COMPARISON BETWEEN ANALGESIC EFFICACY OF PARENTERAL PARACETAMOL AND DICLOFENAC FOR POSTOPERATIVE PAIN RELIEF

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"COMPARISON BETWEEN ANALGESIC EFFICACY OF PARENTERAL PARACETAMOL AND DICLOFENAC FOR POSTOPERATIVE PAIN RELIEF"

DOCTOR OF MEDICINE
IN
ANAESTHESIOLOGY

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ABBREVATIONS

1. ASA: AMERICAN SOCIETY OF ANAESTHESIOLOGY
2. IASP: INTERNATIONAL ASSOCIATION FOR STUDY OF PAIN
3. NSAID: NON-STEROIDAL ANTI-INFLAMATORY DRUG
4. CNS: CENTRAL NERVOUS SYSTEM
5. PNS: PERIPHERAL NERVOUS SYSTEM
6. LA: LOCAL ANAESTHESIA
7. COX: CYCLO-OXYGENASE ENZYME
8. TRPV1: TRANSIENT RECEPTOR POTENTIAL CATION CHANNEL SUBFAMILY 5 MEMBER 1
9. SNRIS: SEROTONIN AND NORADRENALINE REUPTAKE INHIBITORS
10. CNCP: CHRONIC NON CANCER PAIN
11. MRF: MEDIAL RETICULAR FORMATION
12. VPL: VENTRO POSTERO LATERAL
13. PAG: PERI-AQUEDUCTAL GREY
14. NRM: NUCLEOUS RAPHE MAGNUS
15. CGRP: CALCITONIN GENE RELATED PROTEIN
16. NMDA: N-METHYL D-ASPARTATE
17. NA^+: SODIUM ION
18. CA^+: CALCIUM ION

19.K^+: POTTASIUM ION

20.MG^+: MAGNESIUM ION

21.LTP: LONG TERM POTENTIATION

22.LOX: LIGNOCAINE/LIDOCAINE

23.CB: CANNABINOID

24.DIC: DISSEMINATED INTRAVASCULAR COAGULATION

25.FDA: FOOD AND DRUG ADMINISTRATION

26.USG: ULTRASONOGRAPHY/ULTRASOUND

27.CPSP: CHRONIC POST SURGICAL PAIN

28.PROSPECT: PROCEDURE SPECIFIC PAIN MANAGEMENT

29.ERAS: ENHANCED RECOVERY AFTER SURGERY

30.VAS: VISUAL ANALOUGE SCALE

31.CVS: CARDIOVASCULAR SYSTEM

32.ECG: ELECTROCARDIOGRAM

33.ICU: INTENSIVE CARE UNIT

34.IV: INTRAVENOUS

35.CO2: CARBONDIOXIDE

36. SD: STANDARD DEVIATION

37. CTRI: CLINICAL TRAIL REGISTRY OF INDIA

38. HR: HEART RATE

39. BP: BLOOD PRESSURE

40. MAP: MEAN ARTERIAL PRESSUE

41. SPO2: PERIPHERAL OXYGEN SATURATION

42.ETCO2: END TIDLE VOLUME CARDONDIOXIDE

43. µ: MICRO

44. gm: GRAM

45. mcg: MICROGRAM

46. kg: KILOGRAM

47. Min: MINUTES

ABSTRACT

Background and objectives:

Post-operative pain is one of the main causes of distress for the patient undergoing elective surgery. Pain in the post-operative period increases heart rate, cardiac work and oxygen consumption due raise in sympathetic outflow. Prolonged periods of this pain can have serious adverse events such as post-operative ileus, nausea, vomiting and urinary retention. Lack of proper analgesia can cause patients to hypo-ventilate which in turn cause reduction in vital capacity and other lung functions. The Concept of pre-emptive analgesia involves application of treatment prior to trauma and surgical intervention to prevent central sensitization of pain pathways that reduces the amount of analgesic requirements.

Post-operative analgesia nowadays is achieved through multiple techniques such as regional anaesthesia and non-opioid analgesics. Most commonly used non-opioid analgesics are paracetamol and diclofenac and therefore a comparison of the analgesic efficacy of these agents is important.

Methods:

The study aims to assess the analgesic efficacy and safety of Intravenous Paracetamol versus Intravenous Diclofenac for post-operative pain relief for different types of surgeries namely laparoscopic abdominal surgeries, open abdominal surgeries, head and neck surgeries and other miscellaneous surgeries. This was a prospective, double blinded study conducted where 200 randomly selected ASA grade 1 and 2 adults, of 18-60 years of either sex who underwent elective surgical procedures under GA lasting less than 2 hours were included, divided into Group A who received Intravenous Paracetamol 1 gm, and Group B received Intravenous Diclofenac 75 mg, both administered 30 minutes before end of procedure. Patients were then assessed for post-operative pain according to VAS scale at hourly intervals for 6hrs.

Results

Overall Diclofenac showed better analgesic efficacy than paracetamol for all types of surgeries studied. More over Diclofenac showed analgesic efficacy for 1 hour more than paracetamol. Paracetamol showed better analgesic efficacy for laparoscopic and other miscellaneous surgeries than for head and neck and open abdominal surgeries. Similarly, Diclofenac showed better analgesic efficacy for laparoscopic and other miscellaneous surgeries than for open abdominal and head and neck surgeries, although the efficacy of analgesia was better than that for paracetamol.

Conclusion

Diclofenac showed better analgesic efficacy than paracetamol when used intravenously for post-operative pain management. Diclofenac and paracetamol

both provide better analgesia for Laparoscopic surgery and other minor miscellaneous procedures than for Open abdominal and head and neck surgeries.

Keywords

Diclofenac, Paracetamol, Post-operative pain, VAS Score, Pre-emptive analgesia

INTRODUCTION

INTRODUCTION

Pain has been defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" by International Association for the Study of Pain(IASP)[1].

Pain causes increase in heart rate, cardiac workload and Oxygen consumption due to rise in sympathetic response. Moreover, reduced ambulation and increased risk of deep vein thrombosis can be caused by prolonged periods of post-operative pain.

An acute pain due to trauma following surgery with a pro-inflammatory reaction and instigation of an afferent neuronal barrage is called post-operative pain and is mostly nociceptive[2]. It is different for each patient depending on the area and type of surgery. For example, for head and neck surgeries pain is the maximum followed by abdominal surgeries.[3]

Successful analgesia in the post-operative period is vital as inadequate analgesia can cause psychological and physical trauma and also affects the outcome of the surgery performed. It may also affect the patient's satisfaction from the procedure and medical care. Inadequate analgesia in the Post-operative period can also cause complications such as chronic post-operative pain. This can also cause anxiety which may result in muscle rigidity in an attempt to splint the surgical site. Inadequate analgesia may also cause reduced efforts of breathing by the patient resulting in hypo-ventilation which leads to reduced lung function and oxygenation[4].

Post-operative pain management includes using NSAIDs for mild to moderate pain relief thus reducing the requirement of opioids and preventing their adverse effects such as nausea and vomiting.[5] Paracetamol and diclofenac are the most commonly used agents for sparing the use of opioids and work through different mechanisms.

AIM AND OBJECTIVES

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AIM

To assess the analgesic efficacy and safety of IV Paracetamol in comparison with IV Diclofenac for post-operative pain relief.

OBJECTIVES OF THE STUDY

PRIMARY OBJECTIVE

To assess and compare the efficacy of parenteral Diclofenac versus Paracetamol in post- operative pain management and to assess the need for rescue Opioid analgesia when Intravenous Diclofenac versus Intravenous Paracetamol is used.

SECONDARY OBJECTIVE

To assess efficacy of both agents as post-op analgesia for different surgeries.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

HISTORY OF PAIN AND PAIN MANAGEMENT

Historically, with the discovery of anaesthetic effects of ether on 16th October 1846 by WTG Morton, it was commended as the first time pain was overcome during surgery, although it was later on elicited from patients undergoing surgery under ether/chloroform that pain was far from alleviated. Opiates were commonly used throughout the 19th century, starting with Wilhelm Serturner's 'Somniferous principle' ie Opium in 1804. The industrial production of Morphine in Germany in the 1820s and USA in the 1830s made its availability easy. The Bayer company later introduced di-acetylated salicylic acid brand named Aspirin in 1899 which had remarkable pain relieving properties and also could control fevers[8]. Physicians issue concerns over morphine becoming addictive in the 1870s. The pathway through which aspirin acts was later described in 1971. The more conventional NSAIDs were later tested and introduced in 1965 but their use was restricted due to their adverse effects. The 20th century saw a set of new local anaesthetic agents starting with Procaine in 1905, followed by lignocaine in 1943 and finally bupivacaine in the 1950s.[9,18]

At the beginning of the 21st century, research has indicated a major lapse between understanding the mechanism of pain and the inadequacy of the

treatment provided for the same. This has brought about multiple governing bodies dedicated to the proper management of pain in developed countries, although in developing countries it is often overlooked due to multiple other dire situations. This has made us understand that pain can be acute or chronic and has further brought about a movement towards better pain management strategies. This is mainly due to the adverse effects of incomplete treatment of pain due to multiple social and economic factors, literacy, religious sentiments and logistic issues, which can lead to physiological, psychological and social issues for the patient and his immediate family[2,7]

PAIN AND PERCEPTION OF PAIN

Definition of pain:

In 1979, the sub committee on taxonomy suggested "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" as the definition of pain, which was accepted by the IASP council. This was widely accepted by health care professionals and organisations globally (including the World Health Organisation). In recent times, due to advances in our understanding of pain through research, a need for redefining pain after re-evaluation was required.

In 2018, IASP reconvened with a 14 member, multi-national Presidential Task force, with members who had thorough knowledge and experience in clinical and Patho-physiological aspects of pain. They sought to re-examine the age

old definition and add or remove some aspects of the definition and came up with a few recommendations.

The current definition of pain as of 2020 is "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage." They also added as a note that pain differs from person to person and each patient experiences the pain through their exposure to injury in earlier periods of life.[1]

Perception of Pain

Perception of pain seems to be subjective to each individual and is affected variably by patient's biology, the mental status of the patient and his socio-economic background. Moreover, it is also affected by the patient's previous exposure to pain which builds up his relationship with pain perception. Therefore, the patient's first person account of a painful encounter should be received without judgement and given respect. Furthermore, the experience of pain can be divided as sensory perception of pain in pain pathways and nociception which are fundamentally different.[10]

Pain perception also involves components from central nervous system (Supra-spinal and spinal components) and peripheral nervous system (transmission of painful stimulus) playing important roles. The painful stimulus is picked up by the peripheral nervous system and then transmitted along myelinated A and C fibres ith nuclei in dorsal root group (Figure 1) . They're axonal bodies then transmit to the dorsal horn of spinal cord from

where nerve cells from laminae 1,2 and 5 participate majorly for noxious stimuli perception.[11]

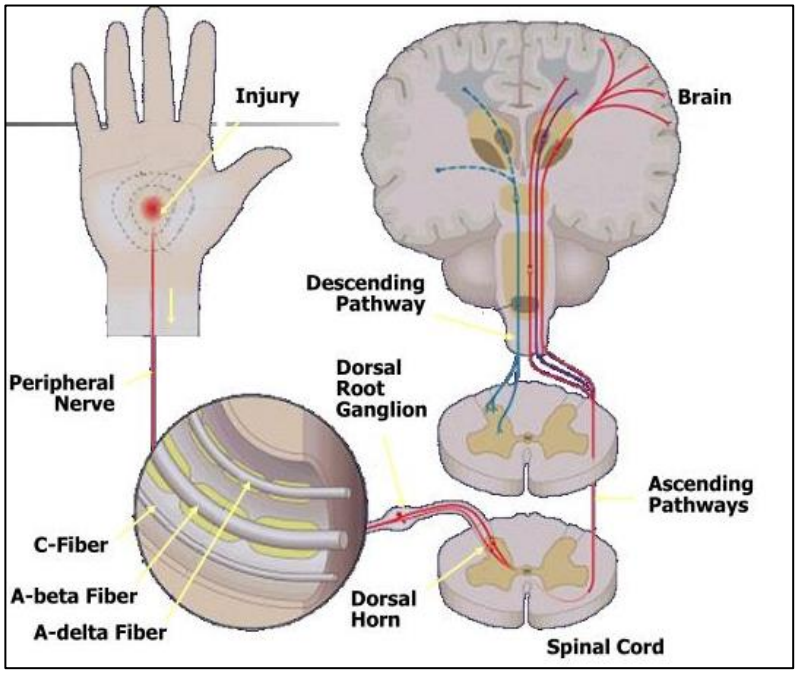


Figure 1: Perception of Pain Pathway

PHYSIOLOGY OF PAIN

The role of the gateway of perception of sensory stimuli in the central nervous system is performed by the spinal cord. It receives multiple types of stimuli from sensory nerves from the periphery throughout its entirety. The 31 paired spinal nerve roots that exit through spaces between the spinous processes and their multiple branches forming the peripheral nervous system play an important role in the transmission and response to noxious stimuli.[12]

MECHANISMS OF PAIN

The pain pathway takes into account 3 mechanisms namely Nociception, peripheral sensitization and central sensitization.

1. **Nociception:**

   The collection of multiple stimuli and recognition of it as a noxious stimulus by the brain is called nociception. This process is done by Nociceptors.[12] They are peripheral sensory nerves specialized to pick

up stimuli from skin which show potential to cause damage such as very cold or very hot temperatures, excessive pressure and chemicals released post injury[15]. These receptors have the following mechanics for proper function (Figure 2):

a) Transduction: This refers to the conversion of one form of stimulus to another and occurs at multiple stages in the pain pathway.

b) Transmission: The excitation of the nociceptor is then transmitted to the target site through a variety of chemical and electrical signals.

c) Translation: The conversion of electrical to chemical signals and vice-versa.

d) Modulation: The up or down regulation is done at various stages of the pain pathway. The signal is either amplified or dampened according to requirement.

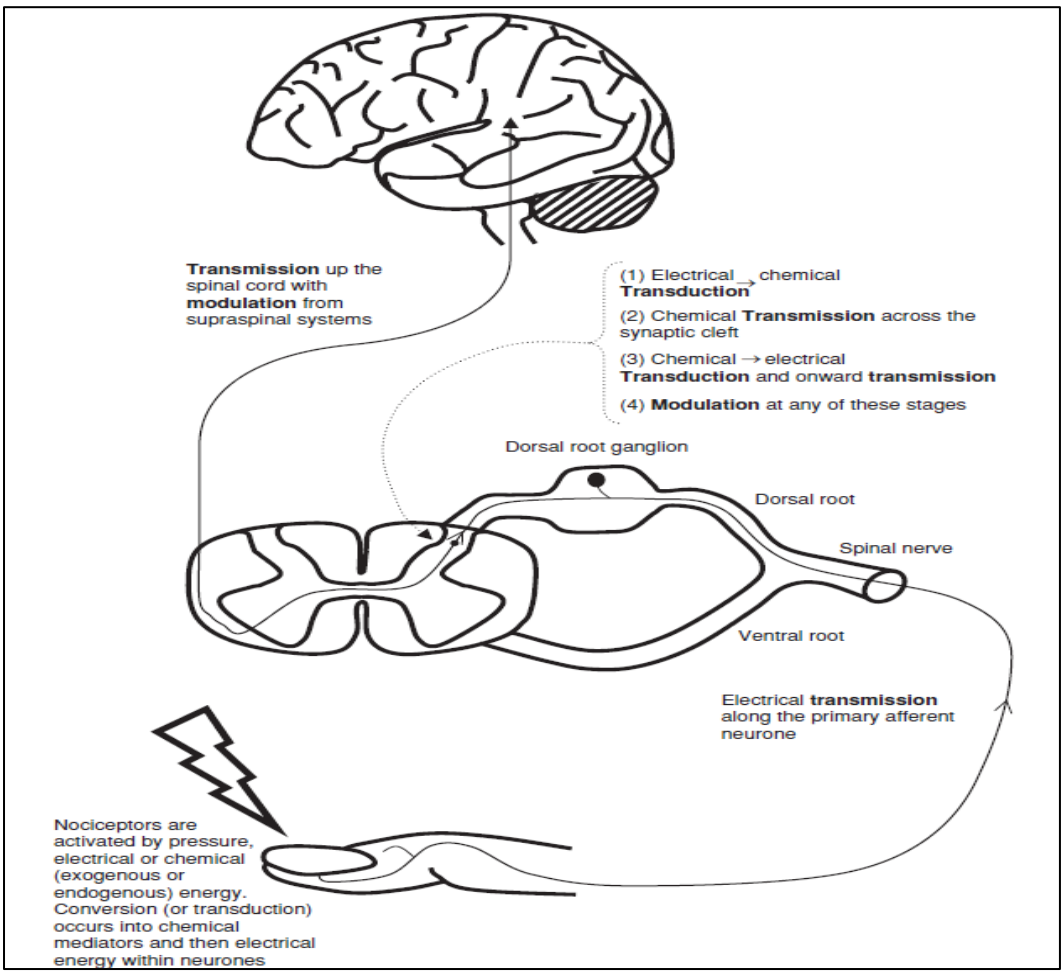


Figure 2: Transduction, Transmission, Translation and Modulation of Nociception[16]

2. Peripheral sensitization:

It refers to the release of a wide variety of chemical compounds reducing the sensory nervous threshold which are liberated in response to inflammatory reaction of tissue to damaging stimuli (Figure 3). This in-turn causes hyper-responsiveness to noxious stimuli otherwise known as primary hyper-algesia.[12] It is defined by heightened sensitivity of peripheral pain receptors to stimulation. Usually this is preceded by inflammation for both receptors on surface of skin and in the deep tissue receptors. At the same time, it lowers the resting threshold of these receptors and thus reduces the stimulation required for response. It also increases the extent of response to these trivial stimuli. This is the stage of pain pathway where NSAIDs, Opioid drugs, Cannabis like compounds and TRPV1 blockers act.[19]

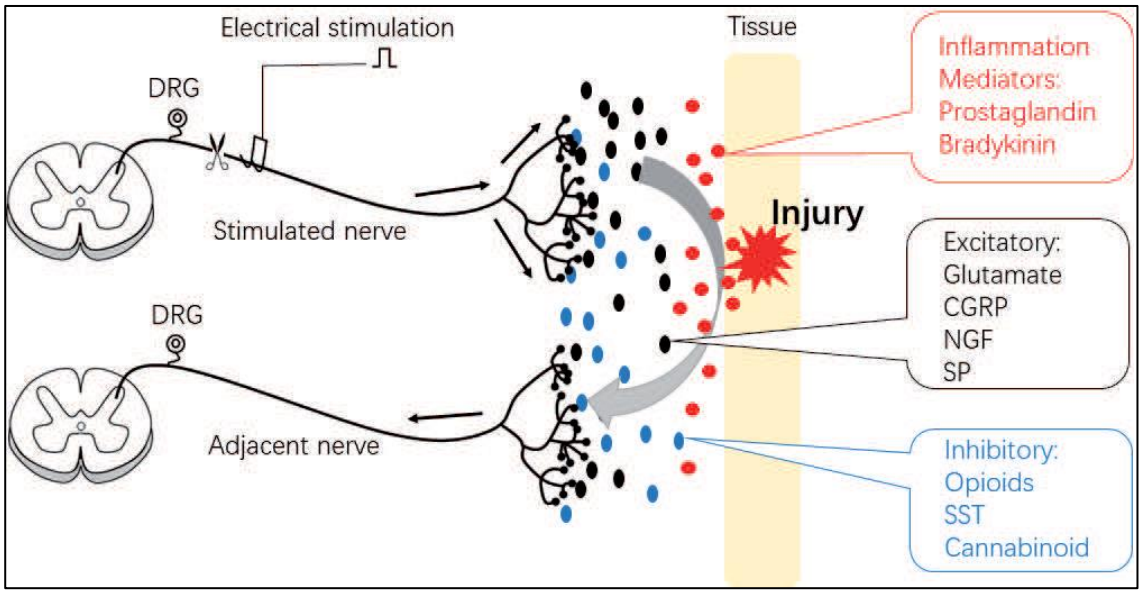


Figure 3: Peripheral Sensitisation[17]

3. Central Sensitisation:

This refers to the physiological responses in the Central nervous system to continual firing of C-nociceptors in response to noxious stimuli for prolonged periods of time (Figure 4). This leads to the Chronic pain syndromes.[12] This can also be characterized as the upregulation of second order neurons to pain stimuli. Primary heightened sensitivity to pain just like peripheral sensitization is seen here. It is the gateway where acute pain gets converted to chronic pain. Furthermore, normal stimulation of even touch receptors may cause pain perception. This is called Secondary hyperalgesia, a salient feature of central sensitization. The drugs which act at this level are SNRIs, antiepileptics and Tricyclic antidepressant drugs.[19]

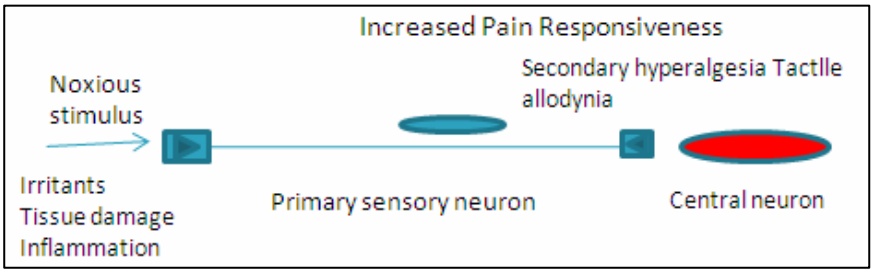


Figure 4: Central Sensitisation[12]

TYPES OF PAIN RECEPTORS

The nociceptors are generally raw nerve endings which are seen in epidermis/dermis, musculature, skeletal joints, organs and the vascular system. Their primary role is to pickup painful stimuli due to extremes of temperature, caustic agents and pressure changes. They require stimulation sufficient to overcome their resting threshold. This process is in place to prevent unwanted

stimulation of CNS which is perceived as algesia. The neurons of these fibres which synapse in the dorsal horn do not adapt. This non-adaptability is a self-preservatory mechanism which prevents patient from undergoing continuous damage.

Specific receptors are specialised to react only to certain types of stimuli, while others react to multiple types of noxious stimuli Eg C and A-delta fibres pickup both extremes of temperature. Also A-Beta fibres, primarily mechanical receptors, respond to tissue inflammation which is transmitted as a noxious stimulus (Figure 5).

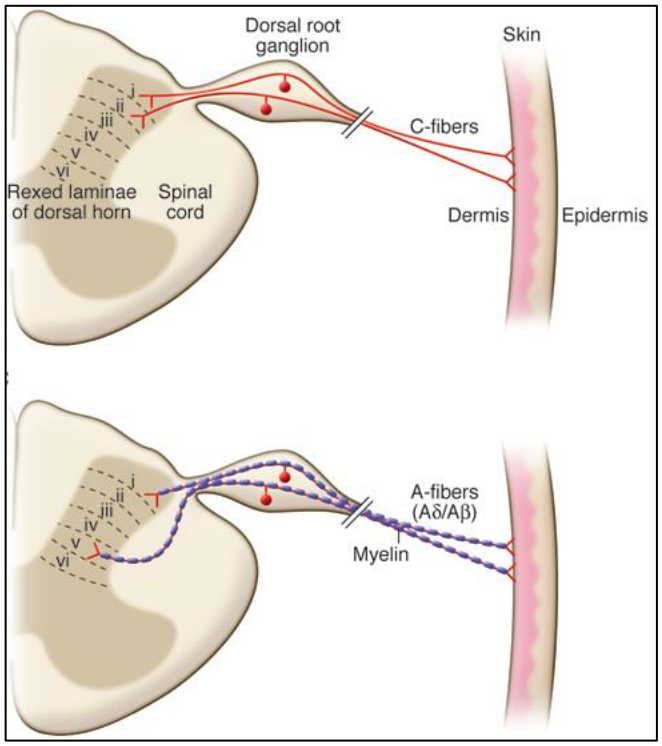


Figure 5: C, A-Delta and A-Beta Fibres and their Pathways.[15]

Further details about these receptors are given in Table 1.

	Aβ fibres	Aδ fibres	C fibres
Diameter	Large	Small 2-5μm	Smallest <2μm
Myelination	Highly	Thinly	Unmyelinated
Conduction velocity	> 40 ms-1	5-15ms-1	< 2ms-1
Receptor activation thresholds	Low	High and low	High
Sensation on stimulation	Light touch, non-noxious	Rapid, sharp, localised pain	Slow, diffuse, dull pain

Table 1 Different types of Afferent Nociceptors.[14]

CLASSIFICATION OF PAIN[19]

1) **Based on pathophysiology:**

a) **Nociceptive pain:** The receptors transmitting this type of pain are A-delta and C Fibres. The activation of these receptors are by chemical stimulus, Mechanical forces and extremes of temperature. They play a major part in the natural defense of the body towards noxious stimuli which could potentially lead to tissue damage. These noxious stimuli are perceived as pain. There is an array of chemical modulators Eg: Cyclooxygenase 1 & 2 (COX 1&2) which are prostaglandins, histamine, serotonin, bradykinin etc.

b) **Neuropathic pain:** This type of pain represents a lesion or damage to the central nervous system Eg: post-herpetic and trigeminal neuralgia, diabetic and peripheral neuropathies, causalgia, some types of pain due to malignancy etc.(For further classification refer to Table 3). The main underlying pathology here is an abberent

excitability of afferents, peripheral activation causing central sensitization, disappearance of primary afferent response and initiation and release of pro-inflammatory cytokines. Each of these factors follow different pathways to cause pain, which cause difference in distribution and intensity of response from the somatosensory cortex.

Type	*Cause*
Trigeminal neuralgia	*Compressin of trigeminal ganglion or its branches*
Postherpetic neuralgia	*Shingles*
Complex regional pain syndrome	*Trauma/infection/surgery/ inflammation*
Diabetic neuropathy	*Persistent hyperglycemia (diabetes)*
Central pain	*Trauma to the spinal cord* *Stroke*
Phantom pain	*Amputation*
Postincisional pain	*Surgery*

Table 2: Classification of Neuropathic Pain[23]

c) **Mixed pain:** This is due to a combination of both the aforementioned processes. They are commonly seen in patients suffering from malignancy or in some complicated neuropathies (Figure 6).

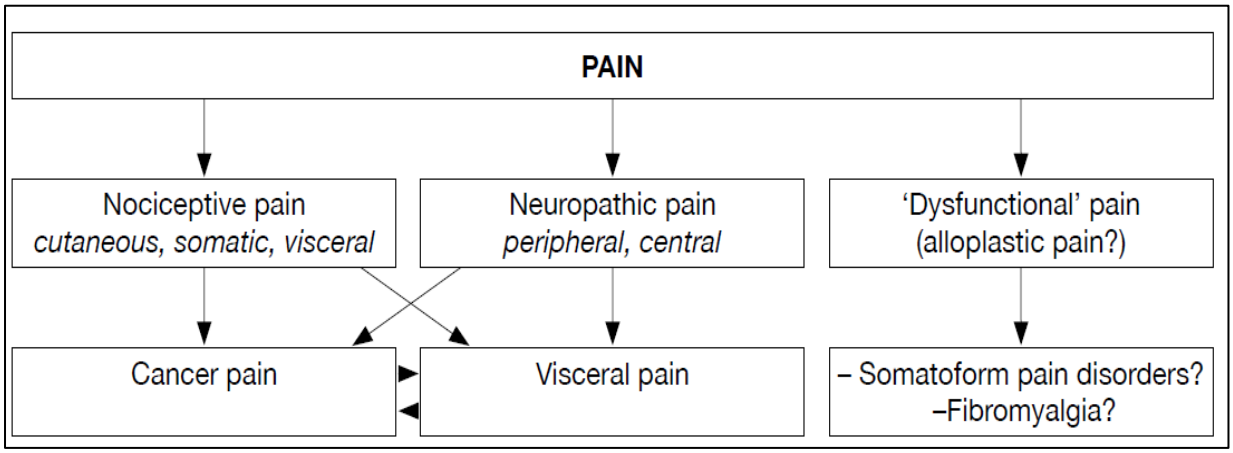


Figure 6 Classification of pain Depending on Pathophysiology.[24]

2) Based on duration:

a) **Acute pain:** This type of pain usually arises due to pre-existing disease or injury and usually last for hours, days, months or until underlying pathology subsides. As this type of pain has a clear pathology, it is more predictable. It is considered a physiological defense against a threat or injury with potential to cause tissue damage and is also seen with reflexes which also play a protective role. The pathophysiology of this type of pain could be an acute emergency like acute appendicitis, secondary to surgery or underlying pathology requiring surgery (Usually seen in peri-operative period), major traumatic events (Road traffic accidents), Thermal injuries or due to labor.

b) **Chronic pain:** If the pain persists even after the underlying etiology has subsided, it is called chronic pain. This type of pain can cause physical and emotional distress. Commonly chronic pain is multi-

factorial in nature and therefore treatment strategies should involve multiple interventional measures to achieve complete relief. This pain can primarily be due to chronic disorders such as malignancy, AIDS, rheumatoid arthritis and lower back ache. They can also be secondary to hyperalgesia (abnormally raised sensitivity to external stimulus) or allodynia (stimuli of innocuous origin).

c) **Breakthrough pain:** These are acute exacerbations of severe pain which was previously under control with treatment. They are a hallmark of pain related to malignancy and can range from a few seconds to hours from onset of the acute exacerbation. They may also be idiopathic in origin, incidentally noticed and may have precipitating factors. They may also be experienced in the time period between two doses of an analgesic agent.

3) **Based on etiology:**

a) **Pain due to Malignancy:** Algesia is one of the most common complaints seen in patients suffering from cancer. Its origin could be nociceptive due to changes in involved tissue pathology or neuropathic if any nerve is invaded by the malignancy causing nerve damage. The intensity may show an incremental increase depending on the stage of malignancy with maximum intensity seen during metastasis. Breakthrough pain is a hallmark of this type of pain due to changes in the underlying neuronal bodies at the level of the dorsal

horn of spinal cord. The management of this type of pain is achieved by optimizing the analgesic therapy (most commonly opioids) to prevent frequent episodes of acute exacerbation when action of the analgesic agent wears off.

b) **Pain due to non-malignant etiology:** This type of pain is also known as chronic non-cancer pain (CNCP). The causative pathophysiology may not be evident, maybe diverse and therefore makes its management difficult. CNCP can further be classified into:

   i. **Neuropathic pain**: Maybe central or peripheral in origin.

   ii. **Inflammatory pain**: Due to infectious pathology, arthritic etiology or post-surgical origin.

   iii. **Muscular pain:** Myofascial pain syndrome.

   iv. **Mechanical pain:** Lower back ache, cervical spinal pain involving neck and shoulder.

The management should start with non-opioid analgesics. If this fails, then opioids can be used as 2nd and 3rd line agents. Sometimes opioid analgesia maybe the 1st line agent depending on the severity of the pain.

4) Based on anatomic location: This refers to the location of the pain rather than the location of origin of the pain.

a) Head face and mouth pain.

b) Cervical pain.

c) Upper shoulder and upper limb pain.

d) Thoracic pain.

e) Abdominal pain.

f) Lower back pain.

g) Lumbar and coccygeal pain.

h) Lower limb pain.

i) Pelvic pain.

j) Anal, perineal and groin pain.

This is used to achieve a diagnosis and does not act as a base for management.

Another method of classification based on location is as follows:

a) **Somatic pain:** This type of pain arises due to superficial damage to skin or mucous membrane which stimulates peripheral nociceptors. It is a sharp and well localized pain. This type of pain can also be central in origin, arising from musculoskeletal structures Eg: Lower back ache, neck pain, musculoskeletal pain and also algesia due to thermal injuries, trauma and ulcers.

b) **Visceral pain:** This type of pain arises usually due to mechanical pressure or damage to visceral organs. They are deep, with poor localization. They may have associated symptoms such as hypotension, nausea or sweating which are due to activation of neurons that are present at the location of pain and transmit signals to the CNS. Some examples include Cholelithiasis, Renal calculi, gastric ulceration or spasmodic intestinal contractions.

c) **Referred pain:** This refers to the type of pain which is projected to sites away from the site of the noxious stimuli. The origin of this pain maybe somatic (involving musculoskeletal system) or visceral (Involving internal organs). The pathophysiology of this type of pain is accredited to the over-excitability of spinal neurons lying alongside or due to the ascending pathway activating the peripheral reflex arc. The well-known examples of this type of pain are myocardial pain and anginal pain.

PATHWAYS OF PAIN:

1. Ascending Pathways (Figure 7):

a) Antero-lateral spino-thalamic tract: Primary afferent pain receptors take the stimuli to spinal cord or to the medulla oblongata in the stem of the brain depending on their location (peripheral locations and head respectively). They release chemical compounds(Eg: Substance P, Aspartic acid, Glutamic acid, somatostatin etc.) at the level of spinal cord/brain which activate secondary neurons which are cells involved in pain transmission. The axonal bodies of these neurons may cross over at the level of spinal cord and may terminate in the thalamus or the brain stem. This transmission usually occurs in the lateral and anterior quadrant of the cord. They mainly terminate in the MRF of brainstem or the thalamic cortex. The spinothalamic tract carries all stimuli from the peripheral nociceptors to these structures. The intensity of stimuli in this tract corresponds to the frequency of firing of neuron at this level.

b) Antero-lateral spinal reticular tract: A large projection of neurons from the cord and branches of the spinal neurons directly terminate in the medulla oblongata reticular formation. From here further neurons terminate in the thalamic body on the ventral and medial side. From ventral thalamus, neurons project into the somatosensory cortical area. The medial thalamic nuclei terminate not only in the somatosensory cortex, but also to a large area of the forebrain.

Common components of both ascending pathways:

In both these pain pathways there are neurons which can be classfied as[20]:

i. 1st order/Primary Neurons: The cell body of this neuron lie in the dorsal root ganglion. They transfer impulses of peripheral noxious stimuli from peripheral nociceptors to the dorsal spinal cord. They are pseudounipolar, with the dorsal root ganglion containing their perikaryons. They have two pairs of axonal bodies, one extending peripherally and the other projecting through the spinal cord to the brain stem[12,20].

ii. 2nd order/ Secondary Neurons: Their cell body lies in the rexed laminae/Cranial nerve nuclei of the dorsal root ganglion. They ascend in the spinal tracts, cross over and terminate in postero-lateral and ventral (VPL) nuclei of thalamus[12,20].

iii. 3rd order/ Tertiary Neurons: The cell bodies of these neurons are located in the Ventro-posterior and lateral nuclei of the thalamus. They project from thalamus to the ipsilateral post-central gyrus also known as primary somatosensory cortex. The organization of this area is according to the area from where the impulses are transmitted. They pass through the internal capsule, in the posterior lower leg, while doing so.[12,20].

2. **Descending pathways (Figure 7):[21]**

Descending pathways primarily act as a modulation mechanism for pain. They have two main chemical transmitters, namely, Nor-adrenaline and 5-HT. There are two areas of the brainstem which are of paramount importance for pain modulation. They are the peri-aqueaductal grey (PAG) and the raphe magnus nucleus (NRM).

a) **Peri-aqueaductal grey(PAG):** This area is found encircling the cerebral aqueduct which is located in the mid-brain. This area is closely associated with modulation of pain. Any electrical stimulus supplied to this area or injection of any opioid analgesic in this area provide intense analgesia far more profound than in any other area of the central nervous system. This area receives afferent nerve fibers from cortex, hypo-thalamus, thalamus and spino-thalamic tracts. They also have

nerve fibers supplying the NRM which when stimulated, block transmission from dorsal horn cells of the spinal cord.

b) **Nucleus Raphe Magnus (NRM):** This a secondary system projecting neurons which act by using serotonin as a chemical modulator. The cell bodies are located in the medulla and they terminate in cells of lamina-II & III. The activation of the Raphe nucleus produces profound analgesic effects by inhibiting interneurons through release of serotonin. This is greater in intensity than the Nor-adrenaline dependent inhibition.

Brain stem neurons modulate noxious stimuli transmission by:

i. Direct inhibition of dorsal horn cells in spinal cord.
ii. Inhibition of neurons from these cells which are excitatory.
iii. Activation of inhibitory cells and their respective neurons.[21]

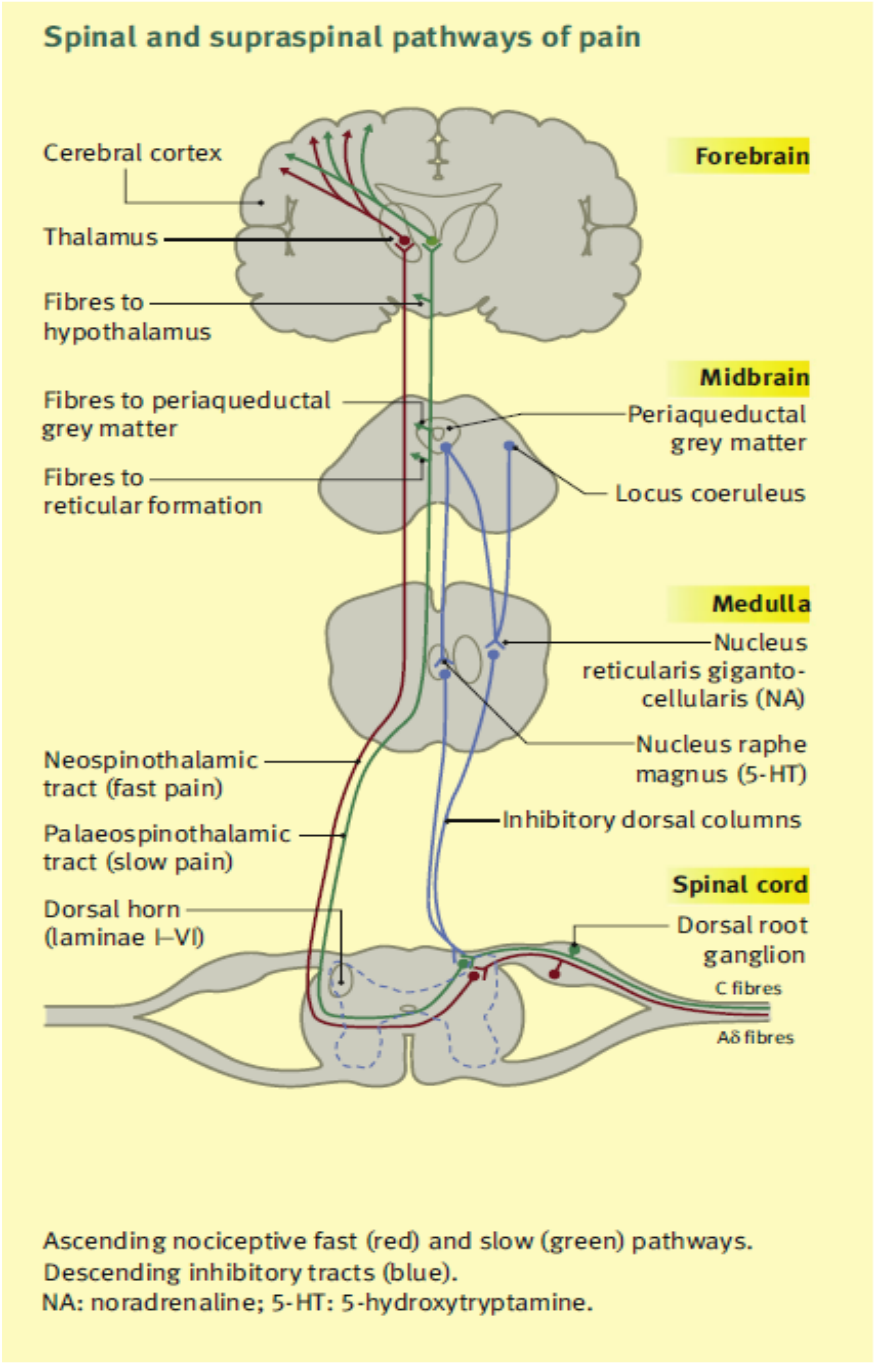


Figure 7 Pain pathway: Afferent/Ascending and Efferent/Descending Pathways [21]

POST-OPERATIVE PAIN AND MANAGEMENT

POST-OPERATIVE PAIN:

I. Introduction:

The extent of pain endured by the patient post-surgery is proportional to the magnitude of damage to tissues at the surgical site. It also depends on the area which is being operated on. For example, thoracic surgeries and upper abdominal surgeries show increased intensities of pain when compared to lower abdominal surgeries. Similarly, lower abdominal surgeries show more intensity of pain than surgeries to the extremities. However, joint replacement surgeries, although technically a surgery conducted on the limbs, shows higher degrees of pain.

Pain in the post-surgical period, when left inadequately treated, can lead to insomnia and disability which have detrimental effects on patient's welfare. This pain may get drawn out into the recovery period and may also prolong hospital stay and is deleterious to the functional outcome of the procedure.

Good analgesic control during this period is also essential to avert calamitous outcomes such a raised blood pressure and ischemic changes to the myocardium. Furthermore, algesia in this period has arrythmogenic potential, can lead to abnormal breathing patterns, paralyze the ileum and can lead to delayed or inadequate wound healing.[25] Adequate post-surgical pain management is also considered to reduce morbidity and disability.[26]

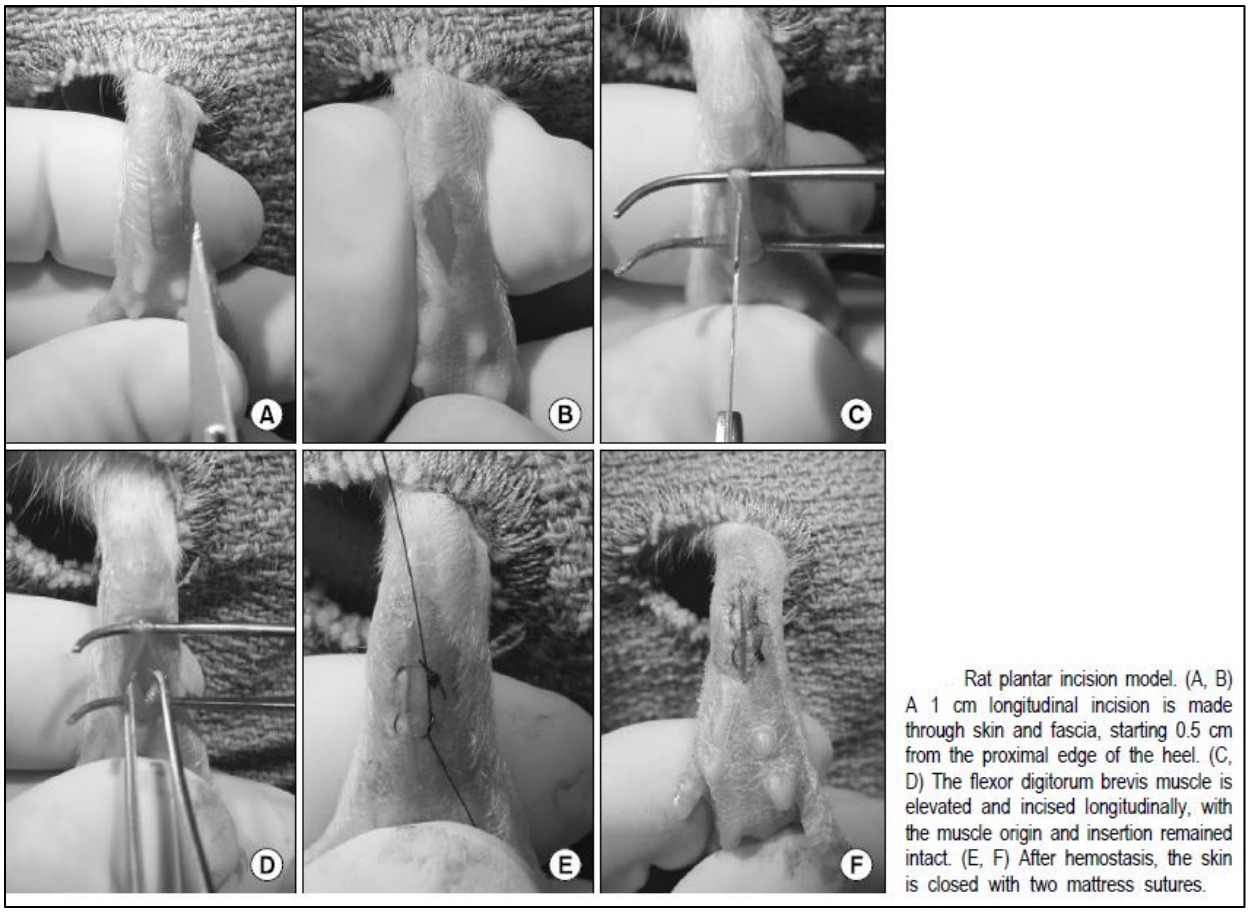
Extreme acute pain during the post-surgical period can convert to Chronic

post-operative pain. In spite of enhancement in awareness due to research, leading to advancements of therapeutic practices toward post-operative pain diagnosis and management, a notable proportion of patients encounter moderate or severe pain, despite receiving analgesic agents, for many days post-surgery. This suggests that there is limited effectiveness of presently practiced analgesic guidelines toward post-operative pain. Although recent additions to these guidelines support multi-drug regimens, opioids still are given a centre-stand. Despite the current multi-modal approach to post-operative pain, with additional regional and neuraxial anaesthesia for specific surgeries, bringing vast improvements in patient satisfaction, a more thorough understanding of post-operative pain pathophysiology is of paramount importance for the development of more efficacious and safe clinical guidelines for the future generations. This will greatly benefit patient care by profoundly decreasing post-operative pain.[26]

II. Experimental Animal models for understanding post-operative pain:

To understand the pathophysiology of post-operative pain, multiple animal models were studied since 1996. The original study conducted in 1996 involved surgically introducing a 1 cm lengthwise incision, under a short period of general anaesthesia, to the plantar muscle and fascia of the rear paw of a rat. Then this incision was primarily sutured (For further details refer to Figure 8). Following this the pain reaction of the rat was studied 1-hour post recovery from anaesthesia. It was seen that the rat developed a short non-evoked guarding reaction to the pain

(for a period of up to 2 days), which was a representation of the non-evoked resting pain (over a couple of days). This was later followed by a longer pain reaction which signified the mechanical stimulation, which was a representation of evoked pain (over days to weeks post-surgery). Mechanical hypersensitivity of the nerves was seen at the site of incision (Primary hyperalgesia) and the immediate area around the incision (Secondary hyperalgesia). Moreover, hypersensitivity to heat but not cold was seen at the site of incision.



Rat plantar incision model. (A, B) A 1 cm longitudinal incision is made through skin and fascia, starting 0.5 cm from the proximal edge of the heel. (C, D) The flexor digitorum brevis muscle is elevated and incised longitudinally, with the muscle origin and insertion remained intact. (E, F) After hemostasis, the skin is closed with two mattress sutures.

Figure 8: Rat Plantar Incision Model.[26]

This same model was transferred from a rat to a mouse with some modifications in 2003. The changes were that the suture incision now measured 5mm, a singular mattress suture was used for primary closure and a modulated assessment was

done of primary and heat hypersensitivity. Further a skin and muscle retraction injury model was also done later on in porcine specimens, which had greater similarities than rats with humans.[29]

III. Pathophysiology of post-operative pain:

Most post-operative pain is due to peripheral nociception, causing primary hyperalgesia, but there are also patients where allodynia (a salient feature of central sensitization where normal light touch stimulation can also be perceived as a noxious stimuli) and secondary hyperalgesia, signs of central sensitization, is encountered. This can be due to a release of inflammatory chemical transmitters such as Substance-P, Calcitonin gene-related protein (CGRP), cholecystokinin etc.[27]

a) NMDA mediated Reversible Central sensitization:

NMDA are membrane bound receptors. They require chemical complexes made of aspartate and glutamate. This complex causes activation of AMPA (amino-3-hydroxyl-5-4-proprionic acid) and KAR (Kainate receptors) which help in controlling inflow of Na^+ and Ca^+ ions and also for the efflux of K^+ ions by activating NMDA receptors.[27] A Mg^+ ion in the receptor has to be displaced for the successful influx of Ca^+ ions. The efflux and build-up of Ca^+ ions on cell body leads to fast and self-sustained firing of neurons even the absence of stimuli. This kind of

prolonged and independent firing of NMDA receptors in the CNS (spinal cord and supra-spinal areas) leads to long-term potentiation (LTP). This process is also known as Transcription independent central sensitization which is NMDA mediated and causes LTP. This exhibits the phenomenon of hetero-synaptic central sensitization ie a low threshold stimulation of A-Beta fibers causes hyperalgesia after C-fiber conditioning.[27] This LTP caused by central sensitization can be reverted by prompt treatment.[28]

b) **Transcription dependent Central sensitization:**

Extended exposure to noxious stimuli will cause transcription dependent central sensitization. This occurs due to activation mRNA transcription which further gets translated into amino acids. This occurs due to rise in prostaglandins, nitric oxide and superoxides in response to inflammation occurring in the dorsal horn and dorsal root ganglion. It also causes irreversible changes in CNS. This can be of two types, namely, activity independent localized type (includes later stages of LTP) and activity independent widespread type.[27]

IV. The physical changes causing post-operative pain:

Pain occurring due to physical trauma to the nerve or aberrant functionality is called post-operative nerve damage. This is the main cause for chronic post-

surgical pain. Although utmost caution is taken by operating doctor to prevent this, minute traumatic events and physical damage due to stretching of the neuronal fibers during retraction cannot be prevented.

This type of nerve injury is classified as:

i. **Neuropraxia:** Block of transmission of impulses within the axonal body without physical or anatomical damage to the nervous tissue.

ii. **Axonotmesis:** Anatomical trauma to the axon causing interference in nerve conduction with absent or fractional interruption of the connective tissues surrounding it (Neurilemma). Here there is partial damage to the axonal cylinder with nil to minimal damage to the neurilemma. Recovery from this type of injury takes time as the axon has to regenerate. This regeneration maybe hampered by scar tissue.

iii. **Neurotmesis:** Complete anatomical and physiological interruption of the nervous tissue, including both the axonal body and all layers of the neurilemma.

Other mechanisms include:

i. **Scarring:** Formation of scar tissue occurs during the healing process of the skin and surgically injured tissue post-surgery or following trauma. This scar tissue exerts a mechanical pull on the adjacent tissues which may cause compression or agitation of associated nerves which can also cause algesia.

ii. **Tissue damage:** Musculoskeletal and soft tissue maybe traumatized or excised during the operation which can lead to post-operative

pain.

iii. **Wound inflammation:** Extended and chronic post-operative pain is more common following cardio-thoracic and upper abdominal surgeries. In these surgeries the inflammatory reaction surrounding the surgical site is the likely cause.

iv. **Prolonged surgeries, radiation and chemotherapy:** All these can cause chronic post-operative pain.[30]

Other miscellaneous risk factors for development of chronic post-operative pain have been listed in Table 3.

Preoperative factors
Pain, moderate to severe, lasting more than a month
Repeat surgery
Psychological vulnerability
Preoperative anxiety
Female gender
Younger age (adults)
Workers' compensation
Genetic predisposition
Inefficient diffuse noxious inhibitory control *
Intraoperative factors
Surgical approach with risk of nerve damage
Postoperative factors
Pain (acute, moderate to severe)
Radiation therapy to area
Neurotoxic chemotherapy
Depression
Psychological vulnerability

Table 3: Risk factors for chronic post-operative pain.[25]

POST-OPERATIVE PAIN MANAGEMENT

PRE-OPERATIVE EVALUATION:

To provide adequate analgesia to a patient post-surgery, it is of utmost importance to properly examine and assess the patient's past encounters with painful experiences and also physically evaluate the patient thoroughly. This will help the anaesthesiologist to make a proper plan of action to provide complete analgesic relief to the patient in the post-operative period [(29)].

A proper plan of analgesic management in this phase includes:

a. Proper augmentation of pre-surgical drugs to prevent symptoms of withdrawal.
b. Alleviating any anxiety or algesia the patient has during the pre-operative period.
c. A multi-modal regimen and its effective administration for analgesia.

Post-surgical relief from pain depends on factors such as the magnitude of pre-surgical pain, the chronological age of the patient, how anxious the patient is before entering the operation theatre, any history of medical depression in the past or is suffering from currently and the skill and expertise with which medical care is given to the patient.

The most vital step in the pre-operative assessment of pain is the quantification of said pain. This is accomplished most commonly by using the 10-point pain assessment score. In this scoring scale 1 represents absence of any pain and 10 means the most severe pain ever encountered by the patient. A continuous re-assessment of this score during various points during this period is of utmost

importance to guarantee patient satisfaction. Therefore, analgesic management in this stage can only be obtained by encouraging frequent communication of any pain from the patient and provision adequate analgesia by the anaesthesia provider.

Pre-emptive analgesia:

Analgesic management by multiple methods such as administration local anaesthetic at surgical site, providing systemic analgesic agents or epidural anaesthesia even before surgical incision is made has the potential to abolish or restrict any occurrence or magnitude of post-surgical pain.

The usage of a multi-modal approach that reduce or obstruct nociceptive stimulation is a corner-stone to achieving efficacious pre-emptive pain relief. These agents may alternatively act by down-regulating or reducing the secretion pain neurotransmitters.[27,58]

The multi-modal approach to pre-emptive analgesia can be achieved through the following methods:

I. **Pharmaco-therapeutics:**

Seeing as how the perception of pain requires multiple carrying receptors situated within the peripheral and central nervous system, a multi-drug regimen is best suited for optimal analgesia. This also reduces the side effects seen with individual agents. Commonly used class of drugs used for these regimens are as follows:

a. **Anti-inflammatories: NSAIDs** act by inhibiting cyclooxygenase (COX) enzyme and thereby reducing synthesis of prostaglandins and their secretion. This is an important enzyme responsible for inflammatory pain. The disadvantage of NSAIDs are the risk of gastro-intestinal symptoms, most commonly seen in elderly, and other side-effects which are agent specific. Another adverse effect seen with them is the risk of bleeding, which has restricted their use. Eg: Non-selective: ibuprofen, **diclofenac**, Selective COX-2:

Celecoxib, Selective COX-1: Ketorolac (Figure 9)

Acetaminophen is another analgesic which acts centrally but is not as potent as NSAIDs to reduce inflammation. The parenteral form of this drug is called paracetamol and is preferred over NSAIDs as they are an efficacious analgesic agent and also has no risk of bleeding. It has a gradual onset of action but despite this they are widely used in multimodal analgesic regimens. Paracetamol administration in post-operative analgesia also has the added advantage of reducing the requirement of opioids and also shown to reduce the side effects of opioid administration.[27,31]

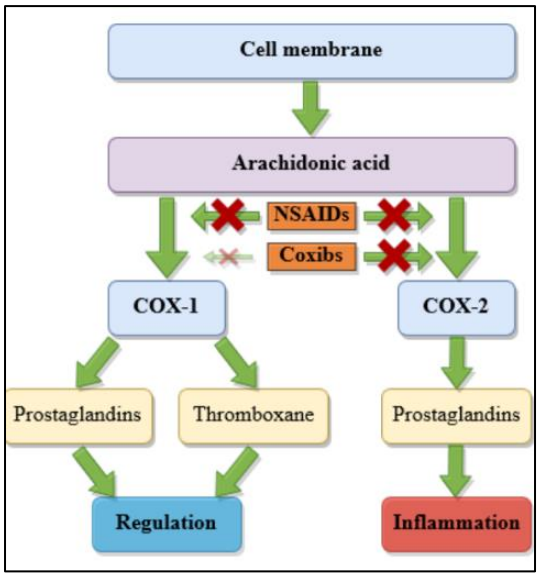


Figure 9: Mechanism of Action of NSAIDs.[33]

b. **Opioids:** They are Mu receptor agonists. Despite the advancement in our knowledge and expertise on analgesic management and newer agents becoming available, opioids still play a major role in post-surgical pain management. They bind at central as well as peripheral sites of the nervous system and modulate the transmission of noxious stimuli through the pain pathway. They can be administered through multiple routes although even today

the most common method of administration is the parenteral route. Their use is majorly restricted due to the side-effects which are seen with their usage. Reduction in respiratory drive is one of the most dangerous adverse effect as it can lead to hypoxia and acute respiratory distress. Therefore, during their use proper pulse-oximetric and respiratory monitoring are recommended. Some of the other adverse effects include nausea, emesis, pruritus and paralytic ileus leading to constipation. Eg: Morphine (prototype molecule), hydromorphone, fentanyl, **tramadol** etc.[27,31]

c. **Anti-depressants:** They play a major role in management of neuropathic pain. Tricyclic antidepressants play a major role by inhibiting the re-absorption of serotonin and nor-adrenaline at the level of central nervous system thereby upregulating the descending inhibitory pathways. Common adverse effects seen with these drugs are xerostomia and somnolence due to their predominant anti-chlinergic action. Serotonin and Nor-adrenaline Reuptake Inhibitors (SNRI) also play a major role in diabetic neuropathy. Eg: Tricyclic antidepressants: Amitriptyline, Nortriptyline and Imipramine; SNRIs: Duloxetine.

d. **Anticonvulsants:** These pharmacological agents play a role by inhibiting the opening of Na^+ and Ca^+ channels in the neurons thereby downregulating them. They're use is restricted due to their adverse effects such as somnolence, nausea and ataxia. Eg: Carbamazepine, lamotrigine, gabapentin and pregabalin.

e. **Topical preparations:** LOX 5% plaster commonly used to control pain caused neuralgia after herpes infection can additionally used to control neuronal pain in a localized area. Capsaicin, a compound extracted from chilies, act by binding VR1 peripheral receptors. They initially cause a burning sensation and

hypersensitivity followed by a period of hyposensitivity and then prolonged downregulation of the localized area.

f. **NMDA Antagonists:** They act by downregulation of NMDA receptors present in central nervous system and therefore inhibit stimulation by amino acids like glutamate. This also downregulates the 'wind up' phenomenon and thus the progression to chronic algesia. They also have an agonistic action on opioid receptors and therefore brings about downregulation of serotonin and nor-adrenaline reabsorption.

g. **Anti-arrhythmic:** they act by occluding Na^+ channels and prevent transmission and therefore have found a role in the treatment of neuropathic pain. Preservative free Lignocaine can therefore be used with continuous infusion for neuronal pain.

h. **Cannabinoids:** Due to continuing research into these group of agents, they have found a use for multiple ailments. The most potent compound in this group, Delta-9-tetrahydrocannabinol and their lab produced versions such as nabilone, show agonistic activity at CB-1 receptor. These potentially can alleviate algesia but are used in a reserved manner due to their psychotropic manifestations and poor tolerance.[31]

II. **Neuraxial and regional anaesthesia:**

a. **Epidural and spinal anaesthesia:** They have an important role in providing analgesia in surgeries involving pelvis, thorax, upper and lower abdominal surgeries. A catheter can be introduced into the thoracic or lumbar epidural space following which a combination of local anaesthetic and opioid infusion can be introduced to cause pain relief.

b. **Paravertebral block:** A paravertebral block is administered by introducing local anaesthetics adjacent to the thoracic spinal

nerves. This causes downregulation of the sympathetic outflow on the ipsilateral side. Injection of different local anaesthetic agents have different duration of action. It is safer to use in situations such as DIC (Disseminated Intravascular coagulation).

c. **Peripheral nerve blocks:** Peripheral nerve blocks can be given for surgeries of the extremities, such as upper limb surgeries. They can only be used as a part of multimodal approach to post-operative analgesia.

d. **Local infiltration:** They have been used effectively for colonic and recto-sigmoid surgeries. They're use is restricted as they have very short half $t^{1/2}$. Eg: Lignocaine, Bupivacaine, Ropivacaine. Currently there is an FDA approved drug for post-op pain relief which could provide up to 72 hours of post-surgical analgesia. [27]

Future Trends and developments:

a) Procedure-specific pain management (PROSPECT):

Different surgeries require different modalities of analgesia. This understanding has brought about the PROSPECT initiative to study and compare different available multimodal approaches for specific surgeries and to bring about a standardization of protocols for specific surgeries.

b) USG guided blocks as a part of multimodal anaesthesia:

With the increased interest in several regional anaesthesia techniques with USG guidance such as TAP block, quadratus lumborum block, erector spinae block, transversalis fascia plane block etc. it is not wrong to assume

that this has come a mainstay in the future as a part of multimodal approach to pain management.

c) Novel approaches to Chronic Post-Surgical Pain (CPSP):

Cryo-neurolysis is one novel method which is gaining popularity with the availability of portable devices for its administration and its role in reducing opioid requirement for post-op analgesia.

Targeted RNA toxins and deep brain stimulation are also being studied for the management of CPSP but further research and study is required before it can be implemented into everyday practice.

Newer methods of screening for pain such as PainCheck, wherein Artificial Intelligence is used to study the facial expressions of the patients in the post-operative ward to assess pain, can also be helpful to provide adequate analgesia to post-surgical patients.[40]

d) Enhanced Recovery After Surgery (ERAS):

First brought about as an effort to implement multiple methods of analgesia to provide post-surgical pain relief by Dr Kehler, it has now been developed into the ERAS protocols which is patient specific, proof based, multiple modality inclusive grouped approach to improve post-operative analgesia. Although it was initiated only in gastro-intestinal surgeries now it covers a wide variety of procedures.

Including regional anaesthesia and nerve blocks to an already existing multi-drug approach to post-surgical pain management is an essential part of ERAS.[41]

TOPICS SPECIFIC TO THE STUDY

DRUGS

I. PARACETAMOL:

The other name for this drug synonymously used is Acetaminophen.

- **Chemistry:** The chemical name of this drug is N-acetyl-p-aminophenol. A molecule of paracetamol contains a single ring of benzene, a hydroxyl group which is further bonded to a nitrogen atom of acetamide, conforming to a para (1,4) configuration (Figure 10).

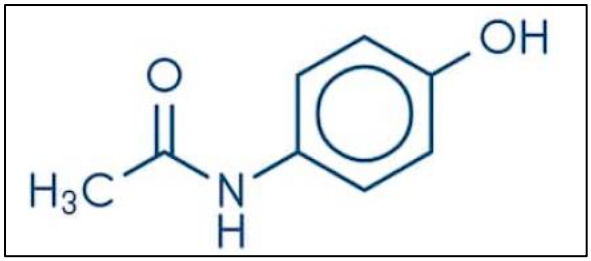


Figure 10: Chemical Structure of Paracetamol.[32]

- **Mechanism of action:** It is has been deduced to have both Peripheral and central targets. It acts by reducing the prostaglandin levels and also lower the level if inflammatory cytokines. Acetaminophen acts on the prostaglandin G/H enzyme (COX-1 &2). This enzyme takes part in the conversion of arachidonic acid to prostaglandin G/H. This molecule gets rapidly changed into inflammatory cytokines.

  The anti-pyretic properties, pain-relief and hypo-inflammatory action of NSAIDs is attributed to the inhibition of the COX-2 enzyme. It

neutralizes the COX enzymes by altering the peroxide site and thus non-competitively having antagonistic activity.

- **Active metabolite:** The N-arachidonoylaminophenol (AM404), a break down product of acetaminophen, obstruct the uptake of anandamide by the neuron and also block neuronal sodium channels and through this pathway provide multiple beneficial analgesic properties.
- **Bioavailability:** Oral route- highest concentrations of the drug in plasma is seen after 30-60 mins, Parenteral: Onset of action within 45-50 mins. Analgesia lasts for 4-5 hrs post 1 gm infusion of paracetamol.
- **Safety:** The tolerance of patients towards this drug and minimal side effects have made acetaminophen warrants its inclusion in any multimodal analgesic regimen. The dose of >4gms of paracetamol is seen to cause toxicity. [32]
- **Role in post-surgical analgesia:** It drastically decreases opioid necessity when used as a part of multimodal analgesia. The bio availability of paracetamol during post-op period when given parenterally is 100% as compared to oral which provides only 75%. Therefore IV administration is preferred for post-surgical analgesia.[35]

II. DICLOFENAC:

- **Chemistry:** It is derived from pyrazolidine and is chemically by adding a phenylated acetic acid molecule and a ring of phenyl which has a couple of chloride atoms. This conformational changes which enable it to bind successfully to the COX enzyme (Figure 11).

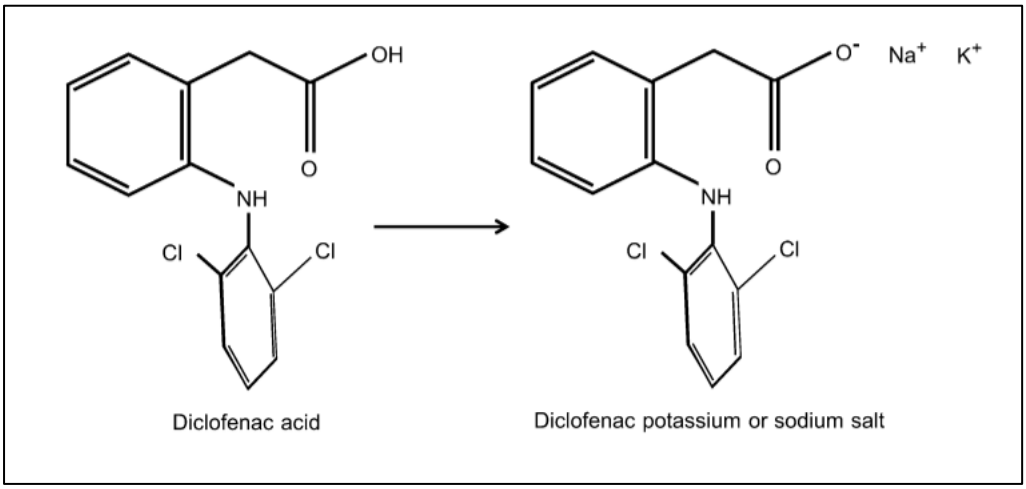


Figure 11: Chemical Structure of Diclofenac and its Salts.[36]

- **Mechanism of action:** It is a non-selective COX enzyme blocker. It has higher affinity for COX-2> COX-1. The inhibition of COX enzymes reduce production of prostaglandin (mainly PGE_2) and thromboxane A_2. This provides efficacious pain-releif and hypo-inflammatory properties.
- **Pharmacokinetics:** The rate of uptake of diclofenac is affected by which salt is used, specific pharmacological makeup and whether patient is on empty stomach or not. Even then systemic uptake is usually expeditious and is in relation with the dose load. They undergo oxidation to form glucuronide and sulfate complexes which are excreted through the renal and hepatic system.
- **Adverse events and cross-reactions:** Its use can manifest an increased predisposition to adverse events in the gastro-intestinal, cardiac and renal system unless administered in recommended doses (not more than 75mg/day). It does not have any cross-reactivity with concomitant dosage with aspirin.[36]

III. TRAMADOL:

Tramadol is a centrally binding man-made opioid analgesic agent which can be administered enterally or intravenously.

- **Advantages and Disadvantages:** Sedation is almost absent and reduction in

respiratory drive minimal. The GI side effects common with other opioids is to a lesser extent with this agent. It is less effective for severe pain than other opioid agents.

- **Chemistry:** Chemically it is named trans-2(dimethylaminomethyl)-1(m-methoxyphenyl)-cyclohexanol hydrochloride.
- **Mechanism of action:** It is partially affinitive to mu-receptor compared to kappa and delta receptors. It is 1600 times less potent than morphine and 10 times less potent than codeine. The + chiral enantiomer has greater affinity for the receptor than – chiral form.
- **Dosage:** Enteral/Parenteral: 50-100mg Q4-6hrs, Intravenous dose should be given over 2-3 minutes or by infusion. Rectal: 100mg QID.
- **Pharmacokinetics:** It's uptake is rapid by oral route and shows 75% availability, although this is restricted by 1st pass metabolism. The Nil per oral status of the patient does not affect the bioavailability. It is broken down into N and O methyl, glucuronide and sulfate substrates. **The active metabolite** o-desmethyl tramadol is also formed. It is **P_{450}** and **CYP2D6** dependent for its degradation and further metabolism. 1 in 6 parts of the administered dose is excreted in urine unchanged while the rest is broken down and excreted. It can get transferred from maternal end to fetal end and a minute fraction is secreted from the mammary glands.
- **Drug Interactions and Adverse events:** The very frequently seen adverse effects are loose stools, constipation, pruritic rash, nausea and dizziness with vomiting, head pain, sedation and vertigo. The less common but hazardous adverse effects include low BP, unconsciousness, tachyarrhythmia, anaphylaxis, reduced awareness, convulsions (even seen at recommended dose range, altered sensorium with hallucinations and rarely breathlessness. Some of the drug cross-reactions have been mentioned in Table 4.[37]

Interacting drugs	Outcomes	Management
Carbamazepine	Decreased Tramadol efficacy due to the induction of metabolism of Tramadol by Carbamazepine	Monitor patients for Tramadol efficacy. Doses may need to be increased, even doubled, in patients who are receiving chronic carbamazepine therapy.
Warfarin	Increased risk of bleeding due to an unknown mechanism.	Closely monitor international normalized ratio (INR) and adjust warfarin doses accordingly. Also monitor for signs and symptoms of bleeding and bruising.
Amitryptyline	Increased risk of seizures due to an unknown mechanism	Use with caution if Tramadol is to be administered to patients receiving concomitant tricyclic antidepressant (TCA) therapy. If possible, avoid this combination, especially in patients with underlying conditions that might predispose to seizures
Promethazine	Increased risk of seizures due to an unknown mechanism	Caution should be used if Tramadol is to be administered to patients receiving Promethazine therapy. If possible, this combination should be avoided especially in patients with underlying conditions that might predispose to seizures.

Table 4: Drug reactions seen with Tramadol[37]

ASSESSMENT OF PAIN

The Visual Analog Scale (VAS)

VAS is the most commonly used scale for assessment of pain in the post-surgical period. Historically it was utilized to assess pain for the first time in the year 1921 by Hayes and Patterson. It is a subjective scale, where the pain severity is reported by the patient [38].

- **Usage:** It basically consists of a 10 cm line with an incremental score of 1 per cm starting with 1 (representing absence of pain) and ending with 10 (corresponding to the most severe pain imaginable) below a Wong/Baker faces rating scale (Figure 12), which is a visual representation of the numerical scale useful in pediatric age group, uneducated patients and also in situations where there is a language barrier. The patient is asked to point to the number or the face

corresponding to his current algesic status. Depending on this patient is differentiated into Mild, Moderate and Severe category. One post-operative analgesic regimen using VAS score is the multimodal WHO Ladder of pain depicted in Figure 13.

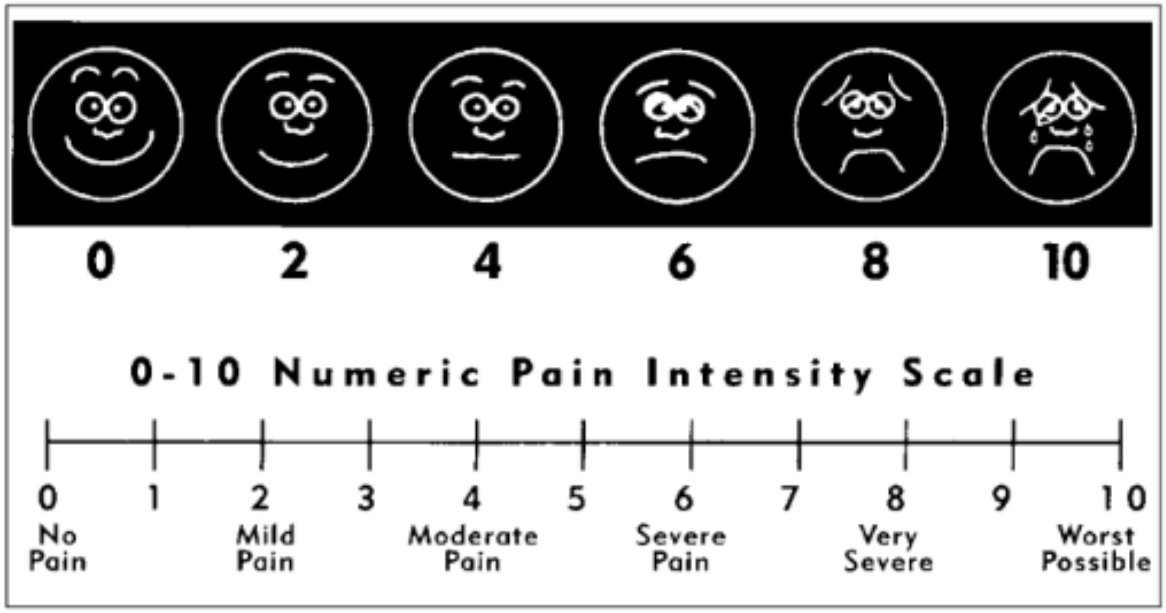


Figure 12: Visual Analog Scale[39]

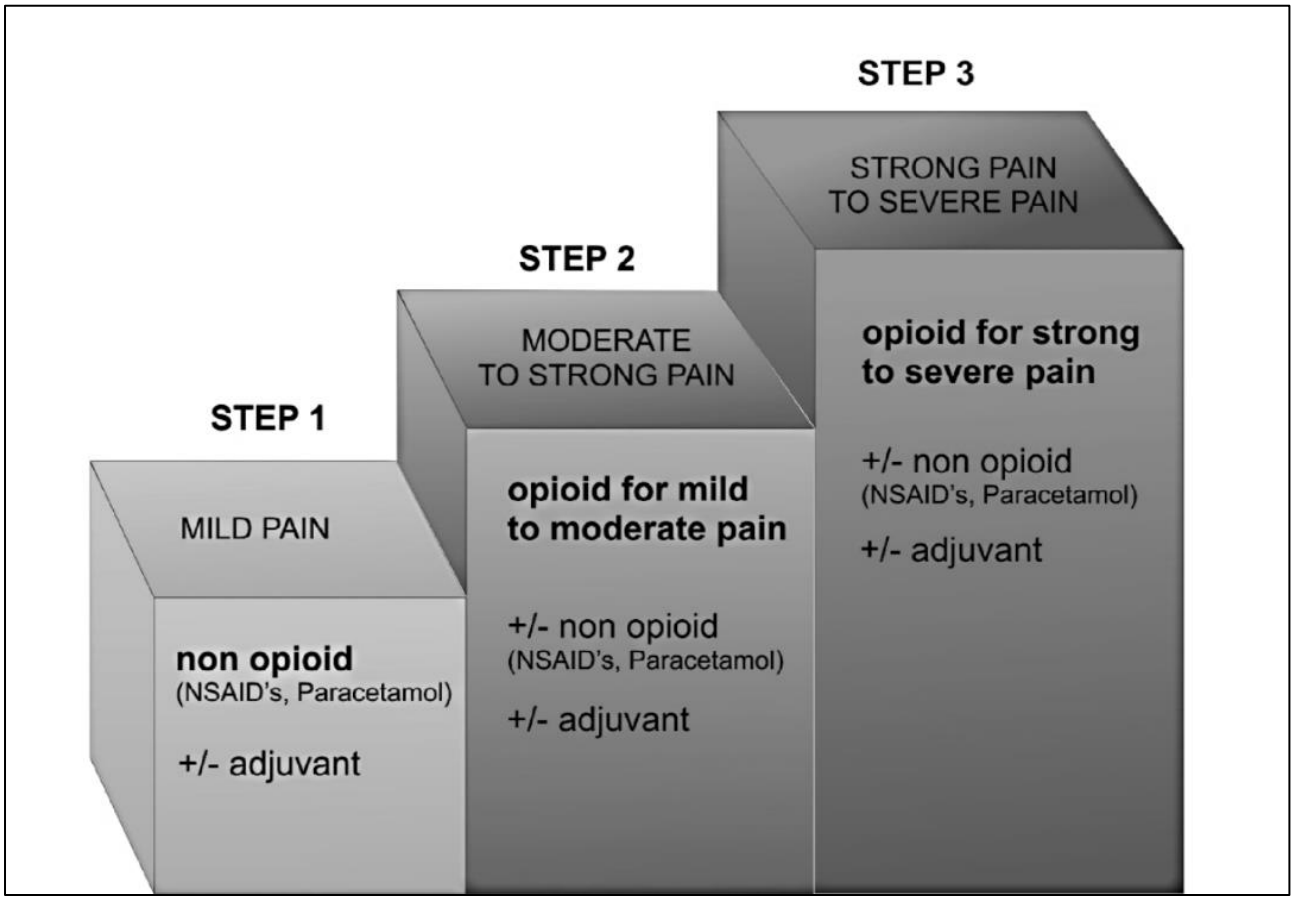


Figure 13: WHO Ladder for Pain Management[34]

REVIEW OF LITERATURE:

The earliest mention of paracetamol in literature was in 1947 by **David Lester et al.**[42] where it was stated that n-acetyl-p-aminophenol was an active metabolite of acetanilide metabolism.

In 1948, **Bernard B Brodie et al.**[43] further studied the metabolism of acetanilide and concluded that the metabolite paracetamol was attributable to the analgesic and antipyretic properties of acetanilide and also that the meth-haemoglobinemia associated with it was due to another metabolite namely phenylhydroxylamine.

In the year 1985, through the study 'Voltaren® as an analgesic after surgical removal of a lower wisdom tooth', **Per-Åke Henrikson et** al.[53] conducted a trial where intravenous diclofenac preparation (Voltaren) was used for the first time and it was compared to the then available fixed dose combination of oral analgesic (acetylsalicylic acid 500 mg, caffeine 50 mg, aprobarbital 20 mg, codeine phosphate 10 mg). It was found that patients given iv diclofenac preparation had lesser pain and also noticeably lesser disability days. They therefore concluded that intravenous diclofenac is a new agent which could be used as an alternative for post-surgical analgesia and inflammation.

N. D. Edwards et al.[54] **,**in the study 'Day case laparoscopy: a survey of postoperative pain and an assessment of the value of diclofenac', evaluated the effectiveness of intramuscular diclofenac used as pre-emptive analgesia in patients undergoing laparoscopic abdominal surgeries as a day care procedure. He observed that patients undergoing laparoscopic sterilization showed significantly greater pain scores at 1st hour post-op than those undergoing

diagnostic laparoscopy. He also observed that the post-operative side effects where higher for diclofenac group when compared to control group although there was no significant difference between the two surgical groups. In conclusion he stated that diclofenac showed no change in the post-operative pain level and rather showed higher incidence of side effects.

In the paper 'Treatment of postoperative pain with diclofenac in uvulopalatopharyngoplasty', **H.Ejnell et al.[(55)]** observed that on the 1st and 2nd day post surgery there was a significant difference between control group and diclofenac group where the diclofenac group required 50% lesser rescue analgesia. It was also said that the adverse effects were lesser when the drug was administered as a suppository.

In the study 'Preemptive analgesic effects of intravenous paracetamol in total abdominal hysterectomy', **Semih Arici et al.[(50)]** observed that pain at rest or during mobilization and the opioid requirement for patients in the control group were significantly higher than for those groups receiving parenteral paracetamol. They also saw that the morphine requirement was higher in post-operative period when paracetamol was given just before skin closure than when given 30 mins prior to end of surgery. From this they came to the conclusion that in TAH patients preemptively administering paracetamol 1 gram provided better post-surgical anaesthesia and lesser consumption of opioids. A similar research paper named 'A Comparative Study on Pre-emptive Analgesic Effect of IV Paracetamol on Reducing the Use of Opioid in Post-operative Pain management' was published by **Manmohan Jindal et al.[(69)]** in 2019, which found that pre-emptively infusing paracetamol reduced requirement of opioids and associated adverse effects.

In the 2012 study, 'Comparison of preemptive intravenous paracetamol and caudal block in terms of analgesic and hemodynamic parameters in children', **Serbülent Gökhan Beyaz et al.**[50] tried to compare the efficacy of paracetamol infusion with a caudal block in pediatric patients and found that paracetamol infusions had identical analgesic potential as caudal block in these patients and also provided hemodynamic stability.

In the publication 'Single dose oral diclofenac for acute postoperative pain in Adults', **Philip Derry et al.**[57] compared 15 studies about enteral diclofenac for post-surgical pain and came to the conclusion that enteral diclofenac was effective with a single dose for treatment of moderately severe post-operative pain. Moreover, it was seen that 50% more pain relief was achieved with diclofenac potassium compared to diclofenac sodium for 4 to 6 hrs. Adverse events were seen equally in both diclofenac and placebo groups.

Pratyush Goel et al.[11] in the year 2010 published 'Pre-emptive analgesia with iv paracetamol and iv diclofenac sodium in patients undergoing various surgical procedures: a comparative study'. In this study VAS scores showed no significant difference between paracetamol and diclofenac groups. However, the duration of analgesia was approximately 4.2 hours for diclofenac and about 4.8 hours for paracetamol. From this result it was inferred that iv paracetamol provided longer duration of analgesia than iv diclofenac.

"Intravenous Paracetamol for Postoperative Analgesia in Laparoscopic Cholecystectomy" was published by **Sayed Mohamadreza et al.**[47] In this it was found that pain scores were significantly lesser in paracetamol group although it did not reduce the requirement for morphine. Therefore, they concluded that although

IV paracetamol provides better analgesia, it was not suitable to be used as a sole agent for post-op pain management.

Bright Jebaraj et al.[48] ,in their publication named 'Intravenous Paracetamol Reduces Postoperative Opioid Consumption after Orthopedic Surgery: A Systematic Review of Clinical Trials', found that 4 previous trials had concluded that intravenous paracetamol reduced the requirement for post-surgical opioids. They then came to the conclusion that intravenous paracetamol was an effective adjunct to opioid agents with good safety margins for orthopedic surgeries.

Intravenous paracetamol infusion: Superior pain management and earlier discharge from hospital in patients undergoing palliative head-neck cancer surgery was published by **Saikat Majumdar, Anjan Das, Ratul Kundu, Dipankar Mukherjee, Bimal Hazra and Tapobrata Mitra[46].** They found that the overall VAS score in the 1st and 2nd post-surgical period and opioid requirement and rescue analgesia requirement was delayed when parenteral paracetamol was used. They also had lesser SICU stays and where discharged from the hospital earlier after Head and neck surgeries. Therefore, they concluded that parenteral paracetamol was efficacious as a pre-emptive agent to provide post-surgical analgesia in head and neck surgeries.

Jhuma Biswas et al.[56] in their study 'Diclofenac is more effective for post-operative analgesia in patients undergoing lower abdominal gynecological surgeries: A comparative study' observed that rescue analgesia requirement was less when diclofenac or a combination of diclofenac and paracetamol was used rather than only paracetamol. They also observed that the VAS score was significantly lower in diclofenac and diclofenac + paracetamol group when compared to paracetamol group at 4 and 12 hrs post-surgery. Moreover Group diclofenac and

Group paracetamol + diclofenac showed no significant difference when it came to VAS scores. From this they concluded that intramuscular diclofenac was more effective than intravenous paracetamol when it came to requirement of rescue analgesia, but intramuscular diclofenac + intravenous paracetamol provided no additional advantage over usage of only intramuscular diclofenac.

In the research paper 'Comparative study of tramadol and diclofenac as analgesic for
postoperative pain' by **Shukla AK et al.**[64] an observation was made that mean VAS scores differed significantly in first 24,48 and 72 hours post-surgery for patients undergoing various abdominal wall and perineal surgeries although significantly different values were only observed for first 24 hours in post-jaboley's procedure patients. From this it was deduced that diclofenac provided more efficacious in acute post-operative period than tramadol, showing how the later agent required more frequent administration.

Roy Altman et al.[36] in their article 'Advances in NSAID Development: Evolution of Diclofenac Products Using Pharmaceutical Technology' did a review of papers published about diclofenac and made the observations such as the serious GI, CVS, and Renal side effects which was proportional to the dosage, The advantage of diclofenac potassium of faster onset of action and rapid uptake from GI when given orally and the advent of locally applicable formulations of diclofenac which enabled localized treatment of algesia and swelling while reducing systemic absorption and thus side-effects. They came to the conclusion that pharmaceutical technology and research has shown to produce advantageous modifications in the properties of diclofenac bringing about the discovery of novel variations of the agent with better safety and efficacy.

In the study 'Comparative evaluation of preemptive use of intravenous Paracetamol and Diclofenac on postoperative analgesia in lower abdominal surgeries done under anesthesia', **Swati Chougule et al.[6]** observed that both paracetamol and diclofenac produced acceptable post-op pain relief. They also observed that patients receiving parenteral paracetamol had better analgesic satisfaction than patients receiving intramuscular diclofenac. The adverse effects were also lesser for patients receiving iv paracetamol when compared to patients receiving im diclofenac. Therefore, they concluded that intravenous paracetamol was safer and more efficacious than intramuscular diclofenac for post-op pain management in patients undergoing lower abdominal surgeries.

In the review article 'Diclofenac Potassium in Acute Postoperative Pain and Dysmenorrhoea: Results from Comprehensive Clinical Trial Reports' **R. Andrew Moore et al.[60]**, from a thorough study of 6 comprehensive research papers found that a comprehensive clinical comparison is far more effective, and is required, than single study comparisons to provide better clarity on the potency and safety of diclofenac as a post-operative analgesic agent.

Alexander Schnabel et al.[65] in their paper 'Tramadol for postoperative pain treatment in children' from their extensive review of 20 randomized trials found that children given tramadol vs placebo, showed no significant benefit over each other for post-operative nausea and vomiting.

Richa V Patel et al.[61] in their research paper 'Comparative effects of intravenous diclofenac versus intramuscular diclofenac on postoperative surgical pain management' found that duration of action for intramuscular diclofenac was approximately 7.2 hrs while for intravenous was around 6.9 hours, with no

statistically significant difference in hemodynamic status, respiratory mechanics or pain scores. From this they concluded that intramuscular and intravenous route of diclofenac are both equally efficacious for post-operative pain management, with minimal adverse effects and good analgesia.

Tanudeep Kaur et al.[51] in their publication 'Comparative Study in the Management of Postoperative Pain with High Dose Intravenous Paracetamol versus Tramadol' found that the VAS score was significantly higher in patients receiving only paracetamol than patients receiving tramadol alone. They also found that additional analgesic requirements were also higher in the group receiving only paracetamol. They concluded that although tramadol provided superior analgesia, the side-effects such as nausea, vomiting and somnolence was more.

In the paper 'Effect of rectal diclofenac (100mg) for postoperative analgesia in adult perineal surgeries', published by **Rajajothi R etal.**[62], it was concluded that 100mg of diclofenac suppository, when used in patients undergoing perineal surgeries, provided extended analgesia when compared to patients not receiving it.

Iolter Cattabriga et al.[49] in their study 'Intravenous paracetamol as adjunctive treatment for postoperative pain after cardiac surgery: a double blind randomized controlled trial' found that less pain during rest at 12, 18 and 24 hrs post-surgery was reported in patients receiving parenteral paracetamol but after this duration the pain intensity did not differ. They also found that the group receiving paracetamol required less opioids although statistical significance was not established. They therefore came to the conclusion that in post cardiac surgical patients, parenteral paracetamol in adjunct with tramadol provides superior analgesia.

Oral versus Intravenous Paracetamol for Perioperative Analgesia in Patients Undergoing Total Abdominal Hysterectomy- A Randomised Double-Blind Controlled Trial was conducted by **Archana Khokar, Medha Mohta, Himanshu Bhasin and Swaraj Jyoti Sonowal**[(44)] in 2021. They compared the efficacy of Oral versus Intravenous paracetamol for peri-operative pain management and found that Oral Paracetamol was better effective costwise than intravenous paracetamol.

'A Prospective Case-control Study on the Comparison of Postoperative Pain Relief with Transdermal Diclofenac Patch and Injection Diclofenac' was published by **Sachender Pal Singh et al.**[(59)] which showed that lesser repeat doses where required when a transdermal application of diclofenac was done compare to 3 injections/day/patient when only intravenous diclofenac was used. From this it was concluded that transdermal patch route was better than intravenous route for the administration od diclofenac.

In the article 'Measurement of Pain Intensity and Evaluation of Analgesic Use in Post-Operative Patients in a Territory Care Hospital', **Anaswara V et al.**[(66)] conducted a prospective study to assess the magnitude of pain using pain scale in post-surgical patients to judge the efficacy of the analgesic regimen prescribed to them post-surgery in the year 2021. They found that most commonly used analgesic agent was diclofenac over paracetamol and the preferred route was intravenous over oral. They also saw that dosage regimen was adjusted in only around 6% of patients even though close to 62% of patients complained of moderate pain. From this they concluded that need specific adjustment of analgesia, identification of predisposing risks and regimen followed for analgesia play a huge part in the quality of analgesic management for the patient.

METHODOLOGY

MATERIALS AND METHODS

SOURCE OF DATA:

This study was carried out in the Department of Anaesthesiology, B.L.D. E (DU) Shri B.M. Patil Medical College, Hospital and Research Centre, Vijayapura. The Study was conducted from Jan 2021 to June 2022 on 200 ASA 1 and 2 patients of age group 18 to 60 yrs who underwent surgeries under general anaesthesia. This study was conducted after obtaining approval from the institutional ethical committee.

METHOD OF COLLECTION OF DATA:

Study Design: Prospective Double-Blinded Randomized Comparative Study.

Study Period: One and half year from Jan 2021 to August 2022.

Sample Size: The anticipated Mean±SD of VAS at 0th hour in Group A 1.1±1.0 and Group B 0.8±0.8 resp. (ref) the required minimum sample size is 100 per group (i.e., a total sample size of 200, assuming equal group sizes) to achieve a power of 85% and a level of significance of 5% (two-sided) for detecting an actual

difference in means between two groups.

$$N = 2\left[\frac{(Z_{\propto} + z_{\beta}) * S}{d}\right]^2$$

Z_∝ Level of significance=95%

Z_β--the power of the study=85%

d=clinically significant difference between two parameters

SD= Common standard deviation

Statistical Analysis

- The data obtained was entered in a Microsoft Excel sheet, and statistical analysis was performed using a statistical bundle for social sciences (Version 20).
- Results was presented as Mean±SD, counts and percentages, and diagrams.
- For normally distributed continuous variables between two groups was compared using Independent t-test For not normally distributed variables Mann Whitney U test was used. Categorical variables between the two groups was compared using the Chi-square test.
- .$p<0.05$ was considered statistically significant. All statistical tests was performed two-tailed.

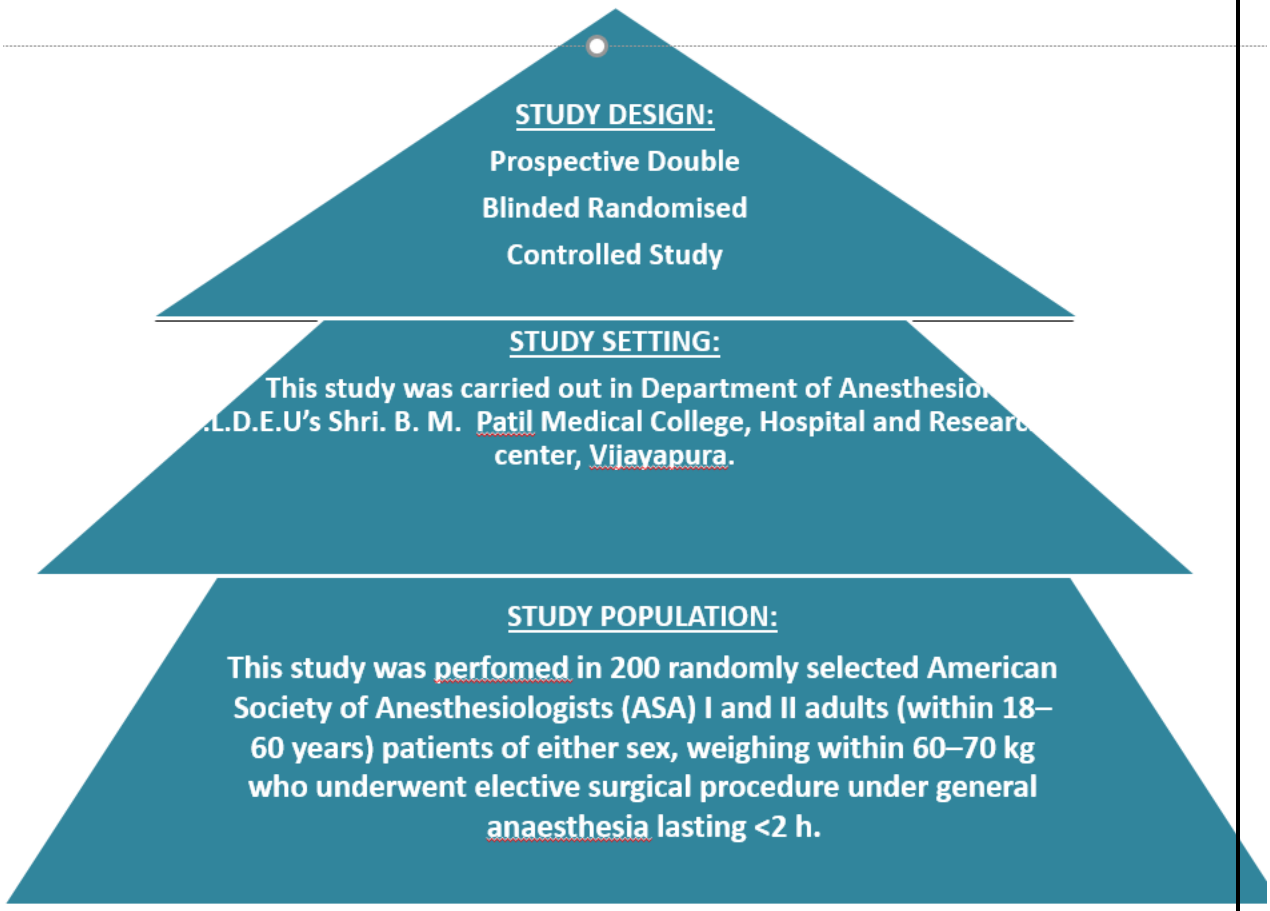


Figure 14: Sample Selection

Double Blinding:

Two anesthesiologists were involved in the study; the first anesthesiologist administered the drug in the intra-op and post-op period. He advised the post-op analgesic instruction by naming the drugs as "A" or "B." He was involved in the

process of collecting the data of that patient. The second anesthesiologist recorded the study parameters at different intervals in the postoperative period without knowing the type of the drug administered. Patients and the Nursing Staff in the postoperative ward were blinded on the kind of drug administered. Nursing Staff were not involved in administering the drug. She/he informed the anesthesiologist to administer the drug whenever the patient complained of pain.

Randomization: Patients were divided by computer-generated random number into two study groups A and B; each consisting of 100 patients as follows:

- **Group A:** (*Paracetamol group*): Patients received IV Paracetamol (15mg/kg)/100mL, 30min before completion of surgery over a period of 15min (rounded off to 1 g).

- **Group B:** (*Diclofenac group*): patients received IV Diclofenac (1 mg/kg) diluted in 100 mL NS, 30 min before completion of surgery over a period of 15 min (rounded off to 75 mg).

STUDY POPULATION

This study was done in 200 randomly selected American Society of Anesthesiologists (ASA) I and II adults (within 18–60 years) patients of either

sex, weighing within 60–70 kg who underwent the elective surgical procedure under general anesthesia lasting <2 h.

INCLUSION CRITERIA:

1. Age 18-64 years
2. ASA I and II
3. A Surgical procedure lasting less than 2 hours.

EXCLUSION CRITERIA

Patients:

1. Unable to comprehend the visual analog scale (VAS) score or Verbal Rating Scale (VRS) score.
2. pregnant and breastfeeding female patients
3. Patients with known allergy to drugs which were used
4. Renal dysfunction
5. Liver Dysfunction

METHODOLOGY:

Pre-anesthetic evaluation:

History- History of any underlying medical illness, previous history of surgery, anesthetic exposure, and hospitalization was taken.

Physical examination: General physical condition of the patient, Vital signs: Heart rate, Respiratory rate, temperature, height, and weight were noted. Examination of the upper and lower respiratory system, cardiovascular system, central nervous system, and vertebral system was performed. Airway assessment by Mallampati grading was done.

Investigations- Hemoglobin levels, total count, platelet count, random blood sugar, blood grouping, and others which were required were done.

Intra-operative:

Following surgical incision:

1. Time was noted (Time-0) and

Parameters:

I. Pulse rate(PR),

II. Systolic blood pressure(SBP),

III. Diastolic blood pressure(DBP),

IV. Mean Arterial pressure(MAP)

V. Oxygen saturation(SpO2)

were recorded at an interval of every 2 minutes (min) from Time-0 for the initial 60 min.

2. After that, at an interval of every 5 min, parameters were recorded till the end of surgery.

3. The ECG was continuously monitored on the display screen, and only the significant changes (if any) from the baseline were recorded under the heading of intraoperative complication.

4. All the patients were given the "test drug" 30 minutes before the completion of surgery after dividing them into two groups by computer-generated random number into:

I. **Group A:** (Paracetamol group): Patients received IV Paracetamol (15mg/kg)/100mL, 30min before completion of surgery over a period of 15min (rounded off to 1 g).

II. **Group B: (**Diclofenac group): patients received IV Diclofenac (1 mg/kg) diluted in 100 mL NS, 30 min before completion of surgery over a period of 15 min (rounded off to 75 mg).

5. Duration of surgery and the type of surgical procedure done was recorded.

6. Intra-operative complications, e.g., fall in SpO2 < 90%, significant ECG changes, etc., was noted.

Postoperative:

1. After completing the surgery, the patient was shifted to the postoperative recovery ward without prescribing any analgesics in any form, either from the anesthesia or surgical side. The patient was monitored till complete recovery from general anesthesia confirmed.

2. Once fully recovered, the patient was shifted to the ward with postoperative instruction for analgesia and other post-anesthesia instructions.

3. In the postoperative period

- Pulse Rate
- Systolic Blood Pressure
- Diastolic Blood Pressure
- Mean Arterial Pressure
- Respiratory Rate

were recorded at 2hr, 4hr, 6hr, 12hr, and 24hr in the postoperative period.

4. VAS score was recorded at the same interval as mentioned above. Reading was taken as follows:

The scale consists of a line measuring 10 centimeters anchored at one end by a label as “no pain” and at the other extreme by a label such as “the worst pain imaginable” or “pain as bad as can be." The patients were simply asked to mark the line to indicate pain intensity in relation to 0 (no pain) to 10 (worst possible pain). The result was interpreted as a distance in centimeter (cm) between 0 to the point marked by the patient.

INTERPRETATION:

1. **Pain Assessment:**

   - Mild pain was considered when the VAS score was between 1 and 3;
   - Moderate pain when VAS Score was between 4 and 6
   - Severe pain was recorded when the VAS Score was > 7.

2. **Postoperative Rescue Analgesia:**

The first dose of postoperative rescue analgesia was given when a VAS score of 7-10 was recorded or on-demand by the patient (whichever is earlier) and repeated if required. Rescue analgesia used was Inj. Tramadol hydrochloride

50mg slow IV whenever needed. Any complication/complaint (if any) like nausea and vomiting, pruritus, sedation, RR <10 per minute or any other abnormal findings were recorded.

3. **Division of cases:**

Patients were divided on type of surgery into:

a) H&N: Patients who underwent head and neck surgeries who received either diclofenac or paracetamol.

b) OAS: Patients who underwent open abdominal surgery who received either diclofenac or paracetamol.

c) LAS: Patient who underwent laparoscopic abdominal surgery who received either diclofenac or paracetamol.

d) OS: Other miscellaneous surgeries.

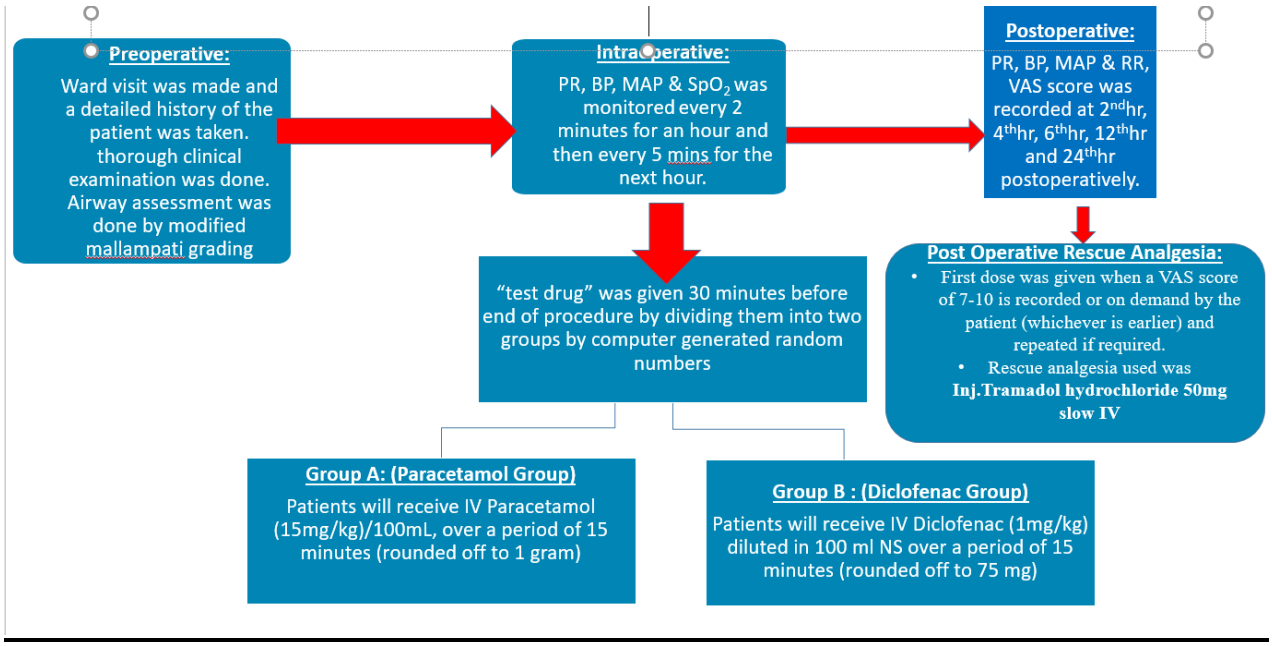


Figure 15: Methodology

RESULTS

200 cases were taken in total, with 98 cases receiving diclofenac and 102 receiving paracetamol according to the inclusion and exclusion criteria.

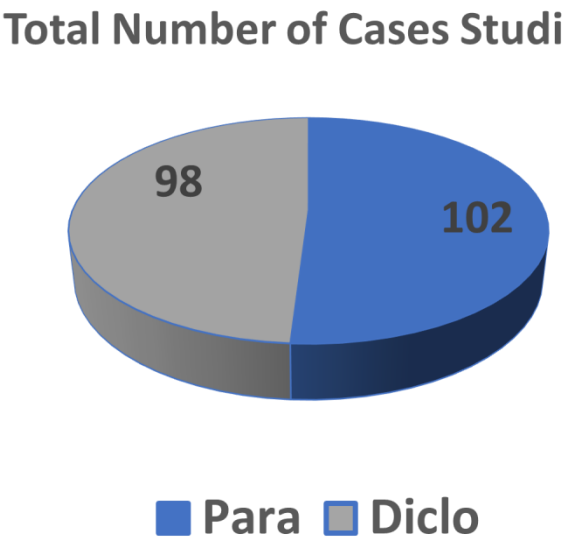


Chart 1: Total number of cases.

The age distribution and weight distribution of patients included in this study are given in Table 5 & 6.

Age Distribution (years)	Para	Diclo
Mean	38.176	35.796
SD	14.702	14.920
P value		0.1136

Table 5: Age distribution.

Weight Distribution (kgs)	Para	Diclo
Mean	59.521	58.082
SD	15.624	10.773
P value		0.1390

Table 6: Weight Distribution

Out of the total 102 cases given paracetamol 35 underwent head and neck surgery, 26 underwent laparoscopic abdominal surgery, 22 underwent open abdominal surgery and 19 underwent other miscellaneous surgeries.

Out of the 98 cases who received Diclofenac 33 underwent head and neck surgery, 24 underwent laparoscopic abdominal surgery, 20 underwent open abdominal surgery and 21 underwent other miscellaneous surgery.

The distribution of cases for each type of surgery for paracetamol and diclofenac are given in Chart 2 and 3 and overall distribution is given in Graph 1.

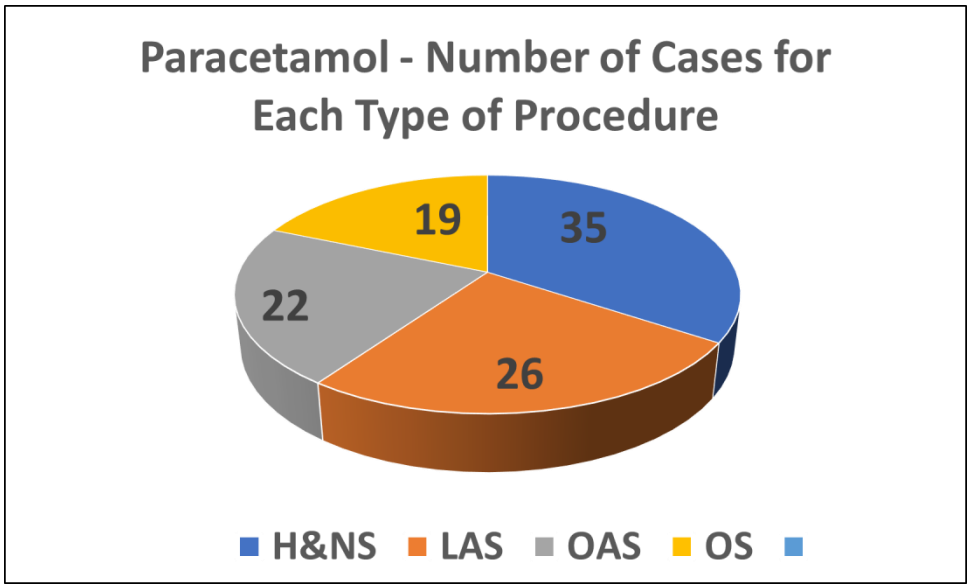


Chart 2: Distribution of cases for Paracetamol.

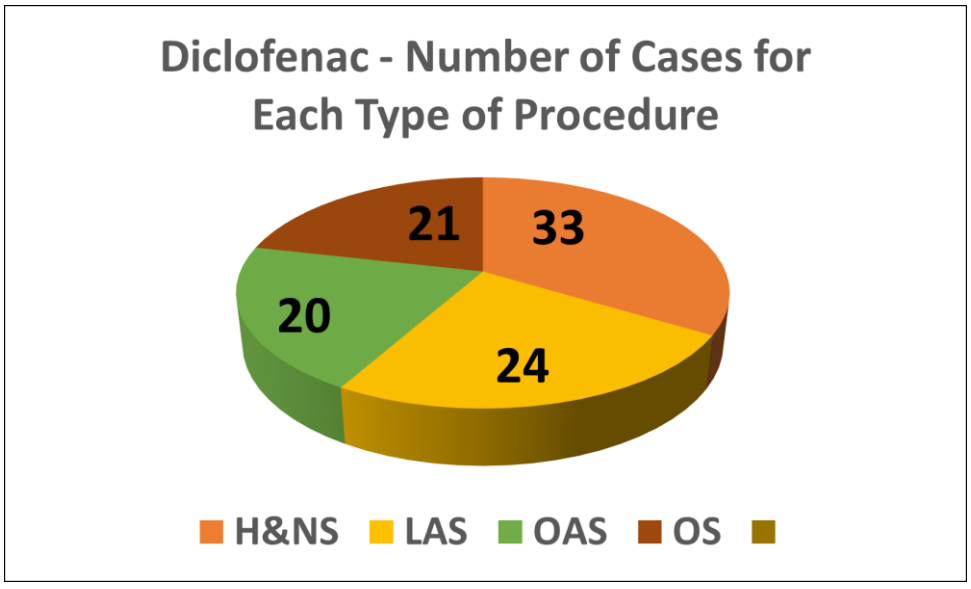
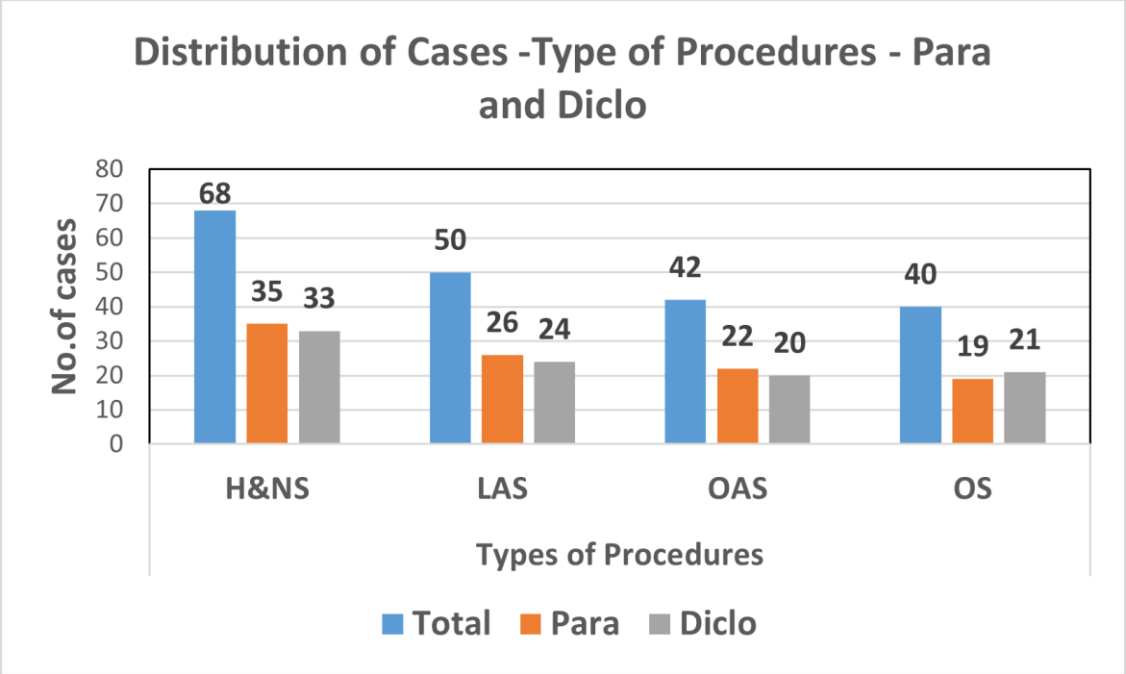
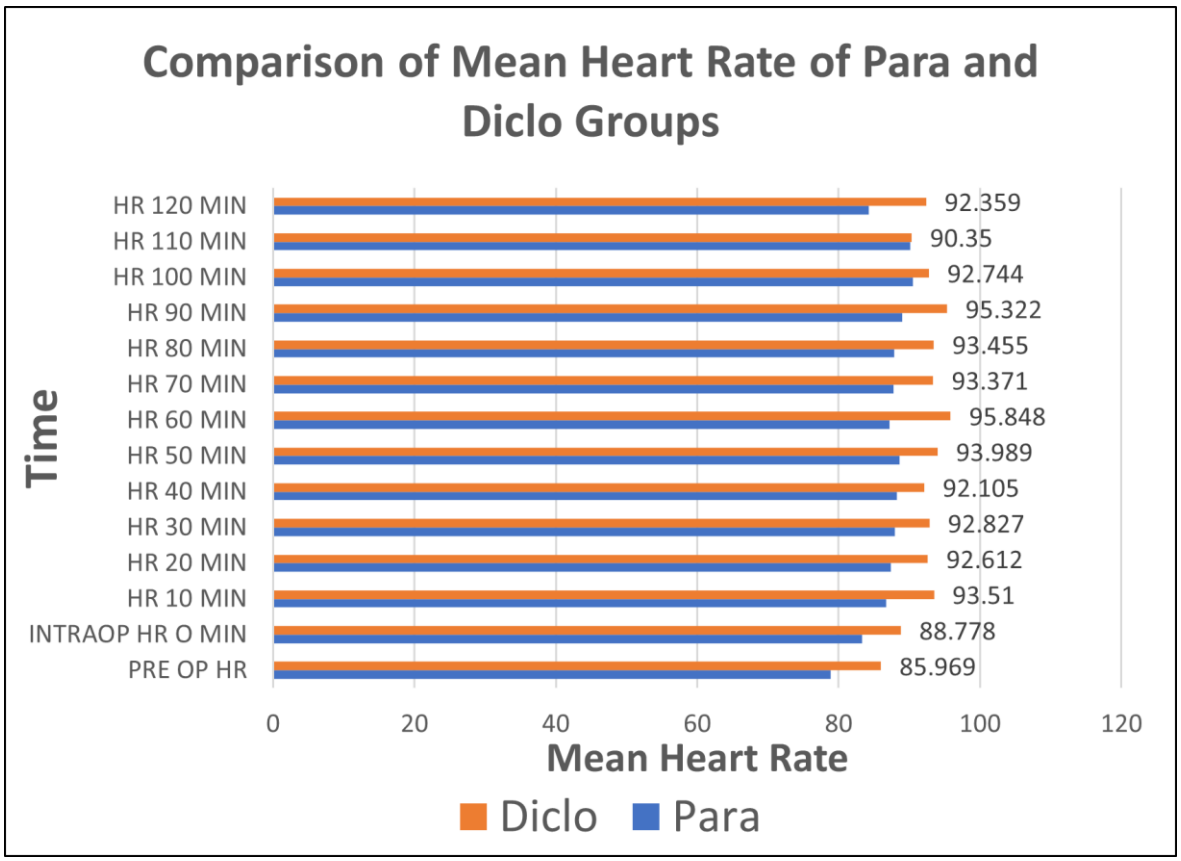


Chart 3: Distribution of cases for Diclofenac.

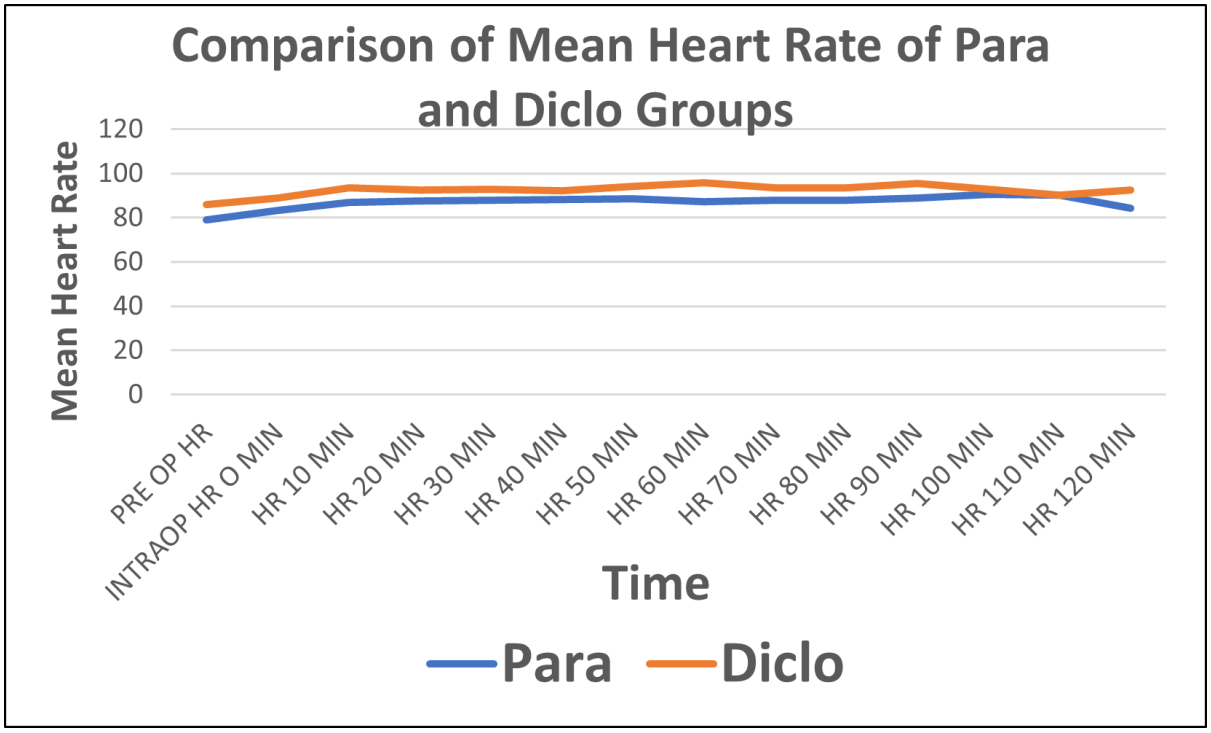


Graph 1: Overall distribution of cases between diclofenac and paracetamol.

The hemodynamic comparison between the 2 agents showed no statistical significance. A comparison of Mean heart rate for the two agents is shown in Graph 2 and 3 and Table 7.



Graph 2: Comparison of Mean Heart Rate.

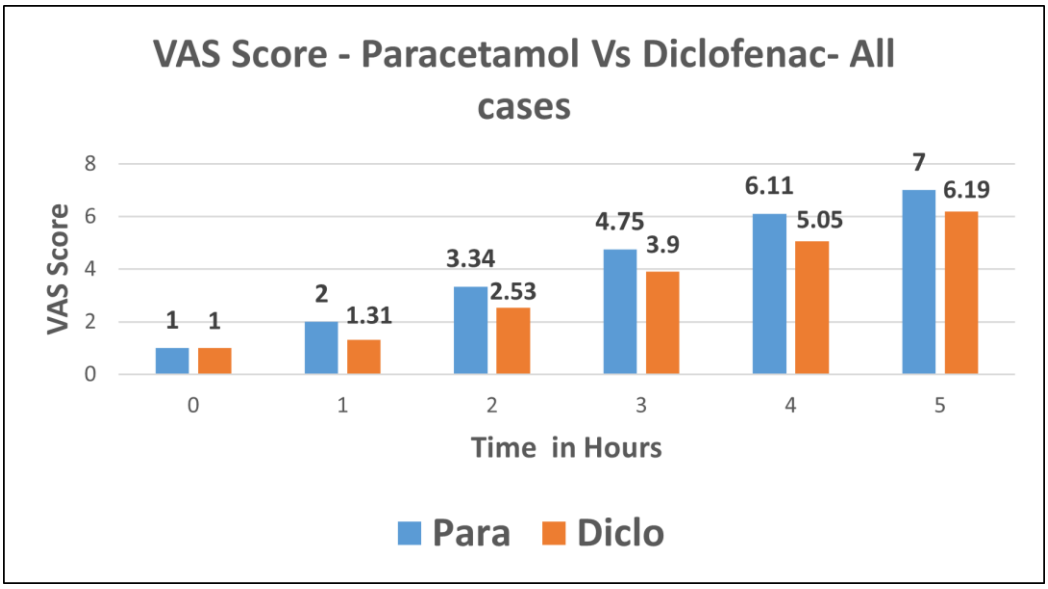


Graph 3: Comparison of Mean Heart Rate.

HR	PARACETAMOL			DICLOFENAC		
	N	Mean	Std. Deviation	N	Mean	Std. Deviation
PRE OP HR	102	78.902	10.897	98	85.969	10.200
INTRAOP HR O MIN	102	83.333	11.677	98	88.778	12.842
HR 10 MIN	102	86.755	13.728	98	93.510	12.482
HR 20 MIN	102	87.402	13.843	98	92.612	8.997
HR 30 MIN	102	87.922	14.635	98	92.827	9.962
HR 40 MIN	97	88.277	12.977	95	92.105	11.999
HR 50 MIN	84	88.619	13.678	92	93.989	11.604
HR 60 MIN	84	87.190	12.665	92	95.848	15.293
HR 70 MIN	74	87.757	13.200	67	93.371	13.631
HR 80 MIN	74	87.838	13.989	66	93.455	13.792
HR 90 MIN	74	88.988	13.451	59	95.322	12.495
HR 100 MIN	43	90.465	9.787	43	92.744	10.086
HR 110 MIN	42	90.143	12.019	40	90.350	9.281
HR 120 MIN	35	84.229	9.277	39	92.359	9.446

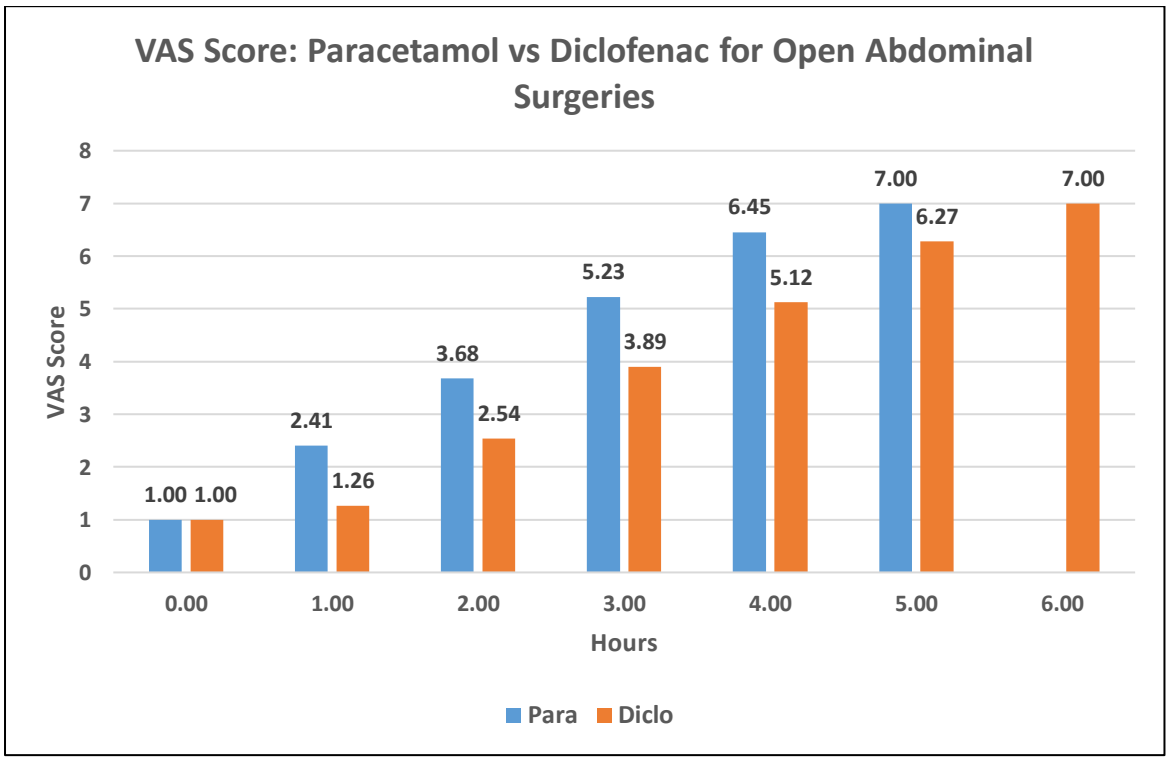
Table 7: Comparison of Heart rates.

The VAS score comparisons were as follows:



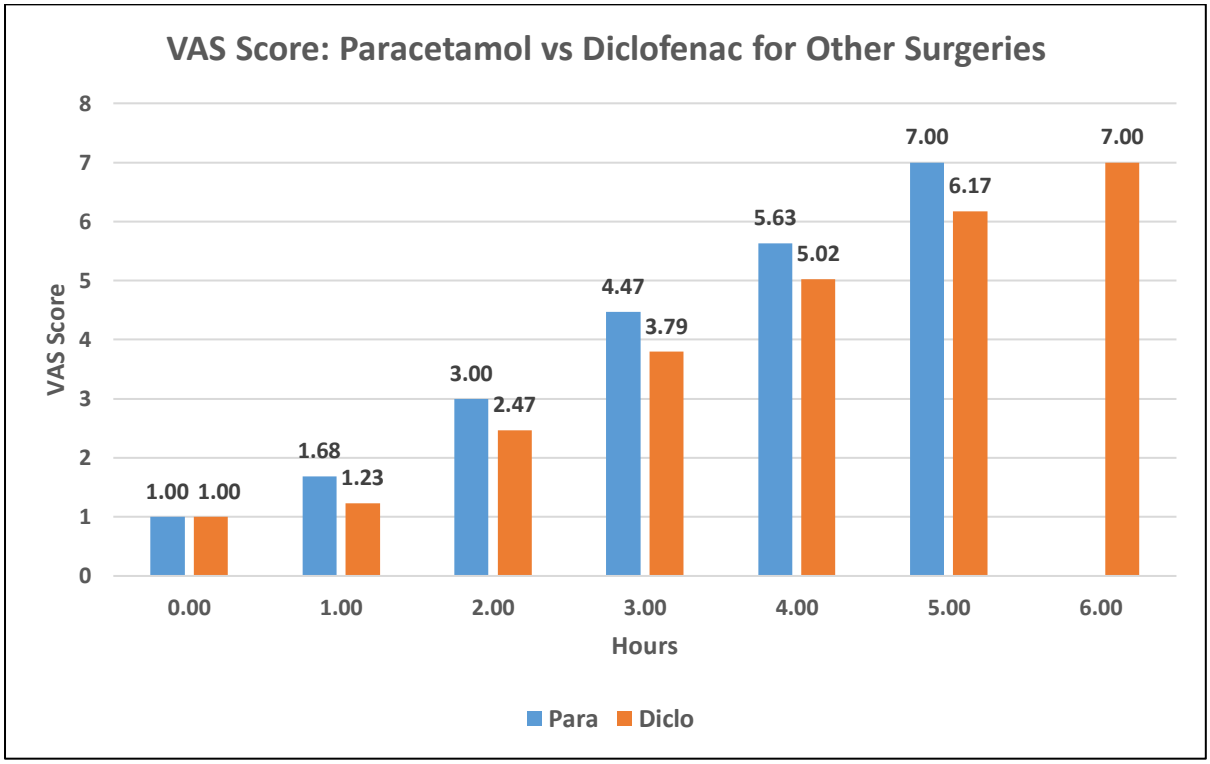
Graph 4

As seen in graph 4, Diclofenac showed significantly lower values for VAS score in 2nd, 3rd, 4th and 5th hour post-operatively with a p value of 0.0024 which is statistically significant.



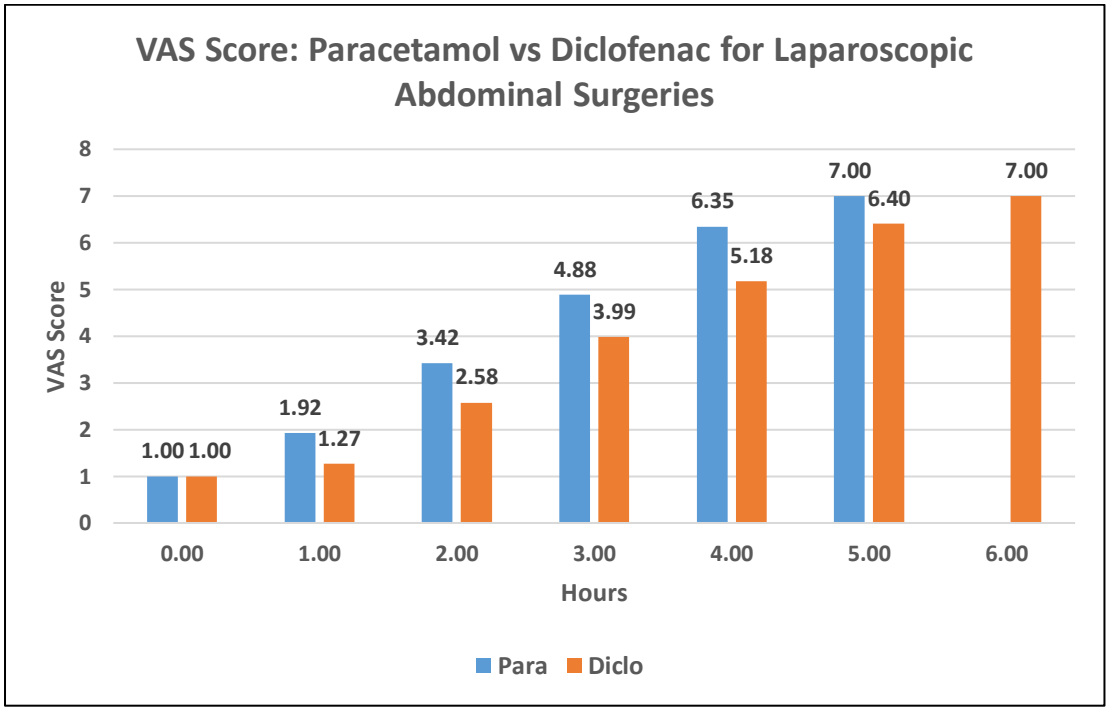
Graph 5

As shown in graph 5, VAS score for Open abdominal surgeries was significantly lower in Diclofenac group when compared to paracetamol group with a p-value of 0.006.



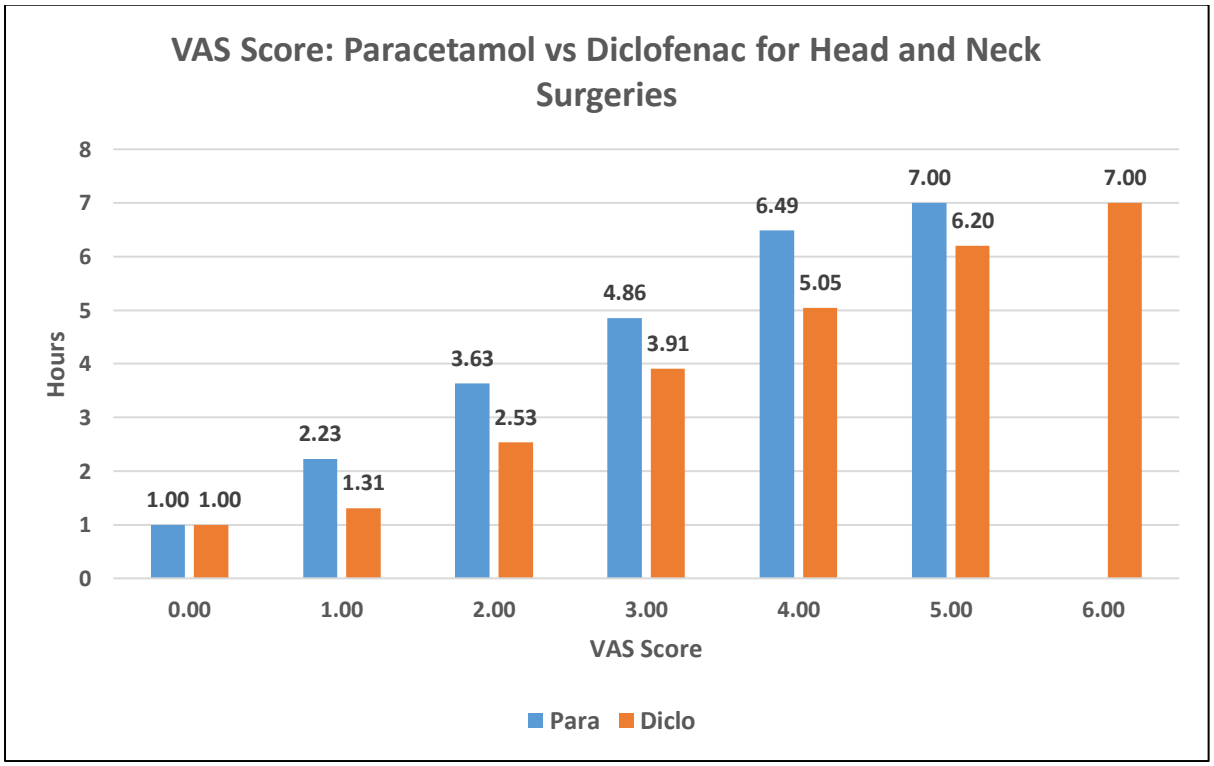
Graph 6

In graph 6 we can see that Diclofenac also showed significantly lower VAS scores for other miscellaneous surgeries when compared to paracetamol with a p-value of 0.0024, giving analgesic efficacy for upto 6 hours in some instances.



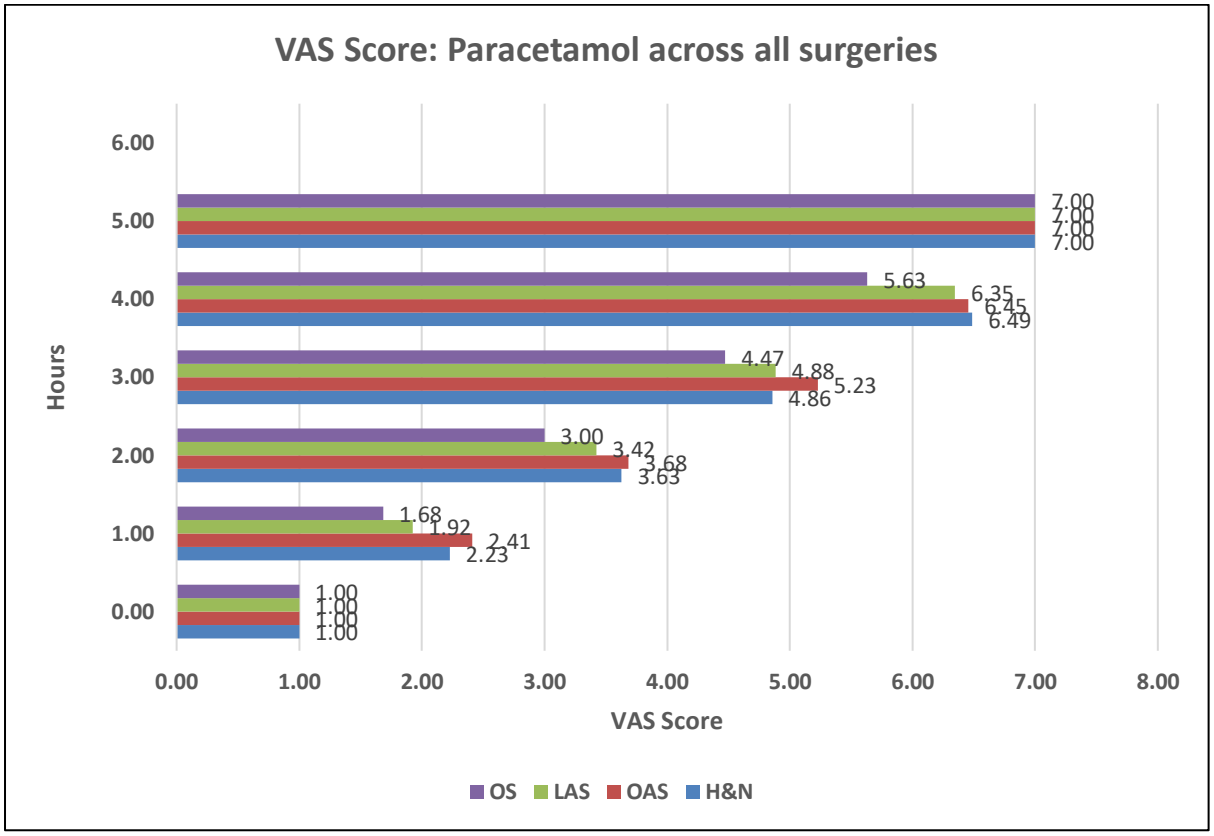
Graph 7

As seen in graph 7, Even for laparoscopic abdominal surgeries diclofenac showed better post-operative analgesic efficacy than paracetamol with a p value of 0.004.



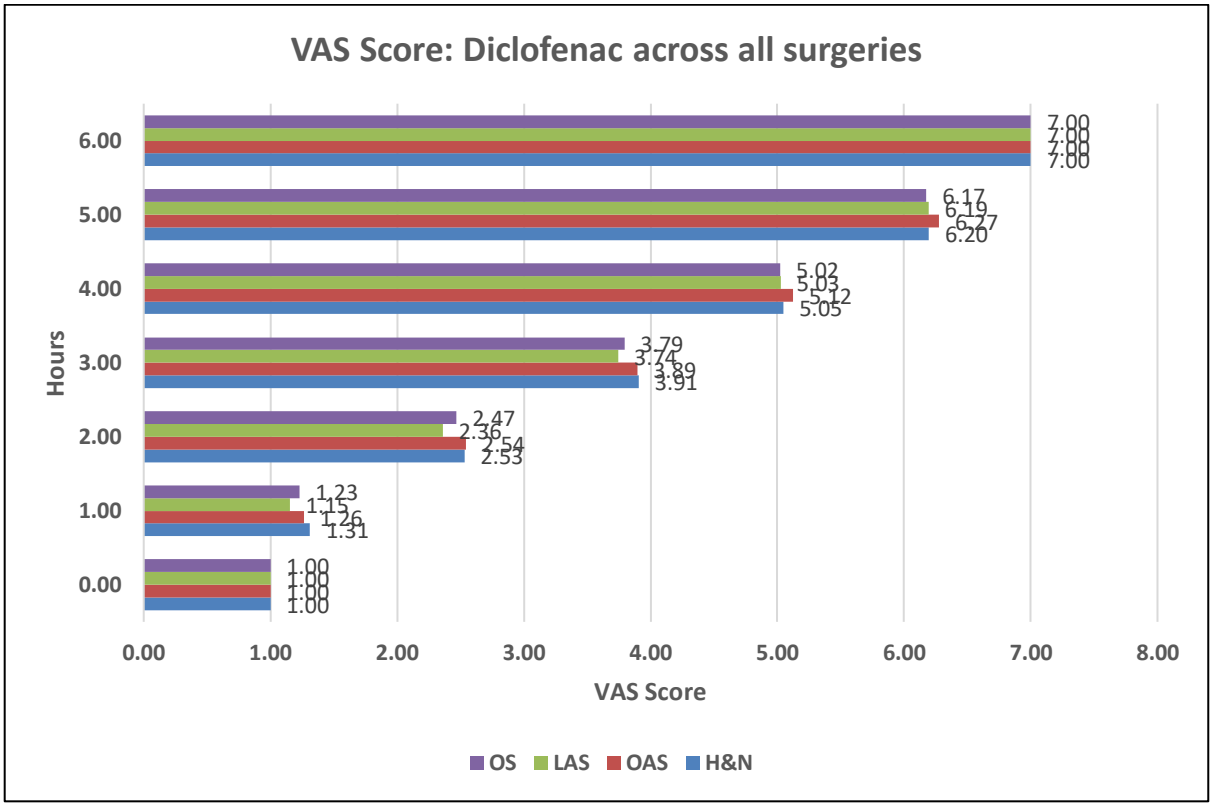
Graph 8

As seen in Graph 8, Diclofenac also showed better analgesic efficacy than paracetamol for Head and neck surgeries as well with a p-value of 0.003.



Graph 9

Overall Paracetamol showed best analgesic efficacy for other miscellaneous surgeries followed by laparoscopic abdominal surgeries followed by head and neck surgeries. It showed the worst efficacy for Open abdominal surgeries (Graph 9).



Graph 10

As seen in Graph 10, Diclofenac showed best analgesic efficacy for laparoscopic abdominal surgeries followed by other surgeries then by head and neck surgeries. Worst efficacy was again seen with Open abdominal surgeries.

The p-values and their significance is shown in table 8.

p value indicating Significance of better Performance of Diclofenac when compared to Paracetamol		
Type of Surgery	P value	Significant or not
H&N	0.003	Significant
LAS	0.004	Significant
OAS	0.006	Significant
OS	0.0024	Significant
All cases Combined	0.0024	Significant

Table 8

DISCUSSION

The importance of adequate post-surgical pain relief has been known to man for a long time. Inadequate pain relief is related to tachycardia, increased cardiac workload, higher oxygen demand and rise in sympathetic outflow. In the post-operative period this can lead to mental and physical harm and may therefore affect the response of the patient to the surgical treatment provided. It may also affect the patients assurance that the treatment is truly alleviating the morbidity caused by the disease. Post-surgical pain management can be achieved with the use of NSAIDs for mild to moderate pain and also reduce the use of opioid agents which can cause unwanted adverse effects. Thus it is commonly used as a part of the multi-modal approach to post-operative pain alleviation.

The main objective of our study was to assess the effectiveness of parenteral paracetamol in comparison to parenteral diclofenac for alleviation of post-operative algesia, while also studying the magnitude of opioid sparing which can be achieved with each agent for the same. We also compared this for different types of procedures namely laparoscopic abdominal surgeries, open abdominal surgeries, head and neck surgeries and other miscellaneous surgical procedures as a secondary goal.

In an attempt to compare the effectiveness of parenteral paracetamol vs diclofenac for post-surgical pain management after laparoscopic gall bladder excision, **Pinar durak et al**[67] divided 40 patients into 2 groups of 20 and administered parenteral paracetamol (1gm) and parenteral diclofenac sodium (75mg) 15 minutes before end of surgery. They found that the pain scores were noticeably higher in the paracetamol group than diclofenac group which matches our hypothesis. They also concluded that paracetamol should not be used as a sole agent and be used in

conjunction with opioids to provide adequate post-operative pain relief. **Debashish paul et al.**[70] in the year 2015 attempted to prove that NSAIDs can be used as a solo class of analgesic agents by first administering diclofenac 75mg 30 minutes before end of the laparoscopic cholecystectomy followed by 8th hourly administration of intravenous paracetamol 1gm IV in half of the 68 patients involved in the study, while the other half only received only diclofenac and found that concomitant dosage of the two agents provided better analgesia than just diclofenac.

In the year 2016 **Anka Amin etal.**[71] further compared the 2 agents when used alone for post-op pain management and found that paracetamol provided better safety margins and hemodynamic stability, while also providing adequate analgesia for up to 5 hours post-surgery. These contradicting studies brings about the need for a comparative study to assess the efficacy of these 2 agents in different type of surgeries including minimally invasive laparoscopic surgeries.

In the same year the research publication 'Comparison between IV Paracetamol and Tramadol for Postoperative Analgesia in Patients Undergoing Laparoscopic Cholecystectomy' conducted by **Suhail Bandey et al.**[63] aimed to compare tramadol and paracetamol when used for post-op pain releif and found that parenteral paracetamol provided superior pain relief when compared to tramadol. Another research paper 'A comparative study of intravenous paracetamol and intravenous tramadol for postoperative analgesia in laparotomies' published by **Mohammed Shahid et al.**[72] came to the same conclusion.

In 2018, recognizing the need of further research and comparison of paracetamol and diclofenac for laparoscopic surgeries, **Malaya Kumar Patel et al.**[4] compared intravenous paracetamol and intravenous diclofenac in a prospective double blinded study and found that Diclofenac had a slight edge over paracetamol when it came to

efficacy of post-surgical analgesia in laparoscopic surgeries. A similar study was conducted in the same year with a larger sample size by **Kalpana Kharbuja et al.**[3] who contradicted **Malaya Kumar Patel et al.'s** study by stating that parenteral paracetamol had better and extended analgesic efficacy than parenteral diclofenac, with drastically lesser necessity for rescue opioids, for laparoscopic abdominal surgeries. This can probably be attributed to the difference in institutional protocols for multimodal post-surgical pain management.

2 further studies in 2019 by **Anurag Bijalwan et al.**[75] and **Pallavi Kainth et al.**[76] further contradicted **Malaya Kumar Patel et al.'s** study by stating that parenteral paracetamol provided better analgesia and lesser requirement for additional analgesia with opiods.

The latest in the series of research papers studying intravenous analgesic agents for laparoscopic surgeries is 'Postoperative analgesia after laparoscopic cholecystectomy by preemptive use of intravenous paracetamol or ketorolac: A comparative study' published by **Bhawana Rastogi et al.**[52] In this study they found that pre-emptive administration of parenteral ketorolac provided better analgesia and hemodynamic stability than parenteral paracetamol.

Yoganarasimha et al.[68] in 2012 sought to compare the adequacy of intravenous diclofenac versus paracetamol as an analgesic agent to provide intra and post-operative pain relief after abdominal surgeries in the lower segment. After studying 60 patients divided equally into 2 groups and administering one of the agents for one group and the other agent for the second group, they came to the conclusion that paracetamol was more efficacious than diclofenac.

In 2017, **Swati Chougule et al.**[6] studied the potency of IV Paracetamol versus IM Diclofenac for post-surgical pain and post-spinal headache when used pre-

emptively after spinal anaesthesia and found that IV paracetamol provided superior potency while also reducing adverse effects , when compared to diclofenac post-spinal for lower abdominal operations.

Meeting the need for further study into the comparative efficacy of the two agents, a study was conducted by **Pratyush Goel et al.**[(11)] where he divided 60 patients undergoing various surgical procedures into groups of 30 each receiving either intravenous paracetamol 1gm or intravenous diclofenac 75mg half an hour before inducing general anaesthesia following standard protocols. At the end of the study he observed that analgesia provided by paracetamol lasted for around 4 hours while that provided by diclofenac was close to 5hrs. No differentiation of type of surgery was done although it was warranted.

Vinishdharma Thenarasu et al.[(73)] compared diclofenac and paracetamol administered enterally to find the superior drug analgesically for providing post-op analgesia after tooth extraction. At the end of the study they found that diclofenac is more efficacious than paracetamol in this aspect probably due to absence of peripheral cyclo-oxygenase enzyme inhibition by paracetamol.

In the year 2019, **Sharda A Agrawal et al.**[(77)] published a study comparing the potency of parenteral paracetamol versus diclofenac for post-surgical analgesia in open abdominal obg surgeries by dividing a group of 100 patients into 2 equal parts. One half got parenteral paracetamol while the other half were administered parenteral diclofenac every 6 hours for 2 days initiated at 2 hours post-op. She observed diclofenac provided better analgesia at 24hrs and 48hrs post-surgery, although the side effects were more with diclofenac.

In the same year a prospective random study with double blinding was conducted to

compare the potency of intravenous diclofenac when compared to paracetamol for various surgeries, conducted under general anaesthesia, lasting less than 2 hours by **Ushma D Shah et al.**[79] A sample size of 120 meeting the inclusion and exclusion criteria were selected and divided into 2 equal groups of 60. One group received parenteral paracetamol while the other received diclofenac. At the end of the study they noted that no significant variation was there between the VAS score of the 2 groups. This can be attributed to the bias in number of cases based on type of surgery, wherein more general surgeries (n=29) and miscellaneous surgeries(n=9) were taken for paracetamol group while more ENT cases (n=39) were taken for diclofenac group.

Poonam Bisht et al.[78] in the year 2021 conducted a study comparing the efficacy of IV paracetamol and IM diclofenac for post-surgical analgesia after abdominal hysterectomy which was prospective and observational. A group of 120 patients undergoing open abdominal hysterectomy were randomized into 2 groups of 60, one group receiving IV paracetamol followed by 8^{th} hourly repeat doses for 48 hrs, while another received IM diclofenac 8^{th} hourly for 48 hours. From the results it was found that IV paracetamol provided more efficacious post-surgical analgesia and required lesser rescue administration of opioid agents.

During the same year **Muneer Jan et al.**[80] conducted a study to compare the efficacy of these 2 agents when used pre-emptively in orthopedic surgeries. A sample size of 100 patients undergoing orthopedic procedures of the upper appendage were divided into 2 equal groups and were given either parenteral paracetamol or diclofenac 30 mins before skin incision. In this study it was found that diclofenac was a more efficacious, equally safe and economical analgesic agent in comparison to paracetamol when used pre-emptively.

In the same year **Sanum Kashif et al.**[74] published a paper 'Pre-emptive effect of intravenous paracetamol versus intravenous ketorolac on post-operative pain and shivering after septoplasty under general anesthesia: A comparative study' in which it was found parenteral paracetamol had superior analgesic effects when compared to ketorolac.

These contradicting statements by the aforementioned studies bring about a requirement for a study comparing the efficacy of diclofenac versus paracetamol for post-operative pain management. Furthermore, it is clearly seen that the efficacy of the two drugs have to be assessed and compared for different types of surgeries, while also determining the requirement of rescue opioid agent. Therefore, we have conducted this study comparing the analgesic efficacy of parenteral paracetamol and diclofenac when used in different types and anatomical areas of surgeries.

SUMMARY AND CONCLUSION

SUMMARY:

The purpose of this study was to assess the analgesic efficacy of parenteral paracetamol versus diclofenac for post-surgical anaesthesia when used as a pre-emptive agent. The study involved 200 adults in the ASA I and ASA II classes, ranging in age from 18 to 60 years, who were undergoing various surgeries under general anaesthesia. Patients were randomly divided into two group. Group A (Paracetamol group, n=102), Group B (Diclofenac group, n=98). Group A (Paracetamol group): Patients received 1gm IV paracetamol half hour before end of surgery. Group B (Diclofenac): Patients received 75 mg of Diclofenac IV half hour before end of surgery. The VAS score was used to assess postoperative pain at 0, 1st, 2nd, 3rd, 4th, 5th and 6th hour post-surgery. Diclofenac provided better post-operative analgesia when compared to paracetamol, which was statistically significant with a p value of 0.0024. Hemodynamically no differences were seen between the 2 groups. There were no adverse events reported during the study period. Diclofenac is seen to provide better post-operative analgesia when compared to paracetamol across various surgical procedures performed under general anaesthesia.

CONCLUSION:

This present study had shown that Diclofenac (75mg) and Paracetamol (1gm) were found to give good post-operative pain management when used as a pre-emptive agent parenterally for various surgeries conducted under general anaesthesia, resulting in improved recovery and faster discharge from hospital. In both groups, there were no notable adverse events in the post-operative period. The use of parenteral diclofenac was linked to a shorter stay in the hospital with longer duration of analgesia. Parenteral diclofenac and paracetamol are both effective pre-emptive analgesic agents for post-operative analgesia in adults undergoing various operations under general anaesthesia, according to study findings. The diclofenac group, on the other hand, had a much longer duration of analgesia and better recovery post-anaesthesia. This study can conclude from findings that diclofenac and paracetamol, when used as a pre-emptive analgesic agent, are safe alternatives to opioids. More large-scale research may be required to determine the best pre-emptive analgesic and dosage.

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BIBLIOGRAPHY

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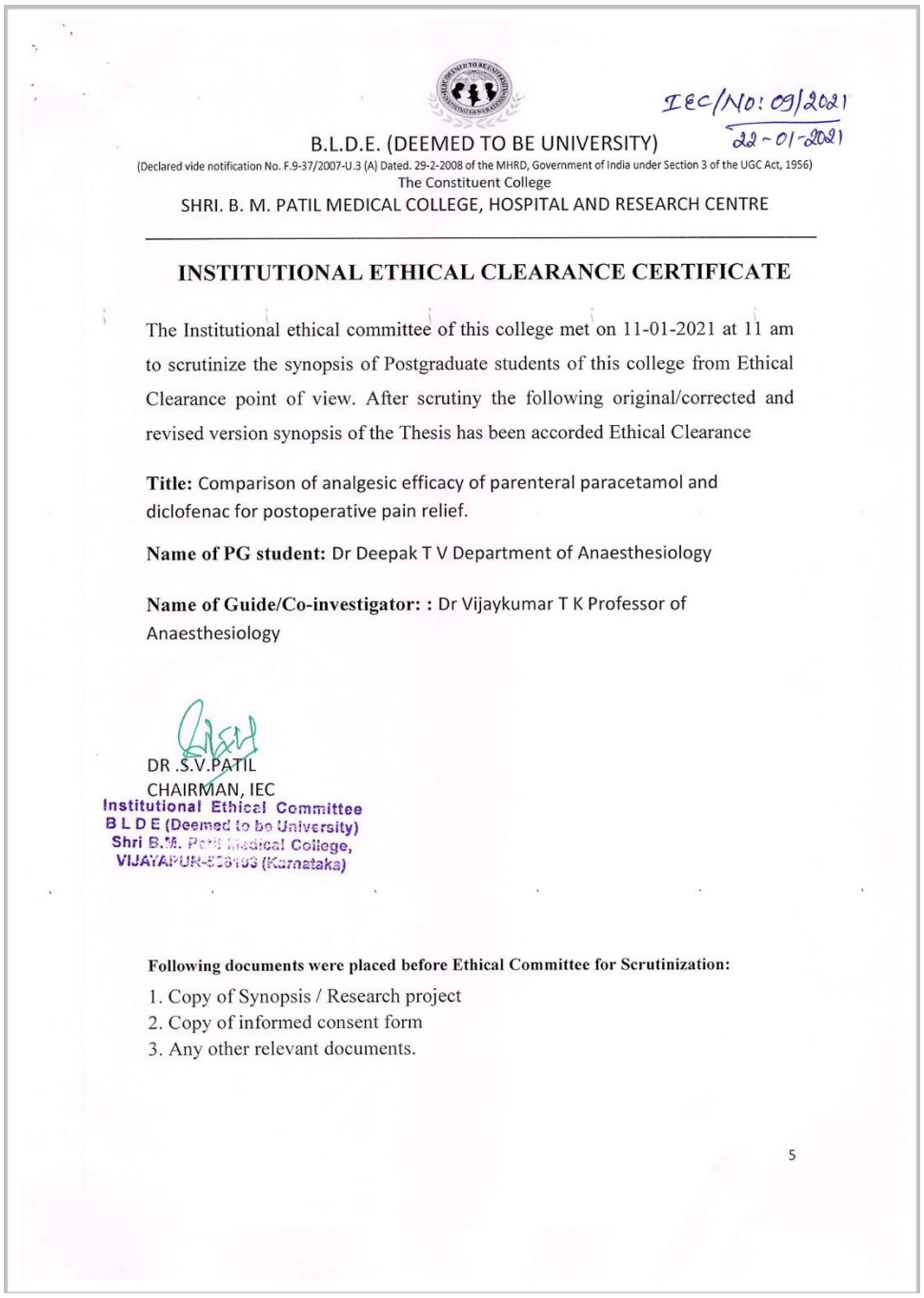
ANNEXURES

ANNEXURE I

ETHICAL CLEARANCE CERTIFICATE



IEC/No: 09/2021
22-01-2021

B.L.D.E. (DEEMED TO BE UNIVERSITY)
(Declared vide notification No. F.9-37/2007-U.3 (A) Dated. 29-2-2008 of the MHRD, Government of India under Section 3 of the UGC Act, 1956)
The Constituent College
SHRI. B. M. PATIL MEDICAL COLLEGE, HOSPITAL AND RESEARCH CENTRE

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Institutional ethical committee of this college met on 11-01-2021 at 11 am to scrutinize the synopsis of Postgraduate students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected and revised version synopsis of the Thesis has been accorded Ethical Clearance

Title: Comparison of analgesic efficacy of parenteral paracetamol and diclofenac for postoperative pain relief.

Name of PG student: Dr Deepak T V Department of Anaesthesiology

Name of Guide/Co-investigator: : Dr Vijaykumar T K Professor of Anaesthesiology

DR .S.V.PATIL
CHAIRMAN, IEC
Institutional Ethical Committee
B L D E (Deemed to be University)
Shri B.M. Patil Medical College,
VIJAYAPUR-586103 (Karnataka)

Following documents were placed before Ethical Committee for Scrutinization:

1. Copy of Synopsis / Research project
2. Copy of informed consent form
3. Any other relevant documents.

5

ANNEXURE II

PLIGARISM CERTIFICATE

20BMANS005-DEEPAK-COMPARISON BETWEEN ANALGESIC EFFICACY OF PARENTERAL PARACETAMOL AND DICLOFENAC FOR POSTOPERATIVE PAIN RELIEF

ORIGINALITY REPORT

6%	5%	4%	2%
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ANNEXURE – III

SAMPLE INFORMED CONSENT FORM:

B.L.D.E.(DU) SHRI B.M. PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE, VIJAYAPUR – 586103, KARNATAKA

TITLE OF THE PROJECT : “”

PRINCIPAL INVESTIGATOR : Dr. DEEPAK T V
Post graduate,
Department of Anaesthesiology
deepak.bmw2012@gmail.com

P. G. GUIDE : Dr. Vijaykumar T Kalyanagopal
Professor,
Dept of Anaesthesiology, B.L.D. E(DU)
Shri B.M. Patil Medical College Hospital
Vijapur

PURPOSE OF RESEARCH

I have been informed that this study is “A COMPARATIVE STUDY OF FENTANYL AND DEXMEDETOMIDINE AS ADJUVANTS TO LEVOBUPIVACAINE FOR CAUDAL ANALGESIA IN CHILDREN UNDERGOING INFRA UMBILICAL SURGERIES”

I have been well explained in the language I best understand about the procedure, purpose of the study, effects and possible adverse effects of the drugs by the doctor. I hereby voluntarily give my consent for the participation of my child in the study. I have been explained that I have the right to withdraw the participation of my child from the study at any point I want. And the treatment of my child will not be changed from the standard treatment being followed in the hospital for the denial of participation in the study.

I allow the clinical information related to my child to be used for research and academic purpose. I have been explained that my child's name and identity was concealed throughout the process and the clinical information related to my child will not be shared with or given to anyone except _____ and the concerned clinician.

I have been well explained that I will not be provided with any incentives or compensation in any form for the participation of my child in this study.

I have been explained about the reason for doing this study and selecting me/my ward as a subject for this study. I have also been given free choice for either being included or not in the study.

CONFIDENTIALITY:

I understand that medical information produced by this study was come a part of this Hospital records and was subjected to the confidentiality and privacy regulation of this hospital. If the data are used for publication in the medical literature or for teaching purpose, no names was used and other identifiers such as photographs and audio or

video tapes was used only with my special written permission. I understand that I may see the photograph and videotapes and hear audiotapes before giving this permission.

REQUEST FOR MORE INFORMATION:

I understand that I may ask more questions about the study at any time. Dr. DEEPAK T V is available to answer my questions or concerns. I understand that I was informed of any significant new findings discovered during the course of this study, which might influence my continued participation.

If during this study, or later, I wish to discuss my participation in or concerns regarding this study with a person not directly involved, I am aware that the social worker of the hospital is available to talk with me.

And that a copy of this consent form was given to me for careful reading.

REFUSAL OR WITHDRAWL OF PARTICIPATION:

I understand that my participation is voluntary and I may refuse to participate or may withdraw consent and discontinue participation in the study at any time without prejudice to my present or future care at this hospital.

I also understand that Dr. DEEPAK T V will terminate my participation in this study at any time after he has explained the reasons for doing so and has helped arrange

for my continued care by my own physician or therapist, if this is appropriate

INJURY STATEMENT:

I understand that in the unlikely event of injury to me/my ward, resulting directly due to my participation in this study, such injury was reported promptly, then medical treatment would be available to me, but no further compensation was provided.

I understand that by my agreement to participate in this study, I am not waiving any of my legal rights.

I have explained to _____ the purpose of this research, the procedures required and the possible risks and benefits, to the best of my ability in patient's own language.

Patient's Name: Age/Sex:

Parents name:

Date: DR. DEEPAK T V

(Investigator)

Signature of the Parents:

Name:

Relation:

Address: Witness to above signature

Phone Number:

STUDY SUBJECT CONSENT STATEMENT:

I confirm that **Dr. DEEPAK T V** has explained to me the purpose of this research, the study procedure that I will undergo and the possible discomforts and benefits that I may experience, in my own language.

I have been explained all the above in detail in my own language and I understand the same. Therefore, I agree to give my consent to participate as a subject in this research project.

_____ _____

(Parent) Date

_____ _____

(Witness to above signature) Date

ANNEXURE IV

SCHEME OF CASE TAKING

PROFORMA

STUDY: COMPARISON OF ANALGESIC EFFICACY OF PARENTERAL PARACETAMOL AND DICLOFENAC FOR POSTOPERATIVE PAIN RELIEF

Patient Details
Name Age Sex Height weight
Ward Group allotted by randomization: A/B

Diagnosis
Surgical procedure

Past History

General physical examination:
Pallor icterus cyanosis clubbing lymphadenopathy edema

Mallampatti Grade:
Vital parameters:
Pulse blood pressure respiratory rate temperature
Systemic Examination
CVS
RS
CNS
PA
Investigations
Hemoglobin: TLC: Platelet count:
Urine routine: HIV: HbsAg:
ASA grade
Parameters:

TYPE OF SURGERY	GROUP A Paracetamol Group		GROUP B Diclofenac Group	
	n	**%**	**n**	**%**
ENT				
General Surgery				
Obstetrics				
Orthopedics				
Others				

VAS Scoring

	GROUP A		GROUP B		**t-test P**	**Significance**
	Mean	**SD**	**Mean**	**SD**		
VAS_0 h						
VAS_1 h						

VAS_2 h						
VAS_3 h						
VAS_4 h						
VAS_5 h						
VAS_6 h						

Intraoperative Parameters 1st hour

Parameters→ Time	Pulse Rate	Blood Pressure	Mean Arterial Pressure	SpO2	Respiratory Rate
0 mins					
2 mins					
4 mins					
6 mins					
8 mins					
10 mins					
12 mins					
14 mins					
16 mins					
18 mins					
20 mins					
22 mins					
24 mins					
26 mins					
28 mins					
30 mins					
32 mins					
34 mins					
36 mins					
38 mins					

40 mins					
42 mins					
44 mins					
46 mins					
48 mins					
50 mins					
52 mins					
54 mins					
56 mins					
58 mins					
60 mins					

Intraoperative Parameters after 1 hour

Parameters→ Time	Pulse Rate	Blood Pressure	Mean Arterial Pressure	SpO2	Respiratory Rate
5th minute					
10th minute					
15th minute					
20th minute					
25th minute					
30th minute					
35th minute					
40th minute					
45th minute					
50th minute					
55th minute					
60th minute					

Parameters→ Time	Pulse Rate	Blood Pressure	Mean Arterial Pressure	Respiratory Rate
2nd hour				
4th hour				
6th hour				
12th hour				
24th hour				

BIO-DATA

Guide Name: Dr. Vijaykumar T Kalyanappagol
Date of Birth: 08/09/1964
Education: MBBS from M R Medical College Kalaburgi
M D from Shri BMPATIL Medical college vijayapur
D A from JN Medical College Belgaum
Designation: Professor in Anesthesiology

Teaching: Total work experience 29 years
PG teaching 20 years
PG guide 10 years
Address: Plot No.43, Basaveshwar Nagar, Opposite BLDE Hospital, Ashram Road,
Vijayapura.

INVESTIGATOR

Name: Dr. Deepak Thekkumpurathe Varrieth
Qualification: MBBS from Shri Sathya Sai Medical College & RI, Kancheepuram

Registration No.: 119479
Address: GA, Abhirami Shruthilaya, No.42, 28th cross street, Indiranagar, Adyar,
Chennai- 600020

ANNEXURE VI

MASTER CHART