COMPARISON OF ANALGESIC EFFECT OF SUBCUTANEOUS BUPIVACAINE INFILTRATION AND INTRAVENOUS DICLOFENAC VS. INTRAVENOUS DICLOFENAC ALONE IN INGUINAL HERNIOPLASTY: A RETROSPECTIVE, SINGLE CENTRE STUDY IN GAZA

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UNIVERSITI SAINS MALAYSIA

2023

COMPARISON OF ANALGESIC EFFECT OF SUBCUTANEOUS BUPIVACAINE INFILTRATION AND INTRAVENOUS DICLOFENAC VS. INTRAVENOUS DICLOFENAC ALONE IN INGUINAL HERNIOPLASTY: A RETROSPECTIVE, SINGLE CENTRE STUDY IN GAZA

by

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Thesis submitted in fulfilment of the requirements
for the degree of
Master of Science

October 2023

ACKNOWLEDGEMENT

I would like to express our gratitude to Allah SWT for giving us the opportunity and helping us endlessly in finishing this project. Then I wish to record my thankfulness to my parents, brother, and sisters for their unstoppable support, and to those who assisted me in the completion of this work either by support or consultation. Also, I owe a great deal to my academic supervisor Dr. Fitreena Binti Amran. For her patience, careful direction, and never-ending support. To Dr. Abdrabou Alatrash who assisted me in the clinical aspects.

Special thanks to the loveliest and the closer to my heart, my parents, i would say that This work wouldn't have been possible without your support. My privileged brothers, you're the cornerstone that gave me the strength needed to keep success.

To my kind uncle Dr. Hassan Joudah. By having you as an uncle I consider myself extremely fortune. I hope you realize how much you are valuable for all of us.

I would like to extend a special thanks to the participants who gave us the time and the confidence, actually without their collaboration, this work could not have been undertaken. I would also like to acknowledge my great lecturers for their endless teaching of us the sciences and steps to success.

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LIST OF DEFINITIONS

Pain	The International Association for the Study of Pain defines pain as "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage," (Raja et al., 2020).
Anesthesia	Loss of feeling or sensation with or without loss of consciousness (Loeser, 2021).
General anesthesia	A drug-induced loss of consciousness during which patients are not arousal, even by painful stimulation (Loeser, 2021).
Analgesia	A state of insensibility to pain that would normally be painful (Loeser, 2021).
Allodynia	The pain due to a stimulus that virtually does not produce pain, e.g., pain resulting from a T-shirt in a patient with post-herpetic neuralgia (Loeser, 2021).
Dysesthesia	An unpleasant abnormal sensation, whether spontaneous or evoked. Dysesthesia is always unpleasant (Loeser, 2021).
Hyperalgesia	Increased pain from a stimulus that normally provokes pain.
Hyperesthesia	Increased sensitivity to stimulation, excluding the special senses. It includes the sensation of touch and thermal stimulation without pain (Loeser, 2021).
Herniorrhaphy	Herniorrhaphy is the oldest type of hernia surgery and is still being used. It involves a surgeon making a long incision directly over the hernia and then using surgical tools to open the cut enough to access it. Tissues or displaced organs are then returned to their original location, and the hernia sac is removed (Huizen, 2017).
Hernioplasty	Hernioplasty is a type of hernia repair surgery where a mesh patch is sewn over the weakened region of tissue (Huizen, 2017).
Post Anesthesia Care Unit	Room of a hospital that is equipped with apparatus for meeting postoperative emergencies and in which surgical patients are kept during the immediate postoperative period for care and recovery from anesthesia (Corrado & Poovathoor, 2010).
ASA Classification	The American Society of Anesthesiologists (ASA) Physical Status Classification System is a risk-stratifying system used mainly by anesthesiologists to help predict preoperative risks; it has been in use for more than 60 years. The system is used to assess a patient's preoperative comorbid conditions and assigns a class ranging from 1-6 (Mayhew, Mendonca & Murthy, 2019).

The Visual Analogue Scale	An instrument used to measure the characteristics or attitudes that are believed to range across a continuum of values, such a scale can be used for clinical research. For example, the measurement of pain intensity that patient feels ranges across the continuum from non to extreme pain (Crichton, 2001).
Numerical Rating Scale	A unidimensional measure of pain intensity, which has a series of verbal anchors that represent the possible pain intensity ranging from 0 to 10 or 20 or 100 while zero means no pain and 10, 20, or 100 matches with worst pain. NRS is similar to that of VAS, with the left end with no pain whereas the right end with the worst pain imaginable. The difference between NRS and VAS is that one uses a straight line with marks showing the numbers while VAS does not include lines and numbers (Lazaridou et al., 2018).

LIST OF ABBREVIATIONS

ASA	American Society of Anesthesiologists
NSAIDs	Non-Steroidal Anti-inflammatory Drugs
SBI	Subcutaneous Bupivacaine Infiltration
IV	Intravenous
HCl	Hydrochloride
ERAS	Early recovery after surgery
B.C.	Before Christ
mL	Milliliter

LIST OF APPENDICES

PERBANDINGAN KESAN ANALGESIA DI ANTARA PENYUSUPAN UBATAN BUPIVACAINE SUBKUTAN DAN DICLOFENAC INTRAVENA DENGAN DICLOFENAC INTRAVENA TUNGGAL DALAM PEMBEDAHAN PASANG SURUT INGUINAL : KAJIAN RETROSPEKTIF , PUSAT TUNGGAL DI GAZA

ABSTRAK

Kesakitan akibat pembedahan adalah masalah serius yang dihadapi oleh pesakit selepas pembedahan. Oleh itu, pengawalan kesakitan selepas pembedahan adalah penting dalam memastikan kesihatan pesakit adalah pada tahap optimum. Kajian menunjukkan bahawa analgesia multimodal dan suntikan ubat bius ke atas luka adalah cara yang berkesan untuk mengurangkan kesakitan ini dan mempunyai peranan yang besar dalam mengurangkan keperluan ubat selepas pembedahan. Kajian ini bertujuan untuk menilai kesan suntikan ubat bius secara subkutaneus mengunakan ubat bupivacaine hydrochloride dan intravena diclofenac untuk melegakan kesakitan selepas pembedahan pada orang dewasa yang menjalani pembedahan angin pasan. Kajian retrospektif ini merangkumi 104 pesakit berumur 18-65 yang menjalani pembedahan angin pasan unilateral di hospital terpilih. Pesakit dibahagikan kepada dua kumpulan di mana setiap kumpulan mempunyai 52 pesakit. Kumpulan A menerima dos 75 mg intravena diclofenac ditambah suntikan subkutaneus 10 ml bupivacaine hydrochloride 0.5% manakala kumpulan B hanya menerima Intravenous Diclofenac sahaja. Kesakitan selepas pembedahan dinilai pada satu, dua, tiga, enam, dan 12 jam selepas pembedahan menggunakan skala analog visual (VAS), yang menunjukkan skala kesakitan dari sifar (tiada kesakitan) hingga 10 (sakit yang melampau). Daripada jumlah 104 pesakit, 92% pesakit adalah lelaki. Purata umur pesakit ialah 36 ± 11 tahun, dan purata indeks jisim badan (bmi) ialah 22 ± 3 kg/m^2.

Kelas fizikal American Society of Anesthesiologists (ASA) adalah tidak penting secara statistik antara kumpulan (90.4% berbanding 84.6%). Pesakit dalam kumpulan A mempunyai skor kesakitan VAS yang jauh lebih rendah pada satu, dua, tiga, enam, dan 12 jam selepas pembedahan berbanding kumpulan B (semua nilai $p < 0.001$). Suntikan subkutaneus Bupivacaine' dan Intravena diclofenac juga didapati berkesan untuk pembedahan inguinal hernia menggunakan mesh (nilai $p < 0.001$ untuk semua). Kesimpulannya suntikan subkutaneus bupivacaine digabungkan dengan Intravena diclofenac memberikan analgesia yang terbaik berbanding monoterapi Intravena diclofenac sahaja selepas pembedahan inguinal hernia.

COMPARISON OF ANALGESIC EFFECT OF SUBCUTANEOUS BUPIVACAINE INFILTRATION AND INTRAVENOUS DICLOFENAC VS. INTRAVENOUS DICLOFENAC ALONE IN INGUINAL HERNIOPLASTY: A RETROSPECTIVE, SINGLE CENTRE STUDY IN GAZA

ABSTRACT

Postoperative pain is a significant problem encountered by patients after a surgical intervention, and there is a crucial need for effective postoperative pain control. Studies showed that multimodal analgesia and wound infiltration are effective ways to reduce this pain and have a substantial role in the reduction of postoperative medications requirement. This study aimed to evaluate the effect of subcutaneous infiltration of bupivacaine hydrochloride and intravenous diclofenac as postoperative pain relief in adults undergoing inguinal hernia repair. A single-centre retrospective case-control study included 104 patients aged 18-65 undergoing unilateral inguinal hernia repair at the selected hospital. The patients were in two groups of 52 each. Group A received 75 mg dose of IV diclofenac plus a subcutaneous injection of 10 mL of bupivacaine hydrochloride (HCl) 0.5% while Group B only received the IV diclofenac alone. The postoperative pain was assessed at one, two, three, six, and 12 hrs after the operation using the visual analog scale (VAS), which exhibited a range of pain from zero (no pain) to 10 (extreme pain). Of a total of 104 patients, 92% of patients were male. The mean age was 36 ± 11 years, and the mean body mass index (BMI) was 22 ± 3 kg/m^2. American Society of Anesthesiologists physical class I was statistically insignificant between both groups (90.4% versus 84.6%). Patients in group A had significantly lower VAS pain scores at 1,2,3,6, and 12hr after the operation and a longer emergence time than group B (all p-values were < 0.001).

Subcutaneous bupivacaine infiltration and IV diclofenac was also found to be effective analgesic technique in inguinal hernia repair using mesh (p-value < 0.001 for all). Subcutaneous injection of bupivacaine combined with IV diclofenac provides superior analgesia to monotherapy intravenous diclofenac after inguinal hernia repair.

CHAPTER 1

INTRODUCTION

1.1 Introduction

Postoperative pain is the most common adverse event encountered by patients after surgery. Almost 80% of patients experience postoperative pain after surgical intervention, with 75% complaining of pain after receiving a single dose of analgesic (Gan, 2017). The pain ranges from moderate to severe and is associated with several consequences that affect the patient's physiological and psychological status. Acute pain often induces fear and anxiety, resulting in behavioral, autonomic, and neuroendocrine changes (Michaelides & Zis, 2019).

Inguinal hernia (IH) repair is a common surgery in all ages worldwide, about 20 million patients underwent IH repair annually (Haladu et al.,2018). Patients with IH are seeking treatment for surgical hernia repair to relieve abdominal pain and limitations in physical activity. However, due to postoperative pain, symptoms frequently persist after surgery (Williams et al., 2020; Group, et al., 1999).

Moreover, postoperative pain may cause delay hospital discharge, loss of appetite, depression, aggression, tissue catabolism, immunosuppression, poor health, and hyperalgesia (Dimova & Lautenbacher, 2010). Therefore, effective postoperative pain management is imperative, and understanding postoperative pain from the patient's perspective is essential for healthcare professionals to identify ways to improve care, this includes identifying the best analgesic mode and an efficient postoperative pain management approach that may prevent this pain phenomenon and its sequels.

With the advances in perioperative pain management, multimodal analgesia has become essential for pain control (Mitra et al., 2018). Multimodal analgesia is a combination of two or more analgesics from different classes. Recent theories suggest the addition of local wound infiltration to the analgesic procedure to reduce postoperative pain and the incidence of postoperative chronic pain resulting from the surgical incision. Studies showed that surgical wound infiltration is effective in reducing postoperative pain in abdominal surgeries, breast surgeries, gynecological surgeries, radical prostatectomy, laminectomy, laparoscopic cholecystectomy, hallux valgus surgery, and herniorrhaphy (Stamenkovic et al., 2021). Surgical site infiltration with local anesthetic shortens the duration of hospital stay, delays the morphine rescue, reduces consumption, contributes to early recovery after surgery (ERAS), and increases patient satisfaction, although when used in combination with NSAIDs (Gelman et al., 2018). The hypothesis of the study is tailored to observe whether subcutaneous infiltration with 10 mL of 0.5% bupivacaine hydrochloride (SBI) in addition to intravenous (IV) diclofenac is more effective than simple administration of IV diclofenac for the management of postoperative pain in inguinal hernia repair.

1.2 Problem Statement

Notwithstanding the current advances in health care, pain is still undertreated and insufficiently assessed, and the incidence of pain is still considerably high. Acute postoperative pain might be challenging and results in psychological and physiological consequences. Additionally, postoperative pain also seems to be cost-extravagant and delays hospital discharge (Sharma et al., 2020).

Also, postoperative pain may activate the sympathetic nervous system, increasing the hazard of myocardial injury and mortality (Turan et al., 2020).

Studies reported that adding a local anesthetic infiltration to the pain management regimen significantly reduces the postoperative pain intensity, length of stay, analgesic consumption and increases patient satisfaction (Gasanova et al., 2015; Kerr & Kohan, 2008).

1.3 Objectives

1.3.1 General Objective

To compare the analgesic effectiveness in group A (diclofenac plus subcutaneous bupivacaine infiltration) and B (diclofenac monotherapy) in the immediate postoperative period.

1.3.2 Specific objectives

a. To determine the demographics of open inguinal hernia repair patients in the studied hospital.

b. To determine the adequacy of pain control among patients in both groups (pain score VAS ≤ 3) or mild pain.

c. To compare the VAS score among group A (IV diclofenac plus subcutaneous bupivacaine infiltration) and group B (IV diclofenac monotherapy) at 1,2,3,6, and 12 hours after inguinal hernia repair.

1.4 Hypothesis

Ten (10) mL of 0.5% subcutaneous bupivacaine infiltration plus IV diclofenac is more effective in management of postoperative pain after inguinal hernia repair and decreases postoperative analgesia consumption compared with simple administration of IV diclofenac.

CHAPTER 2

LITERATURE REVIEW

2.1 Background

Among general surgeries, inguinal hernia is one of the most performed surgery. Postoperative pain following the surgical intervention ranges from moderate to severe (Yazicioğlu et al., 2016). This pain is accompanied by several adverse effects which may produce patient discomfort, and delay recovery and discharge. Moreover, chronic pain may develop following inguinal hernia repair. Strong risk factors for persistent pain include immediate postoperative period and moderate to severe postoperative pain. Previous study showed that 16% of patients undergoing hernioplasty experience chronic pain (Andresen & Rosenberg, 2018).

Patients who underwent elective unilateral groin hernia repair were examined following surgery, and 15.5% of the patients complained of persistent pain for a year after the treatment (Lundström et al., 2017). A total of 170 patients (17.9%) reported groin pain while 29 (3.0%) of those patients had extreme pain (Olsson et al., 2017). Whereas in a previously conducted study, the incidence of chronic pain was higher compared with the recent study (Poobalan et al., 2003). The rate of persistent pain following inguinal hernia repair from 1983 to 2000 was higher than previously reported research, according to a relatively old review, which accounts for around 54% of the total number of studies obtained (Poobalan et al., 2003). Whereas a new study found that chronic pain after a surgical procedure may affect 10-50% of patients (Wylde et al., 2017).

Despite the risk level among ages, chronic pain is tied to extreme long-term discomfort and financial consumption to the patients and institution as well (Paajanen, Scheinin & Vironen, 2010). Therefore, the need for adequate postoperative analgesia is crucial and its choice is pivotal to meet patient satisfaction and avoid the postoperative pain consequences. The concurrent use of numerous medications from various pharmacological classes is an alternative to one-agent therapy. By limiting the dose of each treatment, side effects could be reduced while the desired impact could be maintained or even increased (Solomon & Gebhart, 1994). To reduce postoperative pain, region block with or without wound infiltration is recommended, either as a stand-alone anesthetic/analgesic method or as a complement to general anesthesia (Joshi, Rawal & Kehlet, 2012). Local infiltration as adjuncts to both regional analgesia and general anesthesia has benefits by reducing analgesic consumption (Bamigboye & Hofmeyr, 2008).

Study shows that it is essential that surgical site infiltration is combined with other non-opioid analgesics like non-steroidal anti-inflammatory drugs (NSAIDs) to attain the maximum analgesic efficacy (Joshi & Machi, 2019). Multimodal analgesia captures the efficacy of individual analgesics in optimal dosages that maximize efficacy and attempts to reduce side effects. This essential principle is based on the theory that when medications with multiple mechanisms of analgesia are used, they can have synergistic benefits in preventing or treating acute pain. These regimens must be tailored to individual patients, keeping in mind the procedure being performed, the side effects of individual medications, and the patient's preexisting medical conditions.

In multimodal analgesia, a combination of agents with different mechanisms of action, which may act at different levels of the nociceptive pathways, is used to

produce enhanced analgesic effects (additive and supra-additive [synergism]) (Butterworth, Mackey & Wasnick, 2018). Liposomal infiltration of bupivacaine decreases postoperative pain with no serious perioperative adverse events (Hamilton et al., 2014). Moreover, adding local infiltration to the analgesia regimen will considerably reduce postoperative opioid consumption and improve the postoperative pain level as well as patient satisfaction (Dysart et al., 2019).

2.2 Inguinal Hernia

Inguinal hernia is an outpouching of the abdominal content through an infirm area in the lower abdomen regions. Inguinal hernia can be either direct or indirect, depending on its passage through the inguinal canal (Staff, 2021). Inguinal hernia is common in all ages and it is the most common operation in general surgery. It accounts for about 75% of abdominal wall herniation, particularly among males (Tripathi & Singh, 2021). A study has shown that the repair of inguinal hernia is the most common surgery with an annual rate of 2,800 of 1 million of the population in the United States, the operation is usually performed as outpatient basis with a small rate of perioperative morbidity (Muhammad Nadeem et al., 1969).

In Frence inguinal hernia repair is the most anatomical surgical illness that needs surgery in men with a prevalence of 36 hernias for 1000 men. Inguinal hernia is the most performed surgery after appendectomy, and the annual inguinal hernia repair is 80,000 cases in Great Britain, while in Frence and United States are 100,000 and 600,000 respectively. The recurrence rate depends on the type of repair, duration, and modality of the follow-up. However, the mean recurrence rate ranges from 5% to 10% (Hay et al., 1995). S.-J. Chang conducted a study on children which revealed a high occurrence of inguinal hernia. The study was carried out between 1997 and 2005 and

included a total of 80,000 males and females. The cumulative incidence of inguinal hernia from birth to 15 years old was found to be 0.74% in girls and 6.62% in boys (Chang et al., 2016).

Globally, the number of patients undergoing inguinal hernia repair exceeds 20 million patients annually. Male gender, age, metabolism of the abdominal collagen, low body mass index, family history, and previous contra-lateral hernia and peri-operative risk factors are risk factors for recurrence including poor surgical technique, low surgical volume, surgical inexperience, and local anesthesia are common risk factors for inguinal hernia (Simons et al., 2018).

2.3 Inguinal Hernia Repair Modalities

Inguinal hernia repair can be carried out in three different ways; open, laparoscopic, and robotic surgery, this depends on the availability of equipment and sophisticated items. Open inguinal hernia repair is done by creating an incision in the groin and removing the sac which has the bulged intestine, then the surgeon returns the contents back inside the abdomen while the abdominal muscles is strengthened using sutures or synthetic mesh. Laparoscopic hernia repair is performed by introducing the laparoscope tools through a three small holes in the abdomen, then after, inflating the abdomen with gas (carbon dioxide) which produces space to allow a good vision of the intra-abdominal content and ensure that surgeon can see the organs.

Robotic inguinal hernia repair is a relatively recent method to perform surgery. Robotic surgery employs a laparoscope and is carried out similarly to laparoscopic surgery (small incisions, a tiny camera, inflation of the abdomen, and projecting the inside of the abdomen onto television screens). In robotic surgery, the surgeon operates

the surgical equipment while seated at a console in the operating room. Robotic Surgical technique can be utilized to repair some minor hernias as well as to reconstruct the abdominal wall (Cleveland Clinic logo, 2022).

2.4 The Importance of Pain Perception

Pain means suffering. Since the existence of humanity, pain has been a problem. A careful assessment and diagnosis must take place in order to alleviate this agony and discomfort. Even though there are numerous types of pain that still have no precise treatments, grouping pain into distinct categories might help doctors create treatment plans that will work for the patients. Help for other patients may be possible in the future. Very few doctors, in contrast to other medical professionals, were trained in pain management. Instead, there were "one size fits all" pain management techniques (Pain, 2002).

Personal specific characteristics and genetic variants play an important role in pain tolerance and management among humanity. Therefore, special care for every single person must be considered. The philosopher Plato stated that every individual is unique and possesses distinct innate qualities that set them apart from one another (360 B.C.).” Pain physiology education can be an important therapeutic modality in the approach of patients with chronic pain, given the clinical relevance of inappropriate pain cognitions. Therefore, an understanding of individual differences plays a crucial key in effective pain assessment and management, which turns into the principle for personalized pain treatment, an as yet unrealized goal. Future study is desperately needed to better understand the interactions between biological and psychological processes that have a significant impact on pain perception. Identification of individual differences and their interactions that contribute to the onset and persistence of pain is

a high priority in particular. Moreover, determining individual difference factors that predict responses to pain treatments will inform future efforts toward personalized pain treatment (Meeus et al., 2010; Fillingim, 2017).

Insufficient understanding of the mechanism of pain pathogenesis stands as a hindrance in the management of pain in patients with different diseases which may result in poor patient satisfaction. Utilizing different ways to measure the pain allows for the assessment of multiple pain forms, providing a better understanding of outcome measures received from a specific model as well as the changes in pain sensation and mechanisms over time (O'Brien, Philpott & McDougall, 2017).

A randomized control trial performed on patients with fibromyalgia after intervention and improve patients' knowledge regarding pain neurophysiology showed that those patients had less worry about their pain in the short-term, in addition to the long-term enhancement in their physical function, vigor, mental health, and general health perceptions. Hence, the intervention group reported lower pain scores, and improved endogenous pain inhibition was observed compared with the control group (van Oosterwijck et al., 2013). Likewise, patient understanding, and perception of the pain and their health literacy are pivotal and play important role in coping with pain. Some studies show that patients with low health literacy and medication background have a low ability to find the safe way to treat their pain through non- prescriptive medications and non-medication methods. This allows for better communication among either physician or patient which ultimately results in better pain-reducing modes (Devraj & Griffin, 2013; Joplin et al., 2015). So, identifying the effective treatment procedures by the perception of the basic mechanism of postsurgical

pain may enhance the patient's outcome postoperatively (Pogatzki-Zahn, & Segelcke, 2017).

2.5 Physiology of Pain

The mechanism of pain and its pathways physiologically is a complex process that in its turn converts the noxious signal into neural transmission via the spinal cord, which ultimately translated as pain within the central nervous system. Pain is an unpleasant sensation and uncomfortable feeling. Otherwise, it is considered a protective mechanism whenever the body tissue begins to be damaged because of endogenous or exogenous reasons, hence, the pain acts to get rid of the stimulus.

2.5.1 Nociceptor and Pain Stimuli Transduction

Nociceptors are unspecialized, free, unmyelinated nerve endings that convert (transduce) a variety of stimuli into impulses, which the brain interprets to produce the sensation of pain. The nerve cell bodies are in the dorsal root ganglia or the trigeminal nerve in the trigeminal ganglia, and they send one nerve fiber branch to the periphery and another into the spinal cord or brain stem (Samoilova et al., 2010).

2.5.2 Type of Nerve Fibers and Pain Classifications and Transduction

The nerve fibers are classified into two major types: small diameter, myelinated nerves called C fibers, and large diameter, light myelinated nerves called A δ Fibers. (Figure 2.1) The fast felt within 0.1sec after pain stimulus, it has other names like sharp, prinking, acute pain, and electrical pain. This pain is well explained when exposed to needle pricks or skin cuts or electric shock but is not felt in the deep tissues (Figure 2.2-a). Fast pain could be elicited by two kinds of stimulus: mechanical and thermal. As the fast pain signals are manipulated by mechanical and thermal pain factors their transmission in the peripheral nerves to the spinal cord via small A δ type

of fibers at a velocity ranging between 6-30m/sec. However, slow pain begins 1sec or more even for minutes, it is also termed as slow burning pain, aching, nauseous and chronic pain, this pain is usually prolonged unbearable pain which may lead to tissue damage. Slow pain can be stimulated when exposed to all types of stimulants; mechanical, thermal, and chemical. As the slow chronic pain elicited by chemical stimuli with the persisting thermal and mechanical factors, the slow-chronic pain is transmitted to the spinal cord and brain through the C fibers at a speed between 0.5 and 2m/sec. when the slow pain impact continues it could produce a surge in the sensitivity to pain this is called hyperalgesia, hyperalgesia result from inappropriately pain treatment.

Additionally, combined pain innervation, it's a combination of both fast and slow pain, this pain could obviously and suddenly give a fast-sharp pain sensation (A δ) that is transmitted to the brain, then followed by slow pain which traveled by the C fibers pathway (Figure 2.2-b). This type of pain rapidly results in tissue damage as well it is playing a pivotal role in provoking the patient to react immediately to remove the cause of pain (Hall, 2011).

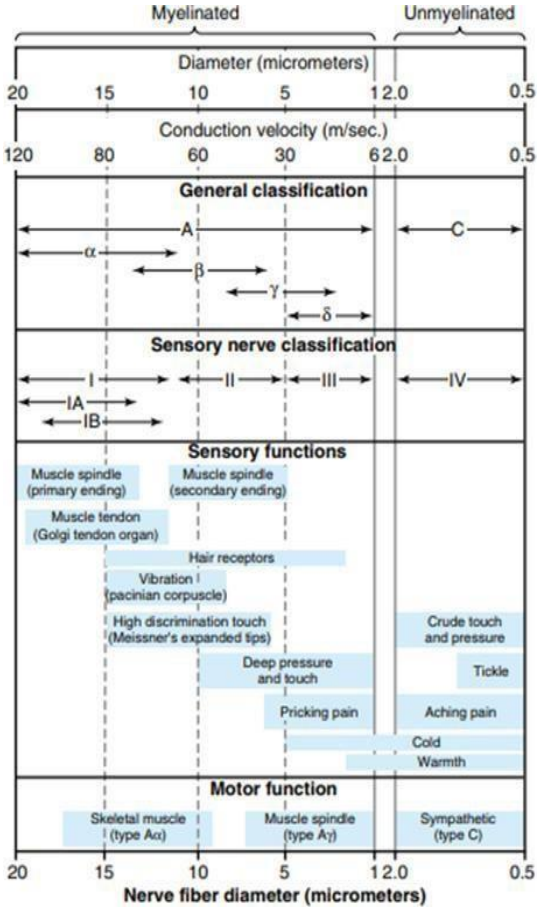
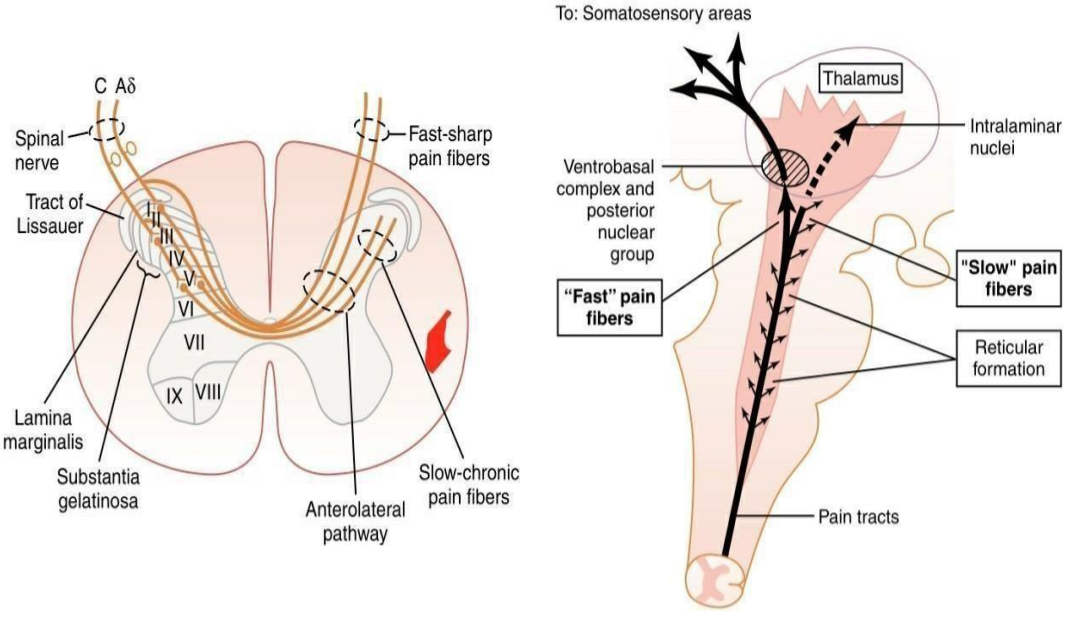


Figure 2.1 Physiologic classifications and functions of nerve fibers.



(a) **(b)**

Figure 2.2 **(a)** Transmission of both "fast-sharp" and "slow-chronic" pain signals into and through the spinal cord on their way to the brain. **(b)** Transmission of pain signals into the brain stem, thalamus, and cerebral cortex by way of the fast-pricking pain pathway and the slow-burning pain pathway.

2.6 Consequences of Pain

Pain is the most object that affects the human entire life which is due to either surgical or medical reasons. This pain may influence the person's physical and psychological aspects, such a delay of ambulation, delayed gastrointestinal emptiness and reduced motility, nausea, vomiting, stress, and depression as well as affects the patient's respiratory and cardiovascular systems resulting in increased blood pressure, heart rate and tachypnea. In addition, pain economically is cost.

2.6.1 Impact of Pain on the GI System

Acute pain which activates the sympathetic nervous system induces the intestinal smooth muscle and reduces the gut motility because of the decrease in the intestinal peristalsis, then dilatation of the stomach and intestine and paralytic ileus may take place (Ruparelia & Giri, 2021). Some studies exhibited that the reduction of gastrointestinal motility after abdominal surgery may last for 2-3days (Wattwil, 1989). Moreover, postoperative urinary retention may occur caused by a pain-induced autonomic imbalance (Breivik, 1998).

2.6.2 Impact of Pain on the CV System

In addition to the gastrointestinal events, the autonomic and neuroendocrine seem to be affected by post-surgical pain. The pain due to tissue injury correlates with the activation of the sympathetic system which ultimately results in increased heart rate, arterial blood pressure, and cutaneous conductus (or galvanic skin activity), likewise, it increases the epinephrine or norepinephrine plasma levels (Ledowski et al., 2012).

The author has found that norepinephrine (NE) was higher at the NAS 5-10 (moderate to severe pain) vs (mild) 0-4 as well the Mean Arterial Pressure (MAP) was

also high but not for epinephrine level or parameters of heart rate variability, heart rate, and respiratory rate. So, the intensity of the pain does not link with the sympathetic stress response to the surgery like the surgical trauma issues. Briefly, less sympathetic stimulation does not mean a low pain level (Ledowski et al., 2012).

2.6.3 Depression, Anxiety, and Mania

When postoperative pain is not adequately managed, it can lead to clinical and psychological alterations that increase the morbidity and mortality rates, as well as incurring financial costs for both the government and patients. Additionally, pain can diminish the quality of life (Sharma et al., 2020 ;Oderda, 2012).

There are limited studies that have shown the direct impact of pain on the psychological state (McWilliams, Goodwin & Cox, 2004). However, other studies illustrated that there is an association between depression, anxiety, and pain intensity. Cheer and laughing deprivations in patients with chronic pain result in depressive symptoms and anxiety which so affect the sleeping pattern. After pain management these symptoms are considerably reduced (Gómez Penedo et al., 2020).

Patients with psychological disorders like depression, panic attack, and generalized anxiety disorder are more affected by the pain which may worsen the psychological condition. In contrast, another study focused on patients experiencing sciatic pain resulting from lumbar disc herniation. The study findings showed that patients who underwent surgery and experienced a 25% reduction in pain also exhibited a rapid improvement in their symptoms of depression and anxiety during the postoperative evaluation. But those whose pain level does not reduce have no positive changes in their psychology (Max et al., 2006).

The presence of pain makes it more difficult to recognize and treat depression. When pain is moderate to severe, impairs function, and/or is refractory to be treated, it is associated with more depressive symptoms and worse depression outcomes (e.g., lower quality of life, lower work performance, and higher health-care use). Similarly, depression is associated with higher pain complaints and disability in people with pain. Depression and pain have molecular pathways and neurotransmitters in common, which has implications for treating both disorders at the same time. A model that incorporates assessment and treatment of depression and pain simultaneously is necessary to improve the outcomes (Bair et al., 2003).

Based on the information provided, it appears that most of the data focuses on the correlation between pain and depression, which has been extensively documented in scientific literature. On the other hand, there is limited literature available regarding the relationship between pain and mania. While the association between pain and depression is well-established, the available bibliography on how pain is perceived in cases of mania is scarce (García, 2021).

In this study, a review of the relationship between pain and mania is made regarding two cases. This about two patients diagnosed with bipolar disorder who were hospitalized for manic episodes, and at the same time they were suffering a serious traumatic injury, the absence of pain was observed while the psychopathological alteration persisted, in turn, as the mood stabilized, the painful sensation increased. For this reason, it is proposed the utility of the absence of pain or hypoalgesia as an assessment of part of the manic symptom (García, 2021).

2.6.4 Venous Thrombo-Embolism

A prolonged period of hospital stay after a surgical operation is associated with the severity of pain; Therefore, a higher level of pain and a longer hospital stays the leading immobilization and limited physical activity this resulting in blood stagnation which ultimately outcome in vascular event concluded by pulmonary embolism and lower limb vascular occlusion. Prolonged immobilization after surgery is a major triggering co-factor for venous thromboembolism. According to existing literature, the prevalence of venous thromboembolism (VTE) following surgical procedures is estimated to be 1%, with pulmonary events and embolization being observed in approximately one-third of cases, leading to a significant increase in morbidity and mortality rates. Nonetheless, the risk of VTE in the context of outpatient surgery is generally low, particularly when considering the implementation of enhanced recovery programs in the postoperative period (Talec & Gaujoux, 2016). Recent studies performed on Asian patients undergone surgery have shown that the incidence of VTE is 13% after general surgery, and 1% of patients experienced a symptomatic pulmonary embolism (Leizorovicz, 2007).

Whereas the incidence of VTE after inguinal hernioplasty in high-risk and mild-risk patients were 0.2% and 0.02% respectively. However, in the low-risk group, the signs of VTE were absent. About 14,000 patients were included in the study and it showed that the incidence of VTE post-inguinal hernia repair was higher in patients who underwent laparoscopic hernioplasty than in those exposed to open hernioplasty (Wang et al., 2020). Despite the pros of laparoscopic surgical technique which briefly provides faster recovery, lower wound infection, and less postoperative pain in compared with an open procedure, the laparoscopic technique is associated with the

risk of perioperative VTE which could be due to either surgical procedure or patient-specific characteristics (Yang & Zhu, 2017).

The risk factors of VTE vary among individuals and may be due to either intrinsic factors, for instance (age, obesity, history of VTE, or thrombophilia) or disease-related (surgical factors and medical factors such as cancer, cardiovascular disease, and acute respiratory failure) (Ageno et al., 2006). Venous thromboembolism presents as a result of complex interactions between congenital and transient or permanent acquired risk factors (Ageno et al., 2006). Predisposing factors such as varicose veins, oral contraceptives, and obesity were not found to be significant in relation to the matter at hand (Shead & Narayanan, 2005; Talec, Gaujoux & Samama, 2016).

2.6.5 Postoperative Pain and Chronic Pain

The development of chronic pain after surgery is considered a major clinical problem that requires extensive investigation about the mechanism of the transition from acute to chronic pain to find out the best strategy that ensures the patient's satisfaction. Chronic pain is classified into nociceptive or neuropathic, nociceptive pain result from the activation of receptors (nociceptors) sensitive to the noxious stimuli and prolonged exposure to these stimuli enhances the responsiveness to the nociceptive nerve fibers, this process is called peripheral sensitization (Scholz, 2014). This, lead to an increase the action potential firing and transmitter release in the dorsal horn in the spinal cord, where the somatosensory information is processed. Dorsal horn neurons respond to the rising input with heightened excitability, a process termed central sensitization. Enhanced depolarization leads to the recruitment of N-methyl-D-aspartate (NMDA)-type glutamate receptors. neuropeptide and NMDA receptor activation produce a sharp elevation in intracellular calcium, triggering signaling

pathways and gene expression changes that promote a long-term shift in the activity of nociceptive circuits and chronic pain (Scholz, 2014).

The incidence of chronic pain is not clear. However, some studies revealed that chronic pain post herniorrhaphy ranges from 30-39% of patients, and mild to severe pain was reported (Manangi, Shivashankar & Vijayakumar, 2014). Chronic pain after the inguinal hernia is also believed to be due to neuropathic, this pain originates from these nerves, including Iliohypogastic, Ilio-inguinal, and genitofemoral nerves, these nerves are the common nerves supplying the inguinal canal and lower abdomen region, and nerve injury has considerably increased the development of chronic pain, therefore, resection of these nerves may be useful to obliterate the pain stimuli (Manangi, Shivashankar & Vijayakumar, 2014). Other risk factors are described below (see Table 2.1).

Table 2.1 Risk factors for chronic postsurgical pain*.

Preoperative Factors	Intraoperative	Postoperative
Female gender	Surgical approach with risk of nerve damage	Psychological vulnerability
Younger age		Anxiety
Preoperative anxiety		Depression
Repeat surgery		Neurotoxic chemotherapy
Psychological vulnerability		Neuroticism
Pain, moderate to severe, lasting more than 1 month.		Radiation therapy to the area
Genetic predisposition		Acute, moderate to severe postoperative pain
Workers' compensation		Postoperative

Adapted from (Reddi & Curran, 2014).

2.6.6 Postoperative Pain and Cost Effect

In today's healthcare landscape, characterized by high costs and significant advancements in medical and surgical fields, healthcare institutions and government bodies are increasingly seeking out analgesic procedures that are safe, efficient, and cost-effective. Consequently, there is a growing interest in low-cost surgical and anesthetic techniques that can provide effective pain management while minimizing financial burden. Moreover, postsurgical pain remains the most challenging event for both health care providers and patients. A study involved 300 participants undergone surgery showed that 75% of patients suffered from moderate to extreme pain through the immediate postoperative period, and 74% of them experienced similar pain intensity after discharge (Gan et al., 2014).

Therefore, numerous groups of clinicians looking for effective postoperative pain relief, and opioid is omnipresent, especially morphine and meperidine. The use of opioids in the management of postoperative pain is not limited solely to the acute phase, but is also employed for the prevention of chronic pain that may arise as a result of persistent acute postoperative pain.

Despite the effective role of opioids in the treatment of pain, opioids may result in opioid-related adverse drug events (ORADEs) concluded by longer hospital stay, nausea and vomiting (N&V), and pruritus which ultimately leads to cost inflation (Oderda, 2012; Kessler et al., 2013).

Study revealed that opioid use has increased through the last years for either in-patient and out-patient, it provides good postoperative pain management for moderate and severe pain, but opioid adverse effects are associated with an increase in overall cost which set as a disadvantage for opioid usage (Rawal, 2016). Insufficient

pain management can lead to longer hospital stays as well as increased rates of patient readmission, making it a key factor in health care costs. Furthermore, inadequate pain relief can contribute to the development of chronic pain in postoperative patients. Therefore, the selection of an appropriate postoperative pain medication is critical for both patient and institutional satisfaction (Gan, 2017).

2.7 Therapeutic Modalities

Regardless of the development in health care and advances in our understanding of neurobiology and physiology of nociception and neurotransmitters postoperative pain is still undertreated. Many different strategies provide effective postoperative pain management. However, these procedures are not always suitable for all patients, use of these approaches depends on the type of surgery and its location in the body such lower abdomen and limbs or upper parts of the body (Joshi, G.P,2019). Additionally, some analgesic procedures need expertized personnel to perform them, for instance, nerve block, caudal and epidural analgesia. In this section, we are going to discuss some postoperative pain relief techniques.

2.7.1 Non-steroid Anti-inflammatory Drugs

Salicylic acid and salicylates are naturally occurring products and the first chemical formation of this group was synthesized in the 1800s and had been used for versatile purposes like antipyretic, antirheumatic, and antiseptic. Later, other similar drugs have the same effects have been discovered and this group was called aspirin-like or Nonsteroids Anti-Inflammatory Drugs (NSAIDs). NSAIDs were divided into groups according to their chemical structure and enzyme/receptors selectivity. The mechanism of action of these drugs was believed to inhibit the activity of prostaglandin. Then next, more understanding of the action of NSAIDs was confirmed

that NSAIDs act by inhibiting of cyclooxygenase (COX) enzyme, this enzyme is classified into at least two isomers: COX-1 which is the constitutive isoenzyme, and COX-2 which is not constitutive and be inducible isoenzyme (Lees, Bäumer & Toutain, 2022; Arif & Aggarwal, 2021).

Cyclooxygenase subtypes vary in their physiological and pathophysiological functions, cyclooxygenase -1 plays a role in gastrointestinal cell protection (Cytoprotective) when released by the gastric mucosa, and when released by endothelial is anti-thrombogenic, as well as maintaining the renal function (Physiological functions), Whereas cyclooxygenase-2 induce in the presence of pain and inflammatory stimuli (pathophysiological process).

Cyclooxygenase is responsible for the conversion of arachidonic acid into thromboxane, prostaglandins, and prostacyclin. NSAIDs inhibit the COX and break the conversion chain, so reduce the enzymes and subsequently reduce the incidence of pain and body temperature, this simply expresses the mechanism of action for NSAIDs (Tolba, 2017). Figure 2.3 NSAIDs are commonly used as perioperative pain relief and selective cyclooxygenase -2 inhibitors are the most drug in the group which has a significant role in the management of pain beside another multimodal analgesic, and their pros outweigh their adverse effects (Schug & Manopas, 2007).

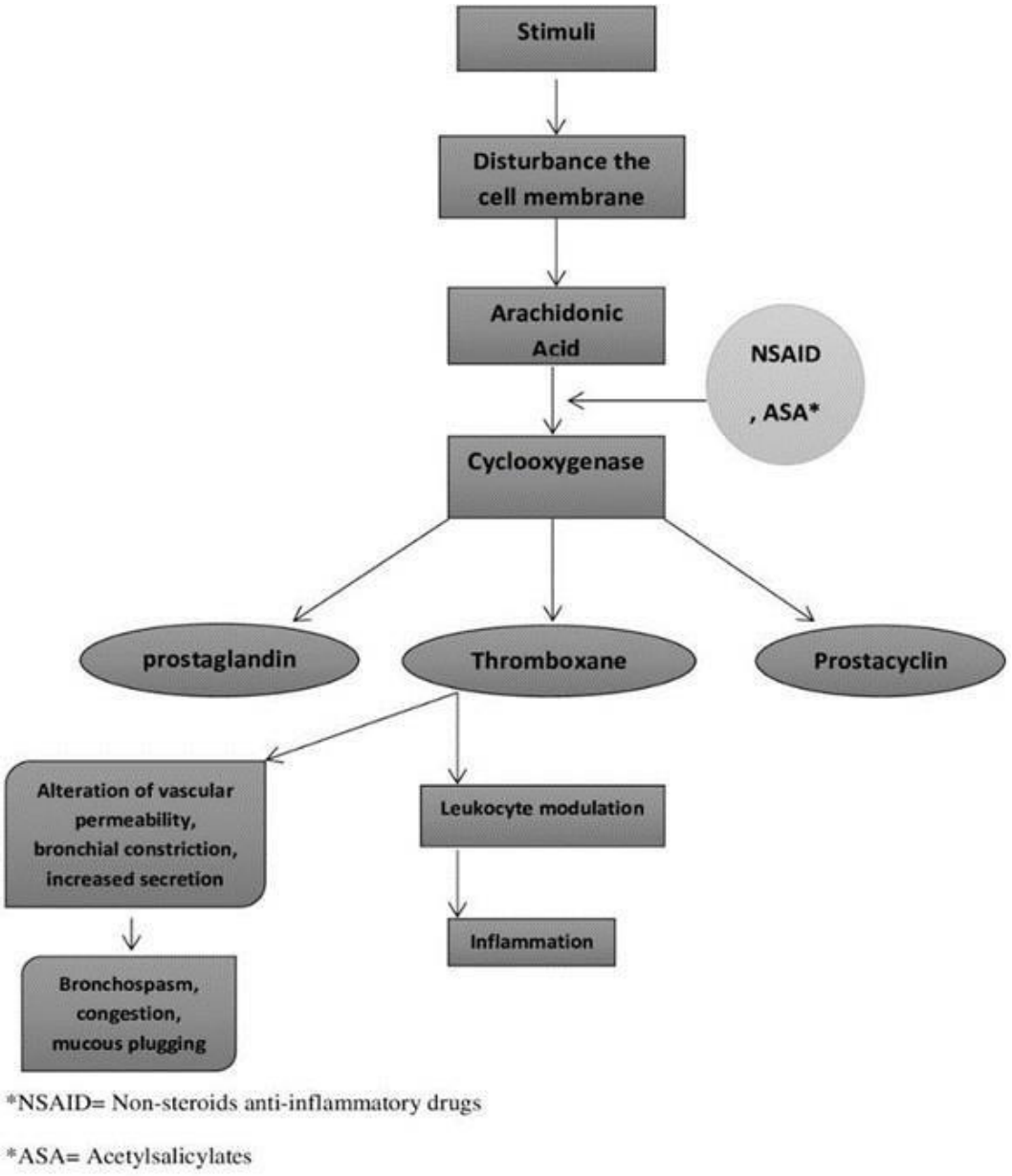


Figure 2.3 Action site of NSAIDs and Acetylsalicylates

Recent research indicates that the use of nonsteroidal anti-inflammatory drugs (NSAIDs) as an additive therapy can be both safe and effective in managing postoperative pain, leading to increased patient satisfaction. Studies suggest that NSAIDs can effectively reduce postoperative pain and opioid consumption without increasing the incidence of adverse effects for either drug class. While it is recommended that NSAIDs be used in all patients, when there is no contraindication,

caution should be exercised in surgeries that carry a risk of postsurgical bleeding or leakage of organ content, such as colorectal anastomosis. This is because certain studies have suggested that NSAID use may increase the risk of anastomotic leakage after administration (Gupta & Bah, 2016).

According to the Food and Drug Administration (FDA) approval, the parenteral administration of ibuprofen is an effective and safe medication for postoperative pain relief. Ibuprofen is a simple derivative of phenylpropionic acid and is available to treat mild to moderate pain when singly used, and moderate to severe pain in adjunct to opioids (Kroll, 2012). A study showed that the administration of 800mg of ibuprofen intravenously has an important role in postoperative pain reduction when being introduced repetitively every 6 hours, as well it resulted in a reduction of postoperative morphine requirement by 19% in patients undergoing total abdominal hysterectomy (Singla, Rock & Pavliv, 2010).

Moreover, NSAIDs are commonly used for postoperative pain management because of their non-sedative properties and their role in the opioid-reducing effect. Diclofenac which is a phenylacetic acid derivative is a relatively non-selective COX inhibitor and the most used drug among NSAIDs. It can be given intramuscularly when being oily prepared, however in aqua preparation can be given intravenous (IV) in diluted form (Shah & Dudhwala, 2019). A prospective, double-blind study randomly included 120 patients who underwent surgical operations under general anesthesia, and those patients were divided into two groups, the Diclofenac group, and the paracetamol group. Study revealed that IV administration of both drugs are effective for postoperative pain relief without significant differences between groups, as well as

diclofenac and paracetamol together, are safe analgesics to be provided IV with no serious side effects (Shah & Dudhwala, 2019).

Diclofenac administration has a different route to be given, therefore, can be introduced orally, suppository, intramuscular, intravenous, and topically. Recently, new studies have shown that the administration of diclofenac as a continuous subcutaneous infusion (intrawound) is effective to produce sufficient postoperative pain relief as much as local ropivacaine infusion with systemically administered diclofenac, in comparison to bupivacaine, pre-operative subcutaneous infiltration of diclofenac has demonstrated superior analgesic efficacy, resulting in reduced reliance on supplementary pain management and decreased overall costs. Additionally, diclofenac's ease of administration and handling in clinical settings further supports its use as a preferred analgesic agent (Lavand'homme et al., 2007; Loh et al., 2020).

Single intramuscular diclofenac significantly reduces the opioid requirement for patients undergoing inguinal hernia and orchidopexy and it seems to be an alternative to caudal analgesia for postoperative pain management in children (Ryhänen et al., 1994). Additionally, the addition of diclofenac to pentazocine was found to be effective and attenuate the postsurgical pain in patients undergoing cesarean section, this met patient satisfaction (Simons et al., 2018). Furthermore, ketorolac tromethamine is another commonly used drug among NSAIDs that alleviate postoperative pain, Ketorolac is a non-selective COX NSAID which is a heteroaryl acetic acid derivative, it can be administered in different ways, orally, intramuscularly, intravenous and topical solution for ophthalmic purposes (Sinha, Kumar & Singh, 2009; Liu & Chen, 2022).