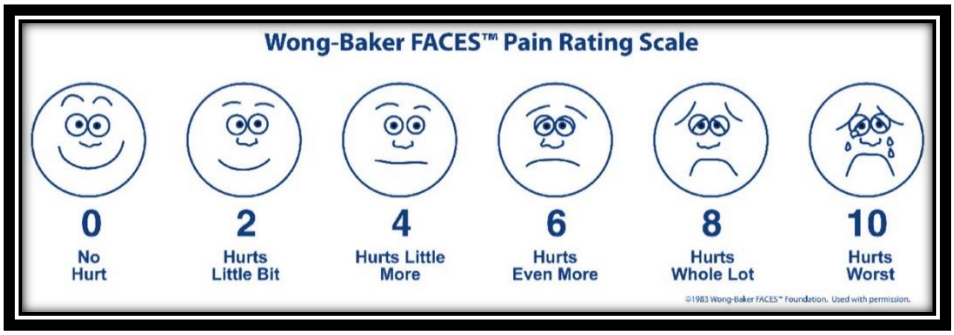


Figure 8. Faces Rating Scale

3. McGill pain questionnaire(MPQ)

In 1971, Melzack and Torgerson developed a scale of rating pain at McGill University in Canada. It is a self-reported questionnaire that guides the doctor with a good description of the quality and intensity of pain that patients are experiencing. It consists primarily of 3 major classes of word descriptors: sensory, affective and evaluative. It contains an intensity scale to determine the properties of pain experienced and are used by patients to specify subjective pain experience.

4. Behavioral rating scale

It is designed for use in critically ill patients who are unable to provide self-reports of pain. Observe the patient for 10 minutes. Assess the patient on the four behaviors (restlessness, tense muscles, frowning/grimacing, patient sounds from none-severe). A pain score is obtained based on the highest behavior observed.

5. Functional activity scale

This is an activity related score. Ask your patient to perform an activity related to their painful area (eg: deep breathe and cough for thoracic injury or move affected leg for lower limb pain).

Observe your patient during the chosen activity and score A, B or C

A – No limitation means 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

6. CHEOPS scoring

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. According to Mitchell (1999) it is intended for ages 0-4. It involves 6 parameters such as facial, torso, cry, legs, child verbal and touch. Minimum score is 4 and maximum score is 13.

7. FLACC (Face, Legs, Activity, Crying and Consolability) scale score[21]

The FLACC pain scale was developed to help doctors to assess the level of pain in children who are not able to self report the pain intensity. It can also be used in adults who are unable to communicate. It is based on observations made regarding the patient's face, the position of their legs, their actions, and whether they are calm or consolable. Zero to two points are assigned for each of these 5 areas of observation. The score is graded as follows:

0 = Relaxed and comfortable

1-3 = Mild discomfort

4-6 = Moderate pain

7-10 = Severe discomfort/pain

Modes of analgesia

A) Preemptive analgesia[22, 23]

Pre-emptive analgesia is a treatment that is initiated before the surgical procedure in order to reduce pain intensity. It has the potential to be more effective than any similar analgesic treatment initiated after surgery. Acute postoperative pain may be reduced and the

development of chronic pain may be prevented. The only way to prevent sensitization of the nociceptive system is to block completely any pain signal arising from the surgical wound from the time of incision until final wound healing. Interventions with flupirtine and gabapentin, may interfere with the induction and maintenance of sensitization.

B) Multimodal analgesia

Balanced or multimodal analgesia involves the use of specific drugs in combination. The concept relies on using several analgesic drugs with different modes of action (eg: non-opioid combined with opioid) or via different routes of administration (eg: local anaesthetic block combined with a systemic analgesic). This approach improves analgesia due to additive or synergistic effects. The dosage of the individual drugs can be reduced, thereby reducing the incidence and severity of adverse effects.

Figure 9.PCA pump

C) Patient controlled analgesia[23]

Patient Controlled Analgesia (PCA) is a method of pain control, where in it allow the patient to administer preset doses of an analgesic, on demand. PCA pump is an electronic micro processing machine which can be programmed to deliver a required amount of medication on the demand, at specified intervals, by pressing of a button (Figure 9). It can also be used to deliver supplemental clinician loading doses of medication. Morphine is the most common drug used to administer via PCA pump.

Post-operative pain management[23, 24]

1. Opioid analgesics

Opioids act as agonists on stereospecific opioids receptors (mu, delta and kappa) at presynaptic and postsynaptic sites at spinal and supra spinal levels and in the peripheral tissues. Opioids mimic the actions of endogenous ligands by binding to opioids receptors, resulting in the activation of pain – modulating system.

2. NSAIDs

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

3. Non opioids – non NSAIDs[25]

Flupirtine exerts its analgesic action through blockade of N – methyl – D – aspartate (NMDA) receptor. 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.

3. Adjuvants

Drugs which by themselves have undesirable side effects or low potency but in combination with opioids, allows reduction of opioid dosing for postoperative pain management.

Examples- Ketamine, gabapetin, pregabalin, dexmedetomidine and clonidine.

4. Local anaesthetics

A local anesthetic is a drug that causes reversible local anesthesia and loss of nociception by interfering with pain transmission in the spinal cord by blocking sodium

channels leading to analgesia. When used on specific nerve pathways (nerve block), effects such as analgesia and loss of muscle power can be achieved. It allows patients to undergo surgical and dental procedures with reduced pain and distress. Lignocaine, bupivacaine, ropivacaine, tetracaine, prilocaine are some of the local anaesthetics in use.

5. Transient Receptor Potential Vanilloid 1(TRPV1) antagonists[26]

TRPV1 is expressed on small myelinated and unmyelinated sensory neurons in dorsal root and trigeminal ganglia, where sensory neurons cluster. It is also found in muscles, joints, the urinary bladder and kidneys. 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 evolved 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.

INTRODUCTION TO NON STEROIDAL ANTI INFLAMMATORY DRUGS

The NSAIDs, are the most widely used of all drugs because of their analgesic, anti-inflammatory and anti-pyretic effects. [27]

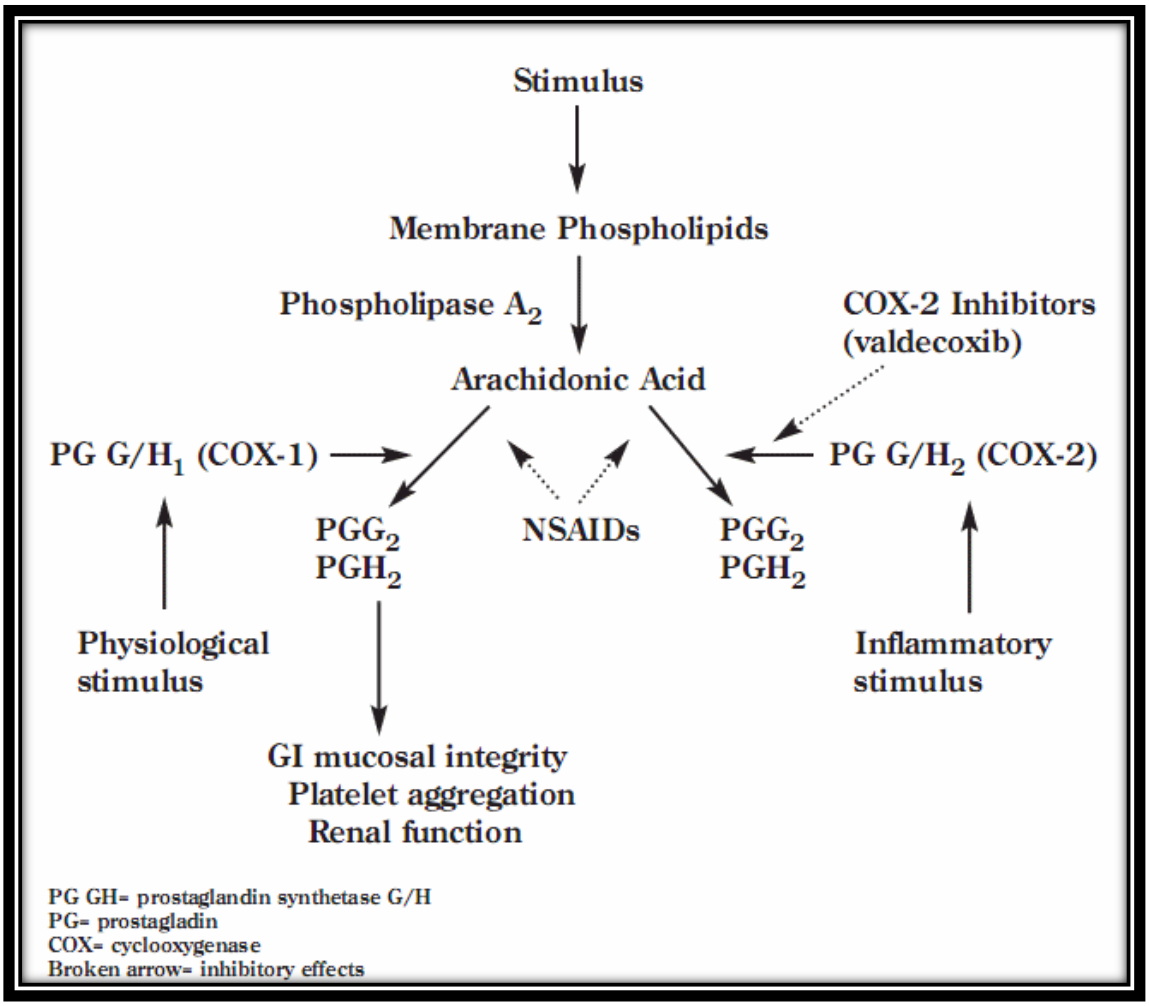


Figure 10. Mechanism of action of NSAIDs

NSAIDs have the ability to inhibit prostaglandin (PG) production by inhibiting cyclooxygenase (COX) enzyme also known as PG G/H synthase. COX enzymes are of two forms: COX-1 and COX-2. COX-1, expressed in most cells, is the dominant source of prostaglandins for housekeeping functions, such as gastric epithelial cytoprotection and hemostasis whereas COX-2, induced by cytokines, stress, and tumor promoters, is the more important source of prostaglandin formation in pain, inflammation, fever and carcinogenesis.[28]

This enzyme converts arachidonic acid to the unstable intermediates such as PGG_2 and PGH_2 and leads to the production of the PGE_2, PGI_2 (Key mediators of central and peripheral pain sensitization) and Thromboxane A_2 (Figure 8). PGE2 contribute to hyperalgesia by sensitizing nociceptors via its receptors EP_1 and EP_4 which causes phosphorylation of transient receptor potential vanilloid 1 and other ion channels on nociceptors and increase their membrane excitability

Centrally PGs enhance pain transmission at the level of dorsal horn increasing the release of substance P and glutamate from first order neurons, increasing the sensitivity of second order neurons and inhibiting release of neurotransmitters from pain modulating pathways.

Advantages of NSAIDs in management of post-operative pain:

NSAIDs are effective in the treatment of post-operative pain. They lack unwanted effects of opiates like nausea, vomiting, sedation, respiratory depression, absence of cognitive impairment and the potential for development of physical dependence. [3, 4]

Commonly used NSAIDs for the management for post-operative pain are diclofenac, lornoxicam, piroxicam, aceclofenac, etorcoxib and parecoxib.

Pharmacology of Diclofenac

Introduction

Diclofenac derives from its chemical name: 2-(2, 6-dichloranilino) phenylacetic acid which was first introduced in the UK in 1979. It was originally developed by Novartis in 1973.

History

The purpose in developing diclofenac sodium was to synthesize a NSAIDs with high activity and exceptional tolerability. Factors considered were drug transport through biologic membranes, the atomic and spatial structure of the molecule and the electronic structure. Based on analysis of other NSAIDs, it was hypothesized that an effective antirheumatic agent should have the following characteristics, an acidity constant between 4 and 5, a partition coefficient of approximately 10, and two aromatic rings twisted in relation to each other. The result was diclofenac sodium, which has an acidity constant of 4.0 and a partition coefficient of 13.4 with a maximum twisting in its ring structure

Structure and chemistry of diclofenac

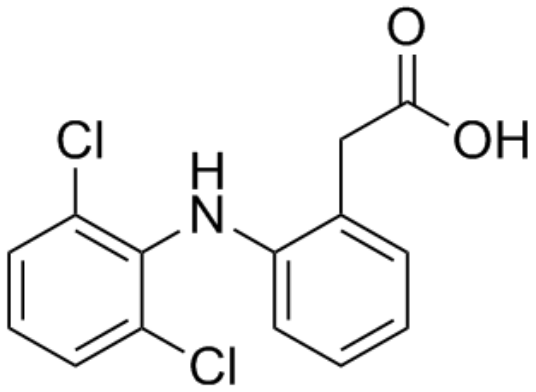


Figure 11. Chemical structure of diclofenac[28]

Chemical name is 2-(2,6-dichloranilino) phenylacetic acid. A white to light beige, crystalline powder which is sparingly soluble in water and in acetone but is freely soluble in alcohol and methylalcohol. The pH of 1% solution in alcohol is between 6.4 and 8.4. [28-30]

Mechanism of action

A non selective inhibitor of cyclooxygenase enzyme, inhibits prostaglandin production which are important mediators of pain. Hence decreases the post-operative pain by decreasing the nociceptive transmission to brain.[31]

Pharmacokinetics

Diclofenac is rapidly absorbed when given as a sugar coated tablet, rectal suppository or intramuscular injection. Absorbed more slowly when given as an enteric coated tablets and when given with food. Only 50% of drug reaches systemic circulation in an unchanged form following first pass metabolism and 99% bound to plasma proteins.

Diclofenac is predominantly eliminated through hepatic biotransformation with less than 1% of the dose being excreted unchanged through the kidneys. The major primary metabolites of diclofenac are 3' hydroxyl diclofenac, 4' hydroxyl diclofenac, 5' hydroxy diclofenac, and 4', 5' dihydroxydiclofenac. Its hydroxylated metabolites undergo glucuronidation and sulphation and are excreted in urine.[28, 31]

Uses

- Rheumatoid arthritis
- Osteoarthritis
- Ankylosing spondylitis
- Bursitis, tendinitis, sprains and strains
- Acute gout
- Renal colic
- Dysmenorrhea
- Migraine
- Post-operative pain in hernioplasty[32], lower limb fractures, tonsillectomy

Dosage and route

Diclofenac is administered either through oral or rectal route in a dose of 75-150mg. A dose of 50mg is used for migraine. Diclofenac can be given by intramuscular injection in a dose of 75 mg once or twice daily for post-operative pain management. It can an also be given as continuous or intermittent intravenous infusion with glucose or sodium chloride. Diclofenac sodium is used as 0.1 % ophthalmic solution.[28]

Table 1. Adverse effects of diclofenac[28]

Systems	**Manifestations**
Eyes	Blurring of vision
Ear	Hearing loss, tinnitus
RS	Pneumonitis, alveolitis, pulmonary fibrosis
CVS	Increase blood pressure, heart failure, MI, stroke (COX 2) inhibitors
GIT	Peptic ulcer, bleeding , perforation
CNS	Dizziness
Blood	Agranulocytosis, neutropenia
Bone	Delayed bone healing process
Liver	Acute noninfectious liver injury
Renal	Acute and chronic interstitial nephritis
Pancreas	Pancreatitis
Skin	Maculopapular rash, systemic lupus erythromatosus, tissue necrosis[33]
Hypersensitivity reaction	Rash, urticaria, bronchoconstriction, angioedema, anaphylactic shock

The most frequently reported adverse effects were gastrointestinal which was reported in 7.6 % of patients followed by CNS related adverse effects which was reported in 0.7% and allergy in 0.4%.

Drug Interactions

- Corticosteroids, selective serotonin reuptake inhibitors, bisphosphonates, antiplatelets such as clopidogrel, ticlopidine may increase the frequency or severity of GI complications when combined with diclofenac
- Since diclofenac is highly plasma protein bound, doses of drugs such as sulfonylurea, methotrexate should be reduced as it displaces other drugs from protein binding sites
- Diclofenac inhibits natriuretic and vasodilatory PGs such as PGE_2 and PGI_2, thereby attenuating the efficacy of diuretics
- Diclofenac should not be given to patients receiving anticoagulants as they interfere with normal platelet function
- Cyclosporine and diclofenac results in deterioration of renal function as well as when given along with triamterene
- Sucralfate reduces the plasma concentration of diclofenac
- Bile acid sequestrants reduces the bioavailability of diclofenac

Pharmacology of Aceclofenac

Aceclofenac is a newer NSAID of phenyl acetic acid group, with remarkable anti-inflammatory and analgesic properties.

Structure and chemistry

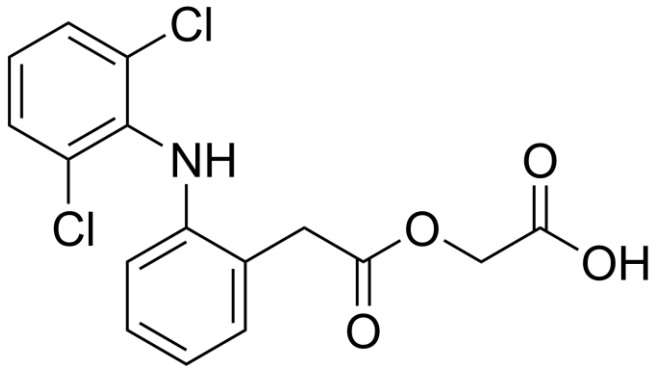


Figure 12. Chemical structure of aceclofenac[29]

The chemical name is (2-[(2, 6-dichlorophenyl) amine] phenylacetoxyacetic acid). It's a white crystalline powder which is insoluble in water, soluble in alcohol, freely soluble in acetone.[29, 34,35]

Mechanism of action

It has more selectivity for COX-2 inhibition. It is faster and more potent than diclofenac. It efficiently interferes with neutrophil adhesion to endothelium and inhibits PGE2. It also decreases expression of interleukin-1 and tumor necrosis factor alpha causing analgesic and anti-inflammatory effect.[35]

Pharmacokinetics

Aceclofenac is well absorbed from gastrointestinal tract and peak plasma concentration is seen at 1 to 3 hours after an oral dose. It is more than 99 % plasma protein bound and has a plasma elimination half-life is about 4 hours. It is metabolised to 4' hydroxyaceclofenac, 5 hydroxyaceclofenac, 4' hydroxydiclofenac, 5'hydroxydiclofenac and

diclofenac. About two third of a dose is excreted in the urine mainly as hydroxymetabolites.[29,34-36]

Uses[37-42]

- Rheumatoid arthritis
- Osteoarthritis
- Post operative pain
- Post dental extraction
- Tonsillectomy
- Episiotomy
- Ankylosing spondylitis

Dosage and route

Aceclofenac is used in the management of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis at an oral dose of 100mg twice daily following food intake. Dose has to be reduced in patients with hepatic impairment. Also available as injectable form to be administered intramuscularly 150mg twice or thrice daily for post-operative pain management.[28]

Table 2. Adverse effects of aceclofenac[28]

Systems	**Manifestations**
Eye	Blurring of vision
Ear	Vertigo
RS	Bronchospasm, stridor
CVS	Palpitations
GIT	Dyspepsia, abdominal pain, nausea and diarrhea

CNS	Palpitations
Blood	Anemia, thrombocytopenia, neutropenia
Liver	Hepatitis
Renal	Nephrotic syndrome
Skin	Rash, urticarial, dermatitis

Drug interactions[28]

- Corticosteroids, selective serotonin reuptake inhibitors, bisphosphonate, antiplatelets such as clopidogrel, ticlopidine should be avoided in preventing GI complications when combined with aceclofenac
- Increased risk of nephrotoxicity when combined with tacrolimus and cyclosporine
- Aceclofenac is highly bound to plasma proteins and thus may displace drugs such as methotrexate, warfarin, glibenclamide, salicylates from their binding sites

Materials & Methods

MATERIALS AND METHODS

This study was conducted from February 2014 to June 2015, in patients clinically diagnosed with oral cancer

Location of study:

This was a prospective and open label study conducted by Departments of Pharmacology and Otorhinolaryngology on the patients admitted to the Departments of Otorhinolaryngology and Head and Neck Surgery in R.L. Jalappa Hospital & Research Centre attached to Sri Devaraj Urs Medical College, Tamaka, Kolar.

Data collection:

A proforma containing detailed information of each patient was designed according to the study protocol. Ethical clearance was obtained from the Institutional Ethics Committee. Written informed consent was obtained from patients and/or their care takers. A total of 76 patients were recruited for the study and were randomized using lottery method into two groups.

Inclusion Criteria

1. Patients of either gender aged between 25 to 70 years undergoing composite

   for oral cancer

Exclusion Criteria

1. Patients on radiotherapy or who had prior surgery for oral cancer
2. Patients who have received NSAIDs or opioids 12 hours before surgery

3. History of peptic ulcer, gastrointestinal bleeding, asthma, chronic obstructive lung disease (COPD)
4. History of hypersensitivity to both the study drugs
5. Pregnant and lactating women

Method of collection of data

Patients undergoing composite resection for oral cancer were divided into group A and group D with 38 patients in each group. Both the groups received fentanyl transdermal patch immediately after surgery. Following this, group A received aceclofenac 150mg and group D diclofenac sodium 75mg intramuscularly immediately after recovery from anesthesia. Twelve hours after this dose, study medication was repeated. On first and second post-operative days, patients received same dose of the drugs twice daily in the respective groups (i.e.24, 36, 48, 60 and 72hrs).

Face, legs, activity, cry, consolability(FLACC) scale score (Table 3) was assessed at 2, 4, 8, 12 and 24 hours post operatively.[21] Visual Analogue Scale (VAS) score (Figure 7) was explained and recorded at 24, 36, 48, 60 and 72 hours post operatively. Pulse rate, blood pressure and respiratory rate were monitored immediately after recovery from anesthesia and at 2, 4, 8, 12 and 24 hours post operatively. Rescue analgesic, tramadol 100mg intravenously was given to the patients if FLACC behavioral score or VAS score was more than 3 during post-operative period. Patient's satisfaction score was assessed at 48 and 72 hours. Adverse effects were recorded and analyzed in accordance with the WHO causality assessment scale.

Table 3. Face, Legs, Activity, Cry, Consolability(FLACC) scale score

BEHAVIOUR	**0**	**1**	**2**
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested, sad, appears worried	Frequent to constant quivering chin, clenched jaw, distressed looking face, expression of fright/panic
Legs	Normal position or relaxed, usual tone and motion to limbs	Uneasy, restless, tense, occasional tremors	Kicking or legs drawn up, marked increase in spasticity constant tremors and jerking
Activity	Lying quietly, normal position, moves easily, regular rhythmic expression	Squirming, shifting back and forth, tense, guarded movements, mildly agitated, shallow splinting/respirations, intermittent sighs	Arched, rigid or jerking, severe agitation, head banging, shivering ,breath holding, gasping, severe splinting
Cry	No cry (awake or asleep)	Moans or whimpers, occasional complaints, occasional verbal outbursts, constant grunting	Crying steadily, screams, sobs, frequent complaints, repeated outbursts, constant grunting
Consolability	Content, Relaxed	Reassured by touching hugging or being talked to, distractable	Difficult to console or comfort, pushing care giver away, resisting care or comfort measures

Sample size calculation: To detect a mean difference of 1.16 in the VAS score at the end of 8 hours post operatively with an effect size of 0.63, alpha error of 5%, power of 80% with a dropout rate of 10%, the required sample size was calculated to be 38 in each group.

Statistical methods:

The demographic data were analyzed using descriptive statistics. The FLACC and VAS score were assessed within the group by repeated measures ANOVA and between the groups unpaired t test. Adverse effects were analyzed by chi-square test. p value less than 0.05 was considered to be statistically significant.

Results

RESULTS

A total of 76 patients undergoing composite resection for oral cancer under general anesthesia were randomly allocated to groups A and D. All patients in both the groups received fentanyl transdermal patch following recovery from anesthesia. Figure 13 represents patient recruitment and follow up. Seventy five patients completed the study.

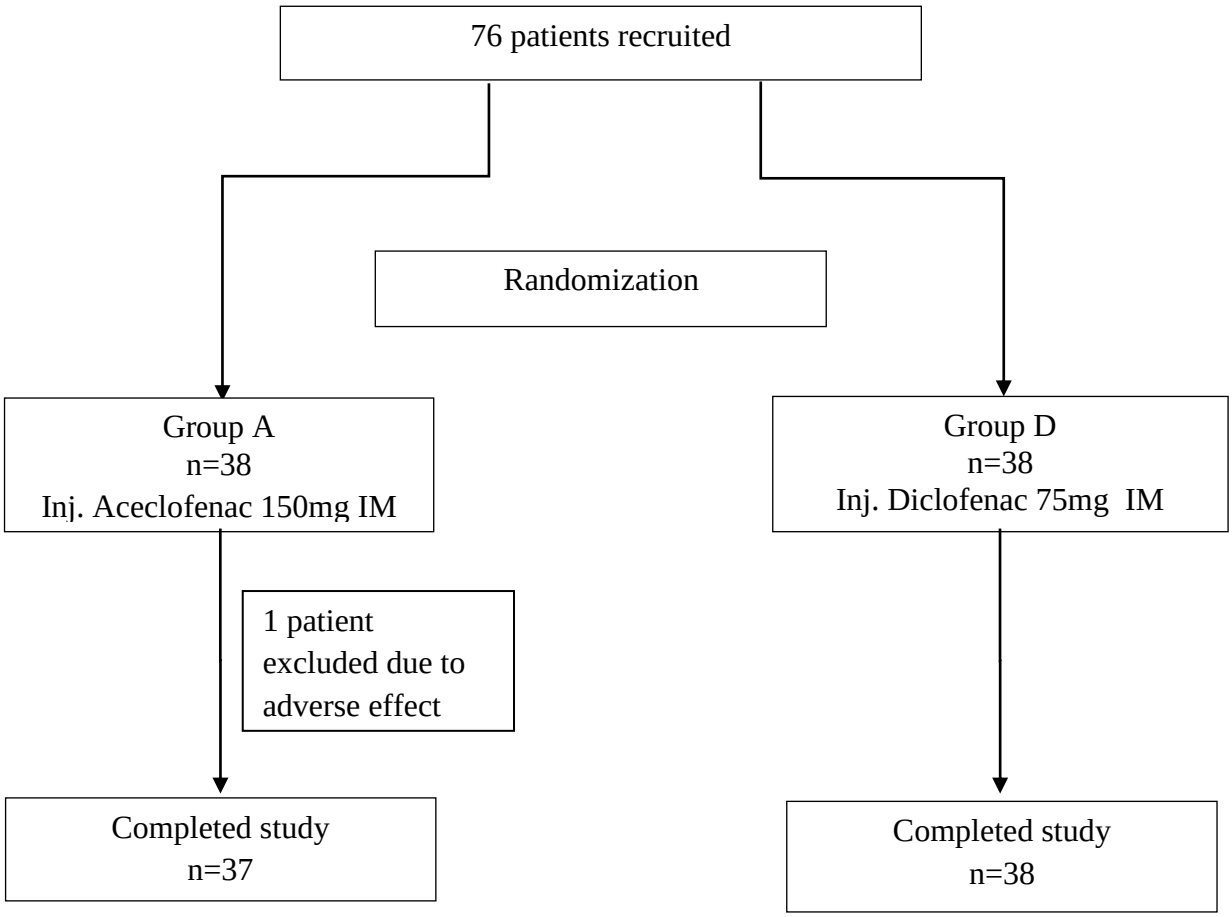


Figure 13. Flow chart representing recruitment and follow up of patients

Table 4. Demographic parameters

Variables	Group A n=38	Group D n=38
Male/female	7/31	8/30
Age(years) (Mean±SD)	56.44±10.89	52.87±11.89
Duration of surgery(minutes) (Mean±SD)	450.00±116.00	416.84±130.63
T_3/T_{4a} stage of oral cancer	7/31	15/23

The demographic parameters were comparable in both the groups. Among 76 patients, 15 were males and 61 were females with a literacy rate of 7.6%.

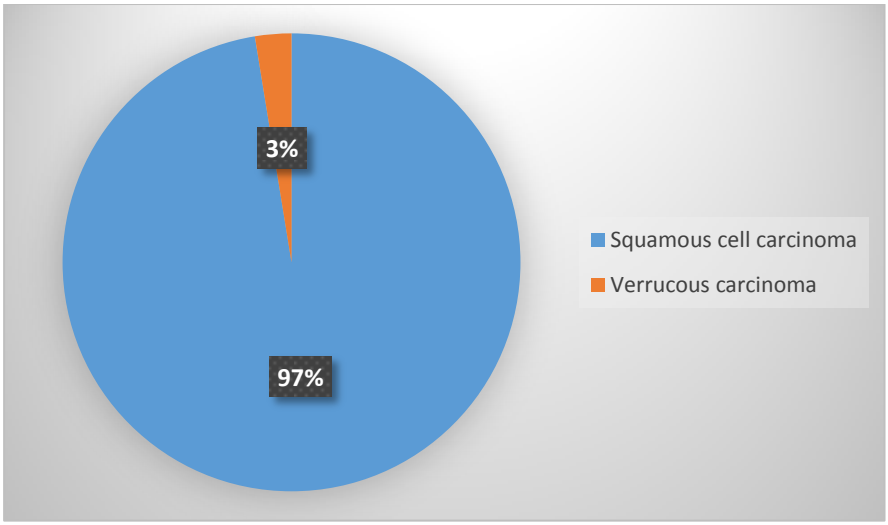


Figure 14. Type of oral cavity carcinoma

The most common type of buccal carcinoma was squamous cell which contributed to 97% of patients.

Table 5. Comparison of mean FLACC scores between two groups

	FLACC score (Mean±SD)				
	2h	4h	8h	12h	24h
Group A n=37	0.94±0.37	1.10±0.65	1.66±0.58	1.71±0.56	1.84±0.54
Group D n=38	1.02±0.49	1.28±0.51	1.42±0.68	1.58±00	1.86±0.66
p value	0.42	0.18	0.10	0.15	0.88

An increase in mean FLACC scores were observed in both the groups at 4, 8, 12 and 24 hours post operatively following recovery from anesthesia. It was not statistically significant at any time interval between the groups as shown in table 5.

Table 6. Post-operative pain score (VAS) within the group

	Group A n=37		Group D n=38	
Time in hours postoperatively	Mean±SD	p value	Mean±SD	p value
24h	2.61±0.75		2.47±0.56	
36h	3.37±1.36	0.001*	3.29±1.50	0.002*
48h	2.84±1.10	0.15	2.55±1.30	0.73
60h	2.47±0.92	0.40	2.39±0.91	0.69
72h	2.47±1.13	0.47	2.08±0.54	0.005*

The mean VAS score increased in patients at 36 hours in both the groups which gradually decreased by 72hours. The reduction in VAS score at 72 hours was statistically significant in patient who received diclofenac (p=0.005) as shown in table 6.

Table 7. Comparison of mean VAS scores between two groups

	VAS score(Mean±SD)				
	24h	36h	48h	60h	72h
Group A n=37	2.61±0.75	3.37±1.36	2.84±1.10	2.47±0.92	2.47±1.13
Group D n=38	2.47±0.56	3.29±1.50	2.55±1.30	2.39±0.91	2.08±0.54
p value	0.39	0.91	0.18	0.70	0.05

The reduction in mean VAS scores was not significant at any time interval as shown in table 7. The reduction of post-operative pain at all-time intervals of assessment was similar in patients receiving either medication.

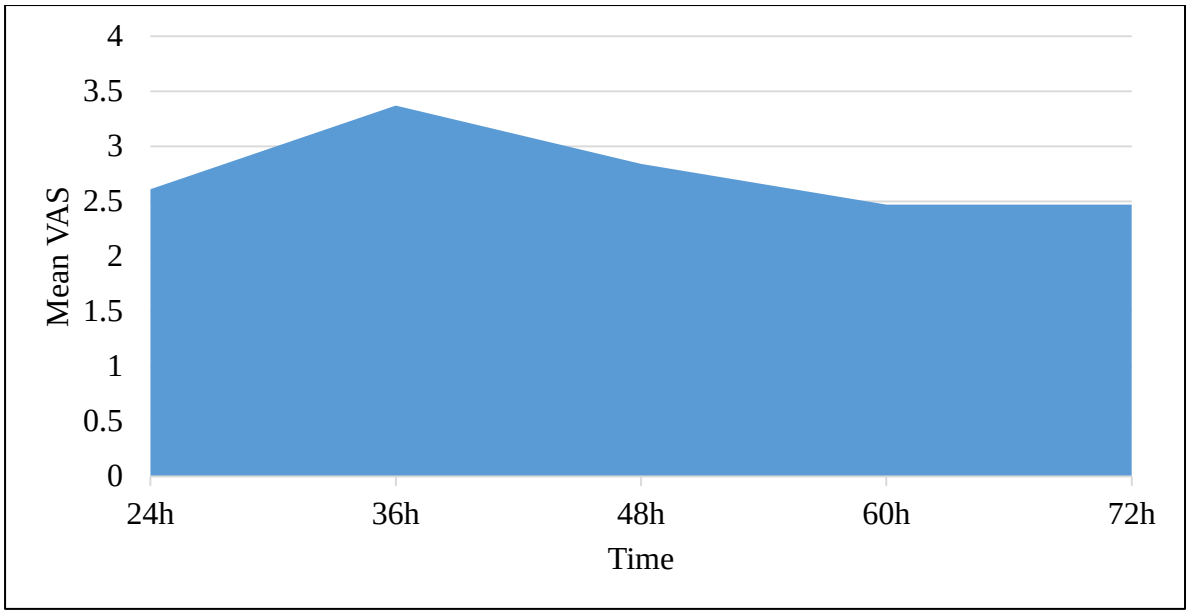


Figure 15. Area under curve-Aceclofenac

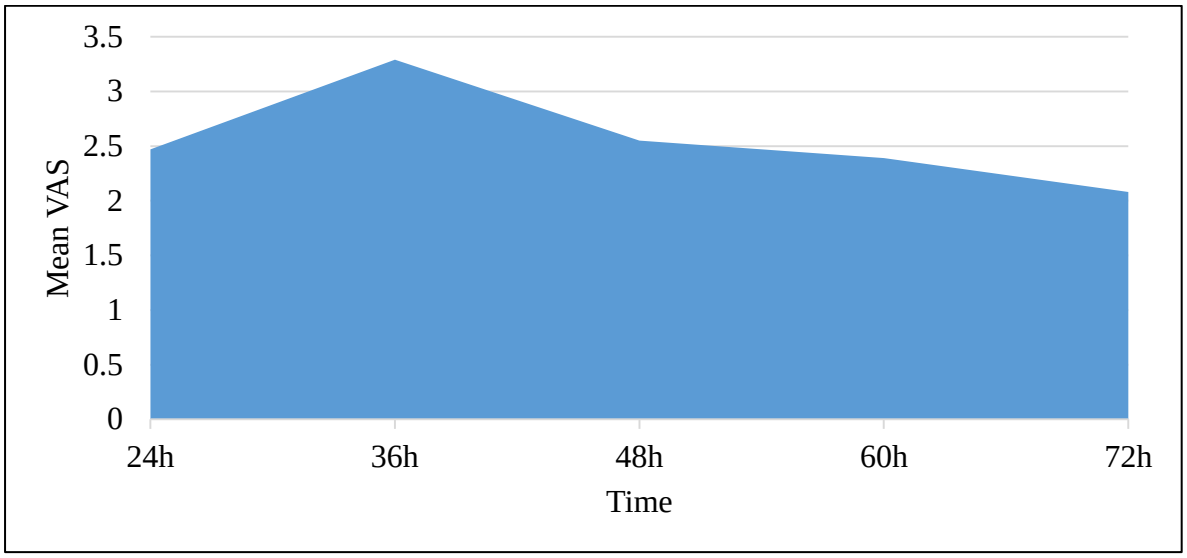


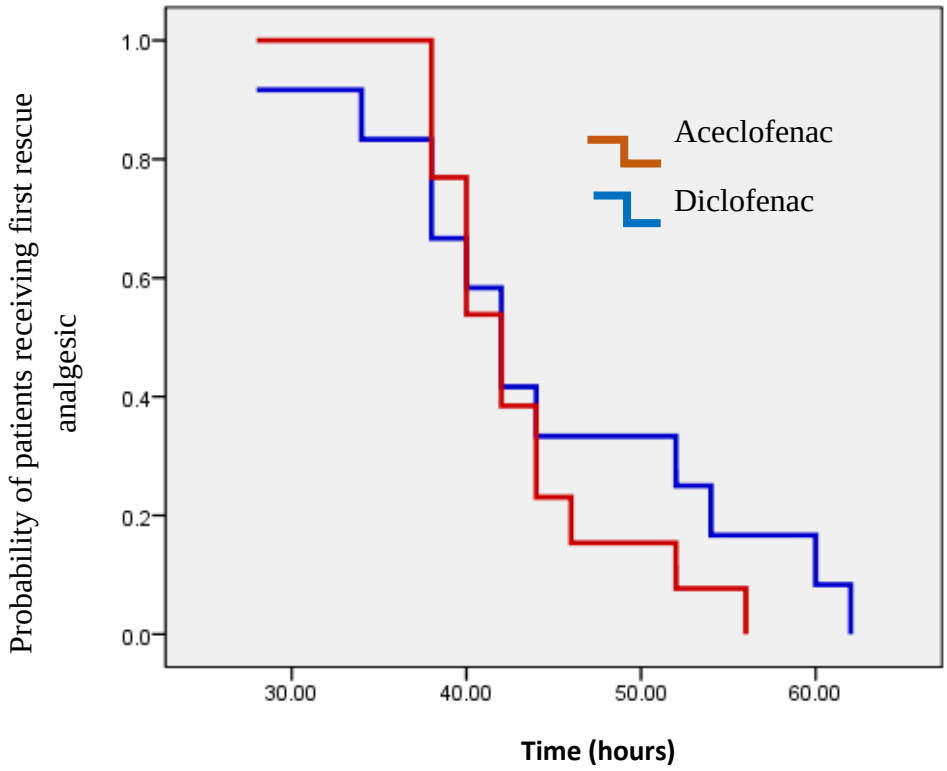
Figure 16. Area under curve-Diclofenac

The area under curve for reduction in post-operative pain in patients receiving medications in both the groups (Figure 15 and 16) was calculated by trapezoid method and the pain intensity from 24 to 72 hours was less with diclofenac (0.88) compared to aceclofenac (0.94).

Table 8. Patients requiring rescue analgesic

	Group A n=37 (Mean±SD)	Group D n=38 (Mean± SD)	p value
No. of patients receiving Tramadol	13	12	
Time to first rescue analgesic (hours)	43.38±10.44	44.00±09.34	0.88
Total amount of Tramadol (mg) used	115.38±37.55	108.33±28.88	0.34

Rescue analgesic administered was tramadol 100mg IV. Patients in group A received first rescue analgesic earlier to patients in group D but it was not statistically significant. The amount of tramadol used in both the groups was comparable as shown in table 8.



Log rank test, p=0.429

Figure 17. Kaplan Meier curve for first rescue analgesic between two groups

Kaplan Meier curve (Figure 17), represents the time from the administration of study drug to the first rescue analgesic used post operatively. The log rank test (0.429) indicates, there is no significant difference in the probability of patients receiving first rescue analgesic with either medication at any time point.

Table 9. Blood pressure and heart rate of patients in both groups

Parameters	Group A(n=37) Mean±SD					
	Baseline	2h	4h	8h	12h	24h
SBP (mm Hg)	124.9 ± 25.69	122.89± 15.85	121.11± 24.38	123.37± 16.28	120.16± 30.15	120.15± 23.09
DBP (mm Hg)	80.42± 15.85	79.63± 16.28	78.13± 15.30	79.23± 15.12	79.76± 15.49	78.34± 14.82
HR (beats/min)	78.45± 17.51	79.70± 16.91	80.05± 17.23	78.52± 16.62	79.73± 16.57	79.18± 16.55

Parameters	Group D(n=38) Mean±SD					
	Baseline	2h	4h	8h	12h	24h
SBP (mm Hg)	127.58 ± 15.71	125.71± 14.83	125.76± 13.01	124.39± 15.40	122.44± 14.16	122.15± 13.39
DBP (mm Hg)	81.71± 11.60	79.89± 8.05	78.07± 7.32	79.55± 8.51	79.50± 9.21	79.00± 9.38
HR (beats/min)	81.32± 12.31	80.29± 11.46	80.28± 11.51	80.02± 10.32	78.28± 11.05	78.10± 9.79

HR - Heart rate, SBP - Systolic blood pressure, DBP - Diastolic blood pressure

The systolic blood pressure was decreased in both the groups, upto 24 hours from baseline but diastolic blood pressure and heart rate did not alter as shown in table 9. However, blood pressure and heart rate was within normal range and it was not statistically significant between the groups.

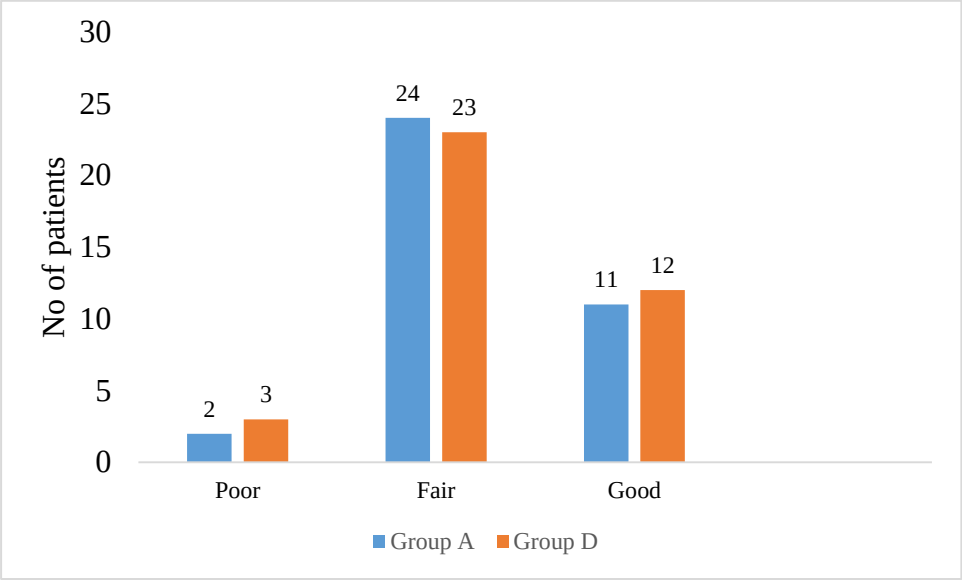


Figure 18. Patient satisfaction score at 48 hours

At the end of 48 hours, 64.9% of patients graded their satisfaction score as fair and 29.8% as good in group A whereas 60.6% as fair and 31.6% as good in group D (Figure 18).

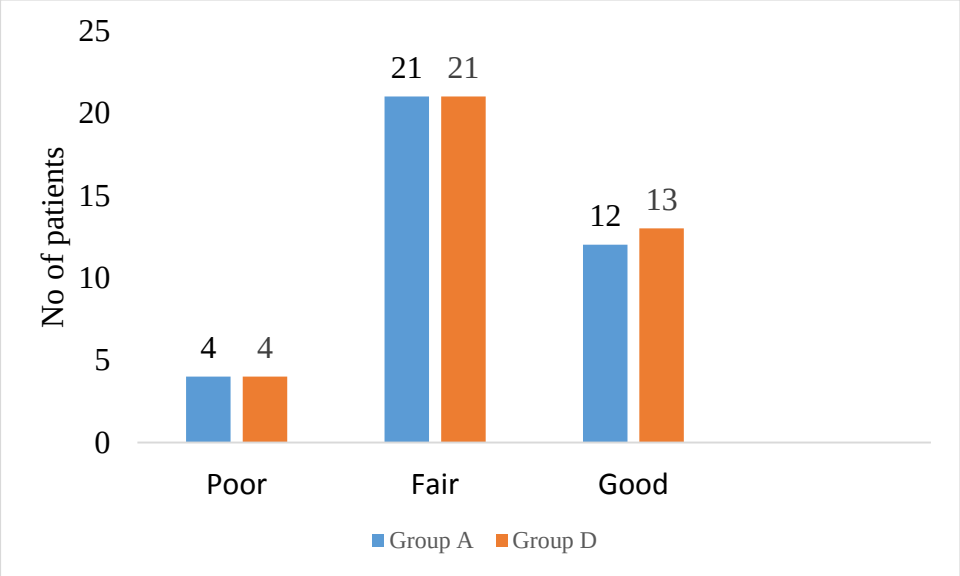


Figure 19. Patient satisfaction score at 72 hours

At the end of 72 hours, 56.6% of patients graded their satisfaction score as fair and 32.4% as good in group A whereas 55.3% as fair and 34.2% as good in group D (Figure 19).

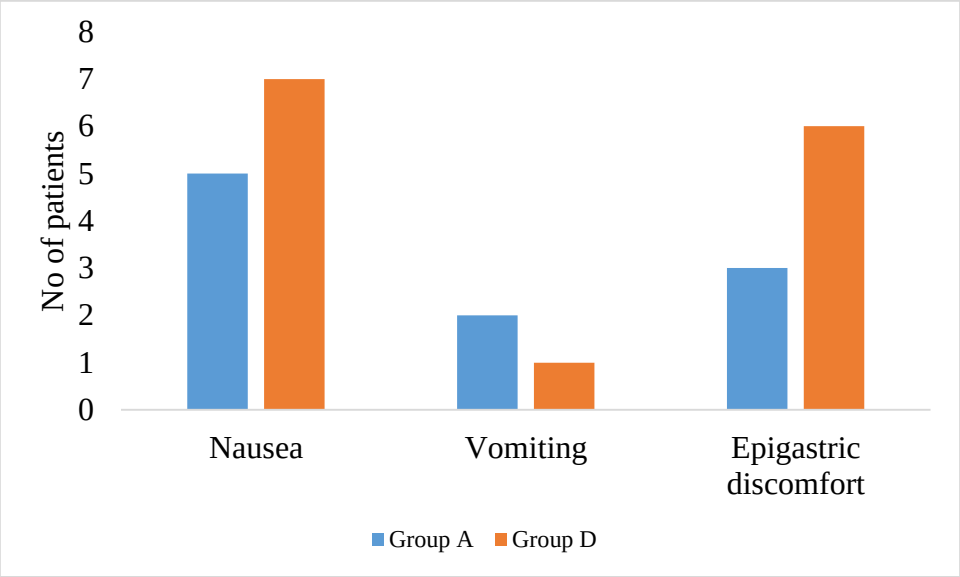


Figure 20. Adverse effects in both groups

One patient in group A was excluded from the study as patient developed rash and hypotension following first dose of injection aceclofenac. Total number of adverse effects noted were 10 in group A and 14 in group D as shown in figure 20. The most common adverse effects were nausea and epigastric discomfort which were not statistically significant in patients receiving either medication.

Discussion

DISCUSSION

In India, prevalence of cancer of the head and neck is 30-35% with oral cancer accounting to 50%.[43] Oral cavity cancer involves cancers of the mucosal surface of the lips, floor of the mouth, tongue, buccal mucosa, lower and upper gingiva, hard palate and retro molar trigone.[43] Head and neck cancer is the commonest cancer in males but in females it is second to cervical cancer. Oral cancers occur due to use of smokeless forms of tobacco such as betel nut, gutkha and paan, which is high in our country. These are placed in the oral cavity for a prolonged duration of time. Most of the patients approach the surgeon when the lesions are in stage 3 or 4. Oral cancers are usually resected surgically with or without adjuvant radiotherapy or chemotherapy based on the invasion into the surrounding structures.[44,45] Resection of cancerous lesion of the oral cavity is associated with severe pain, the intensity of which depends on the site of surgery and the extent of tissue damage. Since pain has both sensory and emotional components, adequate relief of pain is essential for the patient well-being.[46-48]

Opioids and NSAIDs are the mainstay for the treatment of moderate to severe postoperative pain.[49] Since NSAIDs are devoid of opioid related adverse effects, we compared aceclofenac and diclofenac in post-operative pain management following composite resection for oral cancer. Out of 76 patients recruited, we observed 80% of patients were females and 20% males, this can be attributed to females having tendency of stacking up tobacco in lower gingiva for a longer time and males smoking beedi in our region. Similar findings were reported in a study conducted in Spanish Caucasian population, where 57.4% of patients with oral cancer were females.[45]In our study, the patients were in the age group of 40-70 years which is in concordance to another study conducted in a tertiary care hospital in Rajasthan, where the average age of presentation of oral cancer was 50.4 years.[44]

Majority of patients (71%) presented when the tumour was in stage T_{4a}. Often, there is a considerable delay in the diagnosis of oral cancers in India, in spite of the relative ease of oral cavity examination, auto-examination by patients themselves has not been routinely practiced. The other reasons for late diagnosis are ignorance of patients, lack of awareness and inadvertent delay by treating doctors in the peripheries.[44] Histopathological examination revealed 97% patients had squamous cell carcinoma and 3% verrucous carcinoma which is also a variant of squamous cell carcinoma (Figure 14) and a similar finding was reported in another study.[44]

Total of 76 patients were recruited as represented in figure 13. The duration of surgery was comparable in both the groups. FLACC behavioral score was used to assess the pain intensity during the first 24 hours since the patients were unable to communicate orally, either due to endotracheal intubation or partial resection of mandible/structures around it. The FLACC score gradually increased over 24 hours in both the treatment groups but remained below three which represents mild pain (Table 5). This was probably because the patients were under the weaning phase of the anesthetic, influence of fentanyl given intraoperatively, postoperative transdermal fentanyl patch and administration of study drugs.

In the present study, there was reduction of pain indicated by VAS score (Table 6) within the groups at the end of 72 hours when compared to 24 hours, however this reduction was significant in patients receiving diclofenac. Other studies revealed significant reduction in VAS score in patients receiving either flupiritine or diclofenac following craniotomy.[50] When morphine and diclofenac suppositories were used following coronary artery bypass surgeries, both the medications were equally efficacious in reducing post-operative pain from extubation until 72 hours.[51]

We have observed that reduction in pain by aceclofenac and diclofenac was similar at all-intervals of time as shown in table 7. However, a study had reported that intramuscular aceclofenac was superior to diclofenac in lower limb surgery and in another study oral aceclofenac was better than diclofenac in relieving pain following extraction of third molar.[37,39] In Chitlangia et al, pain relief from oral ibuprofen was found to be superior to that of aceclofenac following third molar surgery.[52]

In our study, the intensity of pain experienced by the patients is denoted by Area Under Curve. Patients receiving diclofenac (0.88) had marginally better pain control when compared to aceclofenac (0.94) as shown in figures 15 and 16. Time to first rescue analgesic was not significant between the groups as represented by Kaplan Meir curve (Figure 17). A study conducted in Turkey, has shown that consumption of rescue medication tramadol, was lowest in patients receiving diclofenac compared to lornoxicam and dexketoprofen after 24 hours.[53] Another study has shown that, intramuscular diclofenac was equally effective when compared to combination of diclofenac and paracetamol in terms of rescue analgesic requirement which indicates the combination had no added advantage.[54]

We recorded the patient satisfaction score at the end of 48 hours and 72 hours. As depicted in figure 18 and 19, the pain relief was better with diclofenac at 48 hours, but it was similar to aceclofenac at 72 hours. This was in contrast to a study conducted by Sharma et al where 60% of patients who received aceclofenac expressed their pain relief as excellent following lower limb surgeries when compared to diclofenac.[37]

The adverse effects such as nausea and epigastric discomfort (Figure 20) was higher with diclofenac which is similar to a study comparing diclofenac with aceclofenac following third molar surgery.[39] In a study conducted in Amritsar, it was observed that in patients undergoing major abdominal surgeries, diclofenac patch was as effective as diclofenac

injection in management of pain post operatively. However 14% of patients receiving diclofenac injection experienced adverse effects such as pruritus, erythema, abscess and necrosis.[55]One patient in our study developed maculopapular rash and hypotension following first dose of aceclofenac, hence the drug was discontinued.

The findings of our study imply that early pain relief in postoperative period was better with diclofenac, but in the later part the efficacy of both drugs was similar. In individuals with history or risk of gastritis or peptic ulcer, aceclofenac can be an alternative to diclofenac.

Conclusion

CONCLUSION

- Patients with oral cancer were in their fifth decade and majority were females
- Histopathological examination revealed that 97% patients had squamous cell carcinoma
- Patients received either aceclofenac or diclofenac
- FLACC score indicated mild pain during first 24 hours of post-operative period which was comparable between the groups
- Mean VAS score was reduced at 72 hours when compared to 24 hours in patients receiving aceclofenac and diclofenac, but the reduction was significant with diclofenac
- Mean VAS score was comparable at all-time intervals between patients receiving either study medication
- Less than 35% patients required rescue analgesic with both medication indicating aceclofenac and diclofenac were both effective in relieving pain
- The satisfaction score was categorized as good by 32-34% patients
- The common adverse effects in both the groups were nausea and epigastric discomfort and they were more with diclofenac
- Aceclofenac was as effective as diclofenac in reducing post-operative pain following composite resection for oral cancer. In individuals with history of gastritis or peptic ulcer, aceclofenac can be an alternative to diclofenac

Summary

SUMMARY

Postoperative pain management following composite resection for oral cancer helps to minimize patient discomfort, facilitate early mobilization and faster recovery. Opioids are the main stay for management of postoperative pain, but their side effects such as sedation, constipation, urinary retention and respiratory depression limit their use. NSAIDs are used in postoperative pain management because of their analgesic, anti-inflammatory properties and relative tolerability.

A prospective and open label study was conducted on 76 patients undergoing composite resection for oral cancer to study the analgesic effect of aceclofenac and diclofenac. They were randomized to receive either injection aceclofenac 150mg or diclofenac 75mg intramuscularly after recovery from anesthesia. Twelve hours after this dose, the study medication were repeated. On first and second post-operative days, patients received same dose of the drugs twice daily in the respective groups (i.e.24, 36, 48, 60 and 72hrs).

Face, legs, activity, cry, consolability, behavioral (FLACC) score was assessed at 2, 4, 8, 12 and 24 hours and Visual Analogue Scale (VAS) score at 36, 48, 60 and 72 hours post operatively. Rescue analgesic, tramadol 100mg intravenously was given to the patients if FLACC behavioral score or VAS score was >3 during post-operative period. Patient's satisfaction score was assessed at 48 and 72 hours. Adverse effects were recorded and analyzed.

Majority of patients presented with oral cancer in the age group of 40-70years among them 80% were females. Seventy percent of the patients presented with T_{4a} stage and 97% were squamous cell carcinoma. FLACC score was comparable between the groups. There

was a reduction in VAS score at 72 hours compared to 24 hours with both medications and this reduction was significant in patients receiving diclofenac. VAS score was comparable at all-time intervals between the groups. The intensity of pain was less with diclofenac compared to aceclofenac as depicted by area under curve for both the medications. The number of patients requiring rescue analgesic was similar with both the drugs.

At 48 hours, patients receiving aceclofenac graded their relief from pain as fair (64.9 %) and good (29.8 %) whereas 60.6% as fair and 31.6% patients as good in diclofenac group. At the end of 72 hours, 56.6 % of patients graded their satisfaction score as fair and 32.4 % as good in the aceclofenac whereas 55.3% as fair and 34.2% as good in diclofenac group. The adverse effects such as nausea and epigastric discomfort was higher with diclofenac. Thus, aceclofenac and diclofenac are both equally effective in reducing postoperative pain following composite resection of oral cancer.

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Annexures

PROFORMA

OP. No: IP No: Date:

Serial No:

1. Name: 2. Age: 3. Gender:

4. Educational status: 5. Occupation:

6. Address with phone no.:

7.Present history:

8. Family history of asthma/ COPD:

9.Personal history: Smoking/alcohol/drug abuse/DM/HTN/Bronchial asthma

10.General Physical Examination:

Per abdomen:

CVS:

RS:

CNS:

11.Diagnosis:

12.Date of surgery:

13.Duration of anesthesia:

14.Time of start of surgery:

15.Time of end of surgery:

16.Duration of surgery:

17.Analgesic used intraoperatively

Post-Operative Parameters

	Pulse	BP	RR
Baseline			
2hrs			
4hrs			
8hrs			
12hrs			
24hrs			

FLACC scale score

FLACC	2 hrs	4 hrs	8 hrs	12 hrs	24 hrs
Face					
Legs					
Activity					
Cry					
Consolability					

Visual Analog Scale for assessment of pain [0 – 10]

24 hrs	36hrs	48hrs	60hrs	72hrs

Patient Satisfaction Score

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

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

24 hrs	
48 hrs	
72 hrs	

Any additional post operative analgesia effect - (Rescue medication)

Additional post operative analgesia use					Total amount of analgesic used	Duration of analgesia (min)
Drug	Dose Mg	Route	No. of doses	Timing of drug administration		
Tramadol	100	iv				

<u>Side effects</u>

	2hrs	4hrs	8hrs	12hrs	24hrs	48hrs	72hrs
Dyspepsia							
Gastritis							
Nausea/vomiting							
Diarrhoea							
Constipation							
Any other							

Master chart

Master chart –Aceclofenac

Sl No	OP No-Aceclofenac	Age in yrs	Gender	Diagnosis Carcinoma of buccal mucosa	Duration of surgery in mins	Heart rate						Blood pressure(systolic/diastolic)												Respiratory rate						FLACC scale score					VAS scale score					Rescue medication Tramadol		Number of rescues	Patient satisfaction score								Adverse effects			Type of Ca
						0h	2h	4h	8h	12h	24h	0h		2h		4h		8h		12h		24h		0h	2h	4h	8h	12h	24h	2h	4h	8h	12h	24h	24h	36h	48h	60h	72h	First rescue(h)	Total amount		P	F	G	E	P	F	G	E	48h	60h	72h	
1	980711	52	f	T4aN1Mx	300	67	62	64	62	70	68	120	80	120	80	124	84	120	80	124	80	120	80	16	19	18	16	16	16	0	1	2	1	1	2	2	2	1	2						1			1					SCC
2	992679	70	f	T4aN1Mx	420	77	78	80	82	84	80	120	80	120	80	120	80	120	80	120	80	120	80	20	22	22	20	20	20	0	1	1	2	2	3	2	2	2	1					1				1					SCC
3	997841	60	f	T4aN1Mx	360	66	66	70	64	70	60	120	80	110	80	120	80	120	80	120	76	120	70	19	20	20	20	21	20	1	2	2	2	2	3	2	2	2	2					1				1					SCC
4	994373	60	m	T3N2aMx	480	82	84	86	81	80	78	140	90	140	90	140	90	130	90	140	80	130	80	18	16	14	16	14	16	1	1	1	2	2	2	2	2	2	1					1					1			1	SCC
5	1001077	69	f	T4N0M0	360	95	95	90	94	92	91	140	90	140	80	140	80	140	80	130	90	120	90	16	18	18	18	18	18	1	2	2	2	2	2	3	3	2	2					1				1					SCC
6	1001077	35	f	T4aN1Mx	360	70	70	71	72	70	70	120	80	120	90	120	80	120	80	120	80	120	80	20	21	20	20	20	22	1	1	1	1	2	2	4	2	2	1	38	100	1		1				1					SCC
7	1006651	60	f	T4aN2bMx	420	92	90	92	90	90	88	140	90	140	90	130	90	140	90	130	90	130	90	20	20	18	18	20	20	1	2	2	2	2	2	2	2	2	2					1				1					SCC
8	1002102	55	f	T3N0Mx	300	78	82	72	78	72	78	137	80	130	80	130	80	130	80	130	80	130	80	15	15	15	15	15	15	2	0	2	0	1	2	3	1	1	1						1				1				SCC
9	398877	38	m	T4aN1Mx	360	99	98	96	98	100	96	140	90	130	80	134	80	120	90	130	80	130	80	13	14	13	13	13	13	1	1	2	2	1	2	4	5	2	2	38	100	1		1				1					SCC
10	35916	37	f	T4aN1Mx	660	72	74	64	62	58	64	128	82	120	70	122	76	114	71	115	72	118	72	16	16	16	18	16	18	1	1	1	1	1	2	2	2	6	2	40	100	1		1					1				SCC
11	1019011	55	f	T4aN1Mx	300	80	86	81	77	85	76	172	70	100	60	100	70	110	70	110	70	110	70	16	16	16	16	17	16	1	0	1	1	1	2	2	3	2	6	42	100			1				1			1		SCC
12	56738	40	f	T4aN0Mx	330	76	78	74	79	80	79	128	80	130	80	120	80	130	80	124	80	120	80	16	18	16	15	18	16	1	1	1	1	2	3	2	2	2	2					1				1					SCC
13	17412	75	f	T4aN1Mx	420	106	104	108	100	98	98	140	88	140	80	148	88	138	90	160	110	107	71	18	18	20	18	18	17	2	3	2	2	2	3	4	5	3	4	52	100	1		1				1					SCC
14	18065	45	m	T3N1Mx	300	80	82	80	86	80	82	130	90	120	90	110	70	110	90	160	100	140	90	16	18	16	18	16	18	1	1	2	1	2	3	4	3	3	3					1				1					SCC
15	22226	52	m	T4aN2bMx	510	80	86	82	80	78	78	120	70	120	70	120	70	120	70	120	70	120	70	16	16	16	16	16	16	1	1	0	2	1	2	3	3	2	2						1				1				VC
16	404741	60	f	T4aN1Mx	660	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0				0	0	0	0	0	0	0	0			SCC
17	404745	72	f	T4aN1Mx	300	68	70	75	72	76	84	117	88	120	80	100	77	120	80	130	90	160	90	20	20	20	20	20	20	1	0	1	1	2	3	6	3	2	1	40	100	1		1				1				2	SCC
18	22075	45	f	T3N0Mx	390	72	74	76	78	72	74	130	80	128	78	130	80	120	80	126	80	120	80	18	18	18	18	18	18	1	2	2	2	2	2	3	3	2	2						1				1				SCC
19	22068	45	f	T4aN2Mx	300	80	80	78	80	78	78	100	70	106	70	100	70	106	70	106	70	106	70	20	20	20	20	20	18	1	2	2	2	3	3	3	3	3	3						1				1				SCC
20	25400	45	f	T4aN1Mx	600	96	100	98	96	94	94	150	100	156	110	140	106	156	110	130	90	124	80	80	16	18	18	18	20	1	2	1	2	2	3	4	3	3	3	44	100	1			1				1			3	SCC
21	405631	60	f	T4aN1Mx	420	72	78	86	84	92	84	120	80	110	70	110	70	120	80	120	80	110	70	17	15	16	16	16	16	1	1	2	2	2	3	7	5	3	5	42	200	2		1				1					SCC
22	137704	49	f	T4aN1Mx	540	65	81	91	79	91	99	150	90	130	90	136	90	131	80	131	82	136	90	17	17	17	17	17	17	1	1	2	2	2	3	5	3	3	3	56	100	1		1									SCC
23	1020644	70	f	T4aN1Mx	480	90	87	87	87	88	90	130	80	130	80	110	70	110	70	130	80	120	80	16	16	16	16	16	16	1	2	2	2	2	3	3	3	3	3					1									SCC
24	117306	60	m	T4aN2Mx	480	80	81	82	78	80	80	110	70	120	80	120	80	120	80	120	80	110	70	18	18	18	18	18	18	1	1	2	2	2	4	5	6	2	2	38	200	1		1									SCC
25	1021209	69	f	T4aN1Mx	420	72	76	80	80	80	80	130	80	140	90	130	80	130	80	130	80	130	80	20	20	20	20	20	20	1	0	2	2	2	3	3	3	3	4						1				1		1		SCC
26	1021604	62	f	T4aN1Mx	660	84	94	106	83	87	94	130	100	170	100	166	96	140	90	140	88	140	88	18	18	18	18	18	18	1	1	2	2	2	4	3	3	3	3				1				1					3	SCC
27	1020692	48	f	T3N1Mx	480	68	72	74	80	86	80	110	70	120	80	120	80	120	80	120	80	120	80	18	18	18	18	18	18	0	1	2	2	2	3	2	2	2	2							1							SCC
28	106142	45	f	T4aN2Mx	420	104	98	96	98	96	98	150	90	130	80	120	80	124	82	130	88	132	98	15	15	15	15	15	15	1	1	1	2	2	3	5	4	3	3	40	100	1		1				1					SCC
29	118040	67	f	T3N1Mx	480	90	88	86	80	80	80	140	90	130	90	130	90	130	90	130	90	130	90	16	16	16	16	16	16	1	1	2	2	3	3	4	3	3	3						1				1			1,4	SCC
30	109383	55	f	T4aN1Mx	600	72	68	72	76	78	80	126	84	130	86	126	80	120	80	110	70	120	80	18	18	18	18	18	18	1	1	2	2	2	2	4	3	3	3						1				1			3	SCC
31	93537	73	f	T4aN2bMx	720	67	72	74	70	71	70	140	90	130	80	130	80	130	80	140	80	130	80	20	20	20	20	20	20	1	1	2	2	2	2	5	3	3	2	46	100	1		1				1					SCC
32	37286	55	m	T3aN0Mx	360	86	83	80	80	80	80	130	90	128	60	126	70	120	80	110	80	110	90	16	16	16	16	16	16	1	1	2	2	2	3	4	3	3	3						1				1				SCC
33	137704	49	f	T4aN1Mx	480	90	92	88	86	86	84	120	80	120	80	120	80	120	80	120	80	120	80	18	18	18	18	18	18	1	1	2	2	2	3	2	2	2	2				1				1						SCC
34	133670	60	f	T4aN2cMx	420	68	70	70	68	70	70	110	70	120	90	120	80	120	80	10	80	116	80	16	16	16	16	16	16	1	1	2	2	2	3	5	2	3	3					1				1				1,2,4	SCC
35	102294	70	f	T4aN2cMx	450	64	68	66	60	64	68	100	64	122	84	130	72	110	80	144	77	147	78	15	15	15	15	15	15	1	1	2	2	2	4	3	3	3	3	44	100	1		1				1					SCC
36	95956	56	m	T4bN2Mx	420	94	92	93	90	92	90	110	80	110	80	110	80	110	80	110	80	110	80	17	18	18	18	18	15	1	1	2	2	2	2	4	3	3	3					1				1					SCC
37	77532	62	f	T4aN2Mx	600	80	78	78	76	84	70	140	90	130	88	140	90	136	78	136	88	130	80	18	17	17	18	18	18	1	1	2	2	2	3	3	3	2	2					1				1			5		SCC
38	154321	65	f	T4aN1Mx	540	99	94	96	98	98	96	110	80	110	80	110	70	110	80	110	80	110	80	16	17	17	19	16	16	1	1	2	2	2	2	4	3	3	3				1				1						SCC

Key words: Sl No-Serial Number; m-male; f-female; mins-minute; h-hour; FLACC-Face, Leg, Cry, Consolability; VAS- Visual Analogue Scale; Patient satisfaction Score: P-Poor, F-Fair, G-Good, E-Excellent

Adverse effects: 1-Nausea, 2-Vomiting, 3-Epigastric discomfort, 4-Headache, 5-Cough

Ca-Carcinoma, SCC –Squamous Cell Carcinoma, VC-Verrucous Carcinoma

Master chart - Diclofenac

Sl No	OP No-Diclofenac	Age in yrs	Gender	Diagnosis Carcinoma of buccal mucosa	Duration of surgery in min	Heart rate						Blood pressure(systolic/diastolic)												Respiratory rate						FLACC scale score					VAS scale score					Rescue medication Tramadol		No rescues	Patient satisfaction score								Adverse effects				Type of Ca
						0h	2h	4h	8h	12h	24h	0h		2h		4h		8h		12h		24h		0h	2h	4h	8h	12h	24h	2h	4h	8h	12h	24h	24h	36h	48h	60h	72h	First rescue(h)	Total amount		P	F	G	E	P	F	G	E	36	48	60	72	
1	972713	40	m	T3N2aM0	360	98	90	86	82	80	80	150	90	140	80	130	90	140	90	150	90	140	90	18	19	20	21	18	18	1	2	2	1	2	2	2	1	2	1					1					1						SCC
2	973207	60	f	T3N1Mx	240	80	86	88	82	80	80	100	60	110	70	110	60	110	70	110	60	110	60	22	20	20	23	22	20	1	1	2	2	2	2	3	1	3	3					1				1							SCC
3	976387	40	m	T4aN2cMx	570	100	105	98	96	98	96	130	80	120	80	120	80	120	80	110	80	100	80	18	20	21	18	20	18	1	2	3	0	2	2	2	1	3	2					1				1					1,2,3		SCC
4	978895	65	f	T3N1Mx	300	84	87	91	86	84	80	140	90	130	80	130	80	140	90	130	80	130	80	18	16	18	18	20	16	2	1	1	1	2	2	2	2	3	2					1				1							SCC
5	978123	45	f	T4aN1Mx	360	60	62	60	60	61	62	145	80	149	79	140	80	150	80	140	80	130	60	14	16	14	14	13	14	1	2	2	1	2	2	2	2	3	2					1				1							SCC
6	925650	60	f	T3N2bMx	420	71	75	71	71	70	70	110	70	110	70	110	70	110	70	110	70	110	70	20	18	20	18	18	18	1	2	2	1	3	3	2	3	3	2	34	100	1			1				1						SCC
7	988851	70	m	T3N0Mx	420	99	94	96	98	98	96	110	80	110	80	110	70	110	80	110	80	110	80	16	17	17	19	16	16	2	1	2	1	3	3	3	3	3	2	44	100	1		1				1							SCC
8	991117	28	f	T3N2bMx	420	80	82	84	78	80	80	130	80	120	90	130	80	130	90	120	90	130	80	20	16	18	16	18	16	1	1	1	1	1	2	2	1	2	2					1				1							SCC
9	987910	60	f	T3N1Mx	540	74	70	70	72	71	73	130	90	128	96	128	90	130	90	126	90	132	92	15	14	16	14	16	18	1	1	1	1	2	3	2	2	1	2						1			1				1,3,4			SCC
10	992684	60	f	T4aN2aMx	360	62	60	60	68	60	60	130	80	130	80	130	76	120	76	132	80	126	80	16	16	14	16	14	15	1	1	2	1	2	2	5	1	2	2	38	100	1		1					1						SCC
11	998486	58	f	T4N0Mx	300	108	98	98	94	90	92	130	90	130	90	126	80	130	80	130	90	130	80	20	22	22	22	22	20	1	1	1	2	2	3	2	2	1	2					1				1							SCC
12	1003917	65	f	T4aN1Mx	360	76	74	72	76	72	76	130	80	112	68	118	70	122	70	128	90	126	80	18	20	17	18	20	19	0	1	1	2	2	2	2	2	2	2					1				1				1			SCC
13	1015497	65	f	T4aN2bMx	420	80	82	81	86	80	82	110	70	110	70	110	68	112	68	110	70	110	68	16	15	14	16	16	18	1	1	1	2	3	3	2	2	2	2					1				1							SCC
14	1091352	35	f	T4aN1Mx	360	86	84	82	86	82	84	130	86	130	80	130	70	140	70	130	80	140	84	20	22	21	21	20	20	0	1	2	1	3	3	3	2	1	2					1				1							SCC
15	1018358	40	f	T4aN1Mx	450	98	96	96	98	92	90	120	84	120	80	110	80	110	70	110	70	120	80	22	23	20	20	22	23	1	1	1	1	1	3	2	1	1	1						1				1						SCC
16	1004604	65	f	T4aN2cMx	450	76	80	86	86	86	82	130	70	120	70	130	70	130	70	126	70	124	70	18	18	20	18	16	18	1	2	2	2	2	2	5	4	4	3	28	200	2	1				1								SCC
17	1009225	55	f	T4aN2bMx	330	90	90	86	88	92	84	130	80	130	80	130	80	130	80	130	80	120	80	16	16	16	14	16	14	2	1	1	2	1	2	2	2	2	2					1				1							SCC
18	1018402	40	f	T3N0Mx	720	100	82	76	78	70	72	130	94	130	90	124	90	114	86	120	84	122	88	16	16	13	14	16	14	2	0	1	2	2	2	3	2	6	2	30	100	1		1					1						SCC
19	1018517	60	m	T4aN2bMx	420	80	78	76	74	78	80	150	90	142	86	140	80	130	78	114	72	120	80	14	14	13	14	14	14	2	1	1	1	2	2	6	2	3	2					1					1		1			3	SCC
20	1058764	48	f	T4aN1Mx	240	98	96	100	93	82	82	100	80	98	78	112	82	90	64	92	70	94	70	18	18	18	18	20	18	0	2	0	2	2	2	2	2	2	2					1				1							SCC
21	1004880	50	f	T4aN1Mx	360	72	72	72	73	74	70	120	86	130	82	126	85	128	85	116	86	118	90	15	14	14	14	14	14	1	1	1	1	1	2	3	5	3	2	60	100	1		1					1						SCC
22	1018741	35	f	T3N0Mx	300	76	78	76	76	78	76	140	90	140	90	130	80	130	90	130	80	130	90	16	16	16	12	16	12	0	1	0	0	1	2	2	2	2	2					1				1							SCC
23	1018832	55	f	T4aN0Mx	300	76	68	69	72	68	72	92	64	94	68	108	74	108	76	100	60	100	60	16	16	16	16	16	16	1	1	0	0	1	2	2	6	2	2	54	100	1			1				1			1,3			SCC
24	1018832	42	m	T4aN1Mx	360	79	90	96	93	86	90	130	90	130	80	130	90	130	80	130	90	130	80	18	18	18	18	18	18	1	1	1	2	1	2	3	7	3	3	62	100	1	1						1						SCC
25	1019117	41	f	T4aN1Mx	330	68	70	68	70	66	72	130	90	130	80	130	80	120	90	130	80	130	80	20	18	18	20	18	20	1	1	1	2	1	2	2	2	2	3					1					1						SCC
26	1019190	40	f	T4aN1Mx	240	67	68	61	75	72	73	120	90	112	80	110	68	100	70	100	70	100	70	16	18	16	18	18	18	1	2	2	0	1	2	2	2	2	1						1				1				3		SCC
27	1012828	40	f	T4aN1Mx	420	80	82	80	80	78	80	130	80	128	80	130	80	120	80	120	80	120	80	18	18	18	18	18	18	1	2	2	3	3	3	5	3	2	1						1				1		1				SCC
28	1012410	48	m	T3N0Mx	360	90	88	86	84	90	82	140	90	140	90	136	80	136	90	130	90	128	90	16	16	16	16	16	16	1	2	2	2	2	3	6	4	2	2	38	100	1			1				1						SCC
29	404557	55	f	T3N0Mx	420	68	70	68	72	70	68	120	80	120	80	120	80	120	80	120	80	120	80	15	15	15	15	15	15	1	2	2	2	2	3	6	3	2	2	42	100	1		1					1						SCC
30	13493	45	f	T3N1Mx	390	62	60	60	68	60	60	130	80	130	80	130	76	120	76	132	80	126	80	16	16	14	16	14	15	1	1	2	2	2	3	5	3	2	2	40	100	1			1				1		1				SCC
31	62265	65	f	T4aN1Mx	600	71	75	71	71	70	70	110	70	110	70	110	70	110	70	110	70	110	70	20	18	20	18	18	18	1	1	2	2	3	4	4	3	2	2					1					1						VC
32	405353	60	f	T3N0Mx	300	71	74	78	74	68	78	130	70	132	65	116	76	120	76	127	74	119	70	16	16	16	16	16	16	1	1	1	2	2	3	4	3	3	3					1				1							SCC
33	98125	40	m	T3N1Mx	660	78	64	84	58	57	59	100	78	100	64	107	68	98	70	97	66	101	68	16	15	14	16	15	14	1	1	1	2	2	3	5	3	3	2	52	100	1			1				1						SCC
34	107768	65	f	T4aN1Mx	660	96	92	91	91	88	96	133	95	134	86	140	90	140	88	123	79	126	84	20	20	20	20	20	20	1	1	1	3	2	3	3	2	2	2					1				1							SCC
35	149521	64	m	T4aN1Mx	600	90	76	74	74	74	72	140	90	130	80	140	80	139	80	130	80	130	80	20	20	20	20	20	20	1	1	1	3	1	3	4	2	2	2						1				1						SCC
36	160681	70	f	T4aN1Mx	480	90	92	84	86	92	88	170	100	168	94	170	76	170	100	160	100	160	100	18	19	18	17	18	19	1	1	2	2	2	3	3	3	3	3						1				1						SCC
37	154812	65	f	T3N0Mx	300	70	69	90	76	80	75	136	40	140	80	140	80	130	90	130	90	130	90	18	17	17	17	17	17	1	2	2	2	2	2	7	3	3	3	42	100	1	1				1							1,3,4	SCC
38	159805	70	f	T4aN1Mx	720	86	92	86	96	98	86	142	98	140	90	138	88	140	80	140	90	140	88	17	18	19	17	18	18	1	2	2	3	1	2	5	3	2	2					1				1							SCC

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