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A REVIEW OF KETOROLAC AS A POTENTIAL THERAPEUTIC AGENT

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ABSTRACT

When treating acute pain, non-steroidal anti-inflammatory medications (NSAIDs) might be a part of a multimodal strategy. When NSAIDs are administered via intramuscular (IM) or intravenous (IV) injection, patients who are nil-by-mouth or who are unable to swallow can benefit from the medication's quicker onset than when taken orally. An intramuscular (IM) or IV injection can be used to deliver the NSAID. Additionally, ketorolac has been used to treat a number of illnesses, including cancer, analgesics, antipyretics, and inflammation. When administered either by alone or in combination with other medicines as part of a multimodal approach to analgesia, it is a useful analgesic. This article examines the research on the effectiveness and safety of ketorolac as an analgesic for acute pain from peer-reviewed journals and current clinical guidelines.

KEYWORDS: Ketorolac, analgesic, Anti-inflammatory, anti-cancer, Pain.

INTRODUCTION

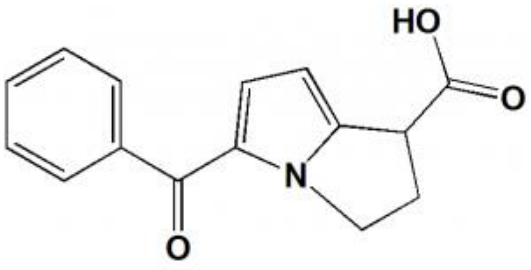
Acute moderate-to-severe pain is treated and managed with a medication called ketorolac. It is a member of the nonsteroidal anti-inflammatory drug class. This exercise explains how to use ketorolac, a helpful drug for treating acute pain, as well as its side effects and precautions. It will also highlight the mechanism of action, adverse event profile, and other pertinent information that interprofessional team members should be aware of when treating

patients with acute, moderate-to-severe pain, including toxicity, monitoring, and contraindications.[1] Ketorolac is a nonsteroidal anti-inflammatory drug (NSAID) used to treat pain. It is marketed under the brands Toradol and Biorolac, among others.[2][3] It is especially advised for pain that ranges from moderate to severe. Less than six days and no more than two days in Switzerland are the recommended treatment durations.[4] It can be administered orally, via the nose, intramuscularly (in a vein or muscle), or as eye drops. Within an hour, effects start to manifest and can last up to eight hours. Sleepiness, lightheadedness, nausea, edema, and abdominal pain are typical side effects. Anaphylaxis, bronchospasm, heart failure, kidney failure, stomach bleeding, and heart attacks are examples of serious side effects. Use is not advised while nursing or in the latter stages of pregnancy. Cyclooxygenase 1 and 2 (COX1 and COX2) are blocked by ketorolac, which lowers prostaglandin synthesis.[5] Patented in 1976, ketorolac received medical approval in 1989.[6] It can be purchased as a generic drug. With more than one million prescriptions written for it in 2020, it ranked 249th among all prescribed drugs in the US.[7][8] In 1993, ketorolac was taken off the German market as a painkiller due to a number of deaths from gastrointestinal bleeding and renal failure.[9] When ketorolac was first brought to Germany, it was frequently misused as an opioid substitute in pain management because people thought its side effects were significantly less severe, it didn't cause dependence, and a dose would work for 7-8 hours as opposed to morphine's 3-5 hours. Ketorolac is a very strong prostaglandin inhibitor that weakens the kidney's own defenses against effects of vasoconstriction, such as blood loss or high levels of endogenous catecholamines.[10]

CHEMISTRY OF KETOROLAC

Formula: $C_{15}H_{13}NO_3$

IUPAC nomenclature:(±)-5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid.



ketorolac

Figure 1 Structure of Ketorolac.

Table 1: Physiochemical Properties of Ketorolac.

S. NO.	PHYSICAL AND CHEMICAL PROPERTIES	
1	Molecular weight	255.27 g/mol
2	Physical appearance	Solid
3	Melting point	162-165°C
4	Solubility	Trimethamine salt solubility is 200 g/L
5	Octanol/water partition coefficient	2.1
6	Presence of ring	Pyrrolizine, phenyl
7	Number of chiral centers	1

Structure Activity Relationship

SAR of propionic acid derivatives can be summed up as follows: • Substitution of an α-methyl group on the alkanoic acid portion of acetic acid derivatives can increase the drug's anti-inflammatory activity.Acetic acid derivatives can have their associated side effects reduced by substituting an α-methyl group on the alkanoic acid portion. Enantiomer activity of the S-(+) enantiomer is higher than that of the (-) enantiomer.[11]

Mechanism of action of KT

Chemically speaking, ketorolac is a derivative of a carboxylic acid that inhibits prostaglandin G/H synthesis 1 and 2, thereby blocking prostaglandin synthesis non-selectively. The body uses prostaglandin as a messenger to control inflammation and contract and relax smooth muscle. As a result, inflammation is avoided by inhibiting prostaglandin synthesis.[12] The principal mechanism of action underlying the anti-inflammatory, antipyretic, and analgesic effects of ketorolac is the competitive inhibition of cyclooxygenase (COX) enzyme, which inhibits prostaglandin synthesis. A non-selective COX inhibitor is ketorolac.[13] It is regarded as an NSAID of the first generation.[14]

Pharmacokinetic aspects of ketorolac

Ketorolac is quickly and entirely absorbed when taken orally, with an 80% bioavailability following oral administration. Following intramuscular administration, the area under the plasma concentration-time curve (AUC) is proportional to the dose administered, and.[15] Cmax is reached 20–60 minutes after administration.[16] Ketorolac exhibits a time to maximal plasma concentration (tmax) of roughly 45–50 minutes following intramuscular administration and 30–40 minutes following oral administration. Food can slow down the rate of absorption, but it has no effect on the overall amount of absorption. Volume of distribution: In healthy human subjects, the apparent volume of distribution of ketorolac is 0.25 L/kg or less.[17] Protein binding: Plasma proteins bind more than 99% of ketorolac.

Metabolism: The liver uses hydroxylation and conjugation to break down ketorolac, but the primary metabolic pathway seems to be glucuronic acid conjugation. UDP-glucuronosyltransferase (UGT) 2B7.[18] is responsible for phase II metabolism, whereas CYP2C8 and CYP2C9 are involved in phase I metabolism.

Ketorolac is mainly excreted by the kidneys, where it can be excreted in urine in approximately 92% of cases. Of this amount, 60% are recovered unaltered, and 40% are recovered as metabolites. Additionally, the feces eliminate 6% of a single dose. Half-life: Since ketorolac tromethamine is administered as a racemic mixture, each enantiomer's half-life needs to be taken into account. The half-life of the R-enantiomer is approximately five hours, whereas that of the S-enantiomer is approximately 2.5 hours. This information indicates that the S enantiomer clears roughly twice as quickly as the R enantiomer. Clearance: Ketorolac has a plasma clearance of 0.021 to 0.037 L/h/kg.4 Additionally, research has shown that the clearance of oral, IM, and IV doses of ketorolac are similar, indicating linear kinetics.14 It should be mentioned that children's clearance is roughly twice that of adults.[19]

Toxicological profile of ketorolac

Toxicity

Higher doses of ketorolac result in an increased rate of side effects. The most commonly reported side effects in patients with an incidence of over 10% are headaches, nausea, dyspepsia, and abdominal pain.[20] Thirteen About 39% of patients experience the majority of mild side effects linked to short-term use, which are related to the nervous and gastrointestinal systems.[21] Ketorolac overdose symptoms frequently include nausea, vomiting, epigastric pain, bleeding in the gastrointestinal tract, lethargy, and sleepiness. Acute renal failure, hypertension, respiratory depression, and coma are some of the less common overdose symptoms. Due to a dearth of data proving its safety in pregnant women, ketorolac is categorized as pregnancy category C. Pregnant women should refrain from taking ketorolac starting at 30 weeks gestation because it raises the risk of the fetal ductus arteriosus closing prematurely in the third trimester, which is one of the NSAIDs.[22] It has been demonstrated that ketorolac is excreted in breast milk. Despite the lack of evidence indicating any negative effects in nursing infants, healthcare professionals should exercise caution when recommending ketorolac to nursing mothers. The advantages should exceed the hazards, and the mother should receive advice on how to keep a close eye on her child and

how to get in touch with the baby's doctor if there are any negative side effects. effect on prostaglandin synthesis may impair fertility.

Role of Ketorolac`as an antipyretic, analgesic and anti-inflammetry properties

Hamdy M *et al.*, 2023 has studied To enhance ocular performance and future formulation development, investigate the preformulation properties of ketorolac tromethamine by creating a high-performance liquid chromatography (HPLC) stability-indicating assay, forcing degradation under stress, solubility, and partition and distribution coefficient measurements. A diode array detector method for isocratic HPLC was created and verified. It was investigated how quickly materials degraded in response to heat, oxidative, acidic, and alkaline stresses. Furthermore, solubility, partition, and distribution were examined at various pH ranges between 3.5 and 7.4. Ketorolac eye drops should be formulated between pH 5.5 and 6.6 for the ideal balance of water and lipid solubility needed for penetration through the lipophilic corneal epithelial barrier. This is preferable to being formulated at the physiological fluid pH 7.4, where the drug is extremely hydrophilic and less permeable.[23] **Jean H *et al*., 2023.** has studied This was a single-center, randomized, double-blind, parallel-group study to evaluate how well scheduled ketorolac and placebo managed post-cesarean delivery pain. Following two postoperative doses of intravenous ketorolac, all patients undergoing cesarean delivery under neuraxial anesthesia were randomized to receive four doses of intravenous ketorolac or placebo every six hours. Six hours following the last study dose, more nonsteroidal anti-inflammatory drug administration was suspended. The amount of morphine milligram equivalents (MME) used overall during the first 72 hours following surgery was the main result. The number of patients who did not use opioids after surgery, postoperative pain ratings, changes in hematocrit and serum creatinine after surgery, and postoperative satisfaction with inpatient care and pain management were examples of secondary outcomes. Using a sample size of 74 per group (n=148), 80% of the population mean difference in MME could be detected, with an SD of 68.7 for both groups after protocol noncompliance was taken into account. The patient characteristics in each group were comparable. Between the time of entering the recovery room and the postoperative hour 72.[24] **Silva C*et al.*,2023** has examined Small stones that impede saliva secretion are the primary cause of sialolithiasis, which primarily affects the salivary glands in the mouth. To ensure the patient's comfort throughout this pathology, pain and inflammation must be treated and controlled. This led to the development of an alginate hydrogel that was cross-linked with ketorolac calcium and applied to the buccal cavity. The profile of swelling and

degradation, extrusion, extensibility, surface morphology, viscosity, and drug release were all examined in relation to the formulation. Ex vivo drug release was investigated in both static Franz cells and dynamic ex vivo settings with a continuous artificial saliva flow. The drug concentrations retained in the mucosa were high enough to deliver a therapeutic local concentration capable of reducing the pain associated with the patient's conditions, and the product exhibits adequate physicochemical properties considering its intended use. The outcomes validated the formulation's suitability for oral application.[25] **Puccetti M *et al.*, 2023.** has worked By using biodegradable metal alloys instead of inert metal alloys, which often require a second surgery, bone repair can be effectively supported. A biodegradable metal alloy combined with an appropriate analgesic may enhance the quality of life for patients. Using the solvent casting method, a poly(lactic-co-glycolic) acid (PLGA) polymer loaded with ketorolac tromethamine was used to coat the AZ31 alloy. The cytotoxicity of the optimized coated alloy, the PLGA mass loss of the polymeric film, and the ketorolac release profile from the coated AZ31 samples were evaluated. In simulated body fluid, the coated sample exhibited a longer-lasting two-week release of ketorolac, albeit at a slower rate than that of just the polymeric film. After 45 days in the PLGA, mass loss was fully achieved. In human osteoblasts, the PLGA coating was able to reduce the cytotoxicity of AZ31 and ketorolac tromethamine. Additionally, PLGA coating stops AZ31 cytotoxicity, which was found in human fibroblasts. As a result, PLGA was able to regulate the release of ketorolac and shield AZ31 from early corrosion. These properties lead us to speculate that osteosynthesis and pain relief may be enhanced by using PLGA coating loaded with ketorolac tromethamine on AZ31 for the treatment of bone fractures.[26] **Joshua E *et al.*, 2023**. has revied on Musculoskeletal pathology must be treated with effective pain management. For their analgesic and anti-inflammatory effects, corticosteroid injections have been used both locally and systemically for orthopedic conditions for a long time. Since they are less harmful than corticosteroids, opioids have long been used in the perioperative setting to maximize pain control. Nonsteroidal anti-inflammatory drugs (NSAIDs) like ketorolac have been demonstrated to be useful as an analgesic and anti-inflammatory drug both inside and outside of the perioperative setting, with a lower risk of systemic and local side effects. Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, a systematic review was carried out. All things considered, the reviewed studies consistently showed that ketorolac has a very good safety profile, both locally and systemically. According to clinical trials, the local application of ketorolac resulted in reduced postoperative pain, shorter hospital stays, and a decrease in the use of

opioids following surgery.its kind to evaluate the safety, effectiveness, and postoperative results of local ketorolac injections in musculoskeletal pathologies. For patients suffering from musculoskeletal conditions, the local application of ketorolac in the intra- and peri-articular setting offers a secure and efficient supplement or substitute therapy.[27] **Siddiquia M *et al.*, 2022**. has studied on The goal of this study was to create quickly dissolving sublingual films of ketorolac tromethamine in order to reduce the drug's gastrointestinal side effects and increase patient compliance by preventing direct contact with the stomach mucosa. In order to assess the impact of these constituents on the overall formulation, this study produced Ketorolac tromethamine sublingual film by solvent casting method using a variable ratio of polymer and plasticizer but a fixed quantity of other excipients and solvent ratio. The morphological and organoleptic characteristics, weight homogeneity, folding endurance, surface pH, thickness, percentage of moisture loss, dispersion, dissolution, and homogeneous drug content were all used to assess the prepared films. Also, FTIR spectroscopy was used to assess the compatibility of APIs and excipients. It was discovered that the prepared films had thin, quick dispersion and dissolving characteristics. As a result, patients can use the sublingual film to quickly relieve pain and experience little adverse effects on their digestive systems.[28] **MarkaziR *et al.*, 2022** has performed As a rich source of growth factors, platelet-rich blood derivatives are being used more and more in the treatment of tendon-related pathologies. In contrast to the group treated with ketorolac and tromethamine, we aimed to determine whether local application of platelet lysate (PL) to enhance rotator cuff repair improves patient outcomes. Forty patients with a clinical diagnosis of rotator cuff tendinopathy were randomly assigned to receive two injections of ketorolac tromethamine every two weeks and three subacromial injections of PL per week. VAS, SPADI, and shoulder range of motion were among the subjective tests performed at baseline, one month, and six months following injection. When comparing the results at the initial and short-term stages for the control and PL groups, it was clearly evident that they were the same; however, when looking at the 6-month period, the PL group appeared to have a remarkably superior performance across all parameters.[29] **Zhang.W. *et al.*, 2022.** has worked on the possible role of ketorolac tromethamine in the treatment of osteoarthritis by looking at how it affects chondrocyte cellular senescence that is triggered by interleukin-1β (IL-1β). IL-1β-challenged HC-A cells showed increased release of matrix metalloproteinase (MMP)-3 and MMP-13, more β-galactosidase (SA-β-Gal) positively stained cells, promoted cell fraction in the G0/G1 phase, and upregulated cellular senescence-related genes (p21 and p53). All of these effects were significantly reversed by ketorolac tromethamine.

Additionally, ketorolac tromethamine significantly suppressed the increased release of prostaglandin E2 and upregulated cyclooxygenase-2 (COX-2) in IL-1β-challenged HC-A cells. Finally, the overexpression of COX-2 significantly neutralized the inhibitory effects of ketorolac tromethamine on the activation of SA-β-Gal and the upregulation of p21 and p53. All together, COX-2 inhibition by ketorolac tromethamine suppressed cellular senescence in aging articular chondrocytes.[30] **Jassim OY *et al.*, 2021.** has studied on The pharmacological interaction and pharmacokinetics of nefopam and ketorolac in chickens have not been studied before. nefopam and ketorolac interacted synergistically, and that nefopam's pharmacokinetic characteristics changed, potentially improving the drug's therapeutic effectiveness in chicks.[31] **Elizabeth Gaul *et al.*, 2021** has determined In the emergency room, complaints of pain are frequent. It would be ideal to have an opioid substitute. When dealing with gastrointestinal disorders or NPO, oral medications are not practical. Administering drugs via IV takes practice and patience. Medication administered intravenously or intramuscularly can cause pain and needlestick injuries. Intranasal drugs don't require trained caregivers, have a quick onset, are simple to administer, and carry no risk of needlestick injuries. Intranasal ketorolac was administered to a total of 28 adults with acute pain.The entire numerical rating scale dropped: 32% reported complete pain relief; the median (interquartile range) dropped by −5 (-6.8 to -4), with a p-value of less than.001. The median [interquartile range] time for pain relief was 5 (2.3, 15.0) minutes. Vital indicators continued to be normal. There were no complications or alterations to the nasal mucosa. Minor side effects primarily burning in the nose, went away in five minutes. Both nurses and patients felt that intranasal ketorolac worked well and that they would use it again. The effects of intranasal ketorolac were swift, safe, and well-tolerated; minor side effects disappeared quickly.[32] **MousaY J *et al.*, 2019**. has analysed non-addictive, potent analgesics with fewer adverse effects are needed these days. Thus, the current investigation assessed the effectiveness of ketorolac as an analgesic, antipyretic, and anti-inflammatory drug in broiler chicks aged 7–21 days, as well as its potential utility in a related field. 50% of the chicks had analgesia at the analgesic median effective dosage (ED50) of intramuscular (IM) ketorolac. Analgesia was created at all recorded timesfor assessing the analgesic effect of ketorolac; however, the highest and best analgesic efficacy was noted at 15 min following ketorolac injection. As a result of formaldehyde injection, the chicks' right paw thickness decreased dramatically when given intramuscular injection of ketorolac. This indicated that the injection had an anti-inflammatory effect. Although there was no liver damage, the chicks' ketorolac therapy may have caused decreased metabolism and function, as determined by measuring the serum AST

and ALT values. Because of its good, consistent, and effective efficacy, the study recommends using ketorolac as an analgesic, antipyretic, and anti-inflammatory drug in the field of veterinary medicine.[33] **Erin Taggart *et al.*, 2013**. has revied on The effectiveness of parenteral ketorolac (KET) in treating acute migraine was investigated in this systematic review. Acute migraine headaches are frequently seen in emergency rooms, however there is conflicting data supporting different treatment options.in relation to KET use. Gray literature sources as well as MEDLINE, EMBASE, Cochrane, and CINAHL searches were done. The included studies were randomized controlled trials in which adult patients with acute migraine were treated with KET alone or in combination with abortive therapy, and the results were compared with placebo or other standard therapy. Two reviewers evaluated the study's quality, inclusion, and relevance separately. Kappa (k) was used to gauge their level of agreement. 95% confidence intervals (CIs) are provided along with the reported weighted mean differences (WMD) and relative risks. The profiles of side effects were comparable in the KET and comparison groups. In general, KET is a useful substitute medication for emergency migraine headache relief.department. KET relieves pain similarly, has less potential for addiction than meperidine, and works better than sumatriptan; however, it might not work as well as agents that combine metoclopramide and phenothiazine.[34] **Paul F. *et al.*, 2012** has concluded Effective perioperative analgesia is well known to shorten hospital stays, enhance patient satisfaction, and aid in the rehabilitation process. As part of a multimodal analgesic regimen, ketorolac is a highly cost-effective parenterally active nonsteroidal anti-inflammatory drug (NSAID) that is often used during and after surgery to improve pain management following both major and minor surgical procedures. By enhancing pain management and lowering opioid-related side effects (such as nausea, vomiting, constipation, urine retention, cardiorespiratory depression, pruritus, and sleep disturbances), ketorolac's opioid-sparing effects can speed up the healing process.as medical professionals and seasoned clinical researchers in this area, we were taken aback by some of the findings of De Oliveira and colleagues meta-analysis on the prophylactic use of ketorolac, which was published in the most recent issue of Anesthesia & Analgesia. This is especially unexpected because it is well known that ketorolac effectively relieves pain, and the majority of experts think that treating pain is easier than preventing it. These authors also came to the conclusion that IM ketorolac administration was preferable to IV. A few of the studies in the meta-analysis were "underpowered" to show a difference, and active comparator-controlled clinical trials were excluded from their analysis, raising doubts about the validity of the conclusion that a 30-mg dose of ketorolac is ineffective for preventing pain. The conclusion about the

administration of ketorolac by IV versus IM can be questioned because there was no direct comparison between the two routes of administration in any of the studies that were cited.[35] **Neil Singla*et al.*, 2010**. has evaluated Intranasal ketorolac (SPRIX®) was evaluated for efficacy and tolerability in patients undergoing abdominal surgery. After surgery, adult patients were randomly assigned to receive either a placebo (n = 107) or 31.5 mg of ketorolac every 6 hours for 48 hours, and then up to 4 times a day for a maximum of 5 days. Both groups had access to morphine sulfate through patient-controlled analgesia as needed.[36] **SinhaVR et *al.*, 2009**. has studied on A non-steroidal anti-inflammatory medication, ketorolac tromethamine (KT) is a member of the heteroaryl acetic acid derivatives class. It is a racemate-based non-selective cyclooxygenase (COX) inhibitor that is being sold. The S-isomer retains the majority of its analgesic and COX inhibitory activity. Oral, intramuscular, intravenous, and topical ophthalmic solutions are the ways in which ketorolac is administered in its tromethamine salt form. The development of different formulation strategies for the appropriate delivery of KT has been prompted by the short mean plasma half-life (t1/2 ~ 5.5 h) and the frequent occurrence of gastrointestinal disturbances such as peptic ulceration, perforation, and bleeding. The article provides a summary of the key ideas that have been applied thus far to the design of diverse pharmaceutical dosage forms for the drug candidate's therapeutically efficient delivery via a variety of routes. The development of sustained release forms of the medication is currently receiving a lot of attention because it would help achieve then ecessary the rapeutic efficacy, better to lerance, and few ergastrointestinal side effects.[37]

K.S. Ong *et al.*, 2004. has reported The effectiveness of preemptive analgesia in reducing postoperative pain is debatable. The majority of earlier research used a parallel design, many confounding inter-patient variables, and were conducted under general anesthesia. Right now In a crossover design, the study assessed the effectiveness of preemptive ketorolac in patients undergoing bilateral mandibular third molar surgery. Thirty-four patients had their identical impacted mandibular third molars extracted twice under local anesthesia in this double blind, randomized, placebo-controlled study. Four main endpoints were used to compare each patient's postoperative pain on the pretreated and post-treated sides: pain intensity as determined hourly for 12 hours using a 100-mm visual analogue scale, time to rescue analgesic, amount of postoperative analgesics taken, and overall evaluation of the patient. Patients on the ketorolac pretreated sides reported significantly lower pain intensity scores than those on the post-treated sides during the 12-hour investigation period. Patients also

reported a lower postoperative analgesic consumptiona significantly longer time to rescue analgesic (8.9 h versus 6.9 h, P=0.005), and a better overall assessment for the sides that had received ketorolac pretreatment (P=0.01). Intravenous ketorolac pretreatment prolongs the analgesia by about two hours and has a preventiveeffect for postoperative third molar surgery.[38] **ForrestJ.B *et al.*, 2002.** has studied on Although ketorolac is approved to relieve postoperative pain, questions have been raised regarding the possibility of fatal side effects. Ketorolac safety data was found to be inconclusive and lacked comparison with other non-steroidal anti-inflammatory drugs in two European regulatory reviews. This study compared the risk of serious side effects in adult patients undergoing elective major surgery between ketorolac and diclofenac or ketoprofen. Techniques. The risks of death, increased bleeding at the surgical site, gastrointestinal bleeding, acute renal failure, and allergic reactions were assessed in this prospective, randomized multicenter trial. Ketorolac, diclofenac, and ketoprofen were administered in accordance with their approved parenteral and oral doses and treatment durations.[39] **Alex Macario *et al.*, 2001.** has determined The development of intravenous formulations and the introduction of oral COX-2 selective NSAIDs that may be used during surgery have prompted a comprehensive evaluation of the safety, effectiveness, and regulatory concerns surrounding ketorolac.To determine if using ketorolac enhanced the quality of analgesia or decreased the frequency of opioid side effects, odds ratios were calculated. Ketorolac decreased the amount of opioid medication by a mean of 36% (range 0% to 73%), depending on the type of surgery. One hour after surgery, 70% of patients in the control groups reported moderate-to-severe pain, whereas 36% of the control patients had Since the revision of dosage guidelines, there has been a decrease in the incidence of serious adverse events. Use of ketorolac should be limited to the lowest dose required. Painkillers that offer potent analgesia with few side effects are required. Odds Ratio, Acute Pain, Analgesia, NSAIDS, Opioid Sparing, Ketorolac.[40] **Zhou*et al.*, 2001**. has worked on the effectiveness of IV propacetamol and ketorolac as analgesics in patients undergoing total hip or knee replacement surgery in a double-blind, placebo-controlled study. The morning following significant joint replacement surgery, 164 patients with moderate-to individuals with moderate-to-severe pain were randomized to receive an IV infusion of either saline, ketorolac (15 or 30 mg), or propacetamol (2 g). During the 6-hour postdosing evaluation period, patient-controlled analgesia with morphine was made available as a "rescue" analgesic upon patient request. Propacetamol produced a significantly greater improvement in pain relief than saline from 45 minutes to 5 hours after the injection, according to an analysis of pain intensity and pain relief scores. During the 6-hour assessment period,

propacetamol did not significantly differ from ketorolac 15 mg and 30 mg in terms of the primary analgesic efficacy variables. Injection site pain was the most commonly reported adverse event associated withpropacetamol. To sum up, Following total hip or knee replacement surgery, the analgesic efficacy of propacetamol (2 g IV) is comparable to that of ketorolac (15 or 30 mg IV).The mainstay of treatment for patients with moderate-to-severe postoperative pain has been opioid analgesics. the use of these medications is linked to dose-related side effects and does not always result in adequate patient comfort. Nonsteroidal anti-inflammatory drug (NSAID) use as an adjuvant after major orthopedic and gynecologic surgeries decreases postoperative opioid requirements and/or enhances the quality of analgesia Interestingly, ketorolac, the parent NSAID, works just as well as morphine. The possibility of increased gastrointestinal harm, renal toxicity, and operative site bleeding with ketorolac use. interest in the use of other nonopioid analgesic classes (e.g., acetaminophen). Combined with patient-controlled analgesia (PCA) morphine, the injectable prodrug of acetaminophen propacetamol has analgesic efficacy comparable to ketorolac. the onset and duration of analgesia of these two nonopioid analgesics because it did not include a placebo (control) group. Thus, the purpose of this double-blind, placebo-controlled study was to Examine the effects of IV propacetamol (2 g) and ketorolac (15 or 30 mg) on patients experiencing moderate-to-severe pain following total hip or knee replacement surgery. Compare the analgesic efficacy of each medication as well as its start and duration.[41] **J Robin DeAndrade. *et al.*, 1994**. has analysed For the treatment of acute pain, ketorolac tromethamine, also known as toradol, is a nonsteroidal anti-inflammatory drug (NSAID) that can be taken orally or intramuscularly (IM). In the United States, the only parenteral NSAID available for analgesic use is intramuscular ketorolac. Clinical studies most relevant to a postoperative patient are thoroughly discussed and the clinical profile is reviewed.Ketorolac's analgesic effectiveness was noticeably better than a placebo and on par with both morphine dosages. As an alternative to opioid therapy, ketorolac can be used intramuscularly or orally to manage acute postoperative pain in the short term in a safe and efficient manner.[42] **Ian A. Greer *et al.*, 1990.** has studied on A strong prostaglandin synthetase inhibitor that can be used to treat postoperative pain is ketorolac tromethamine. Given its established antiplatelet characteristics, we ascertained the impact of ketorolac both singularly and in conjunction with low-dose heparin. regarding hemostasis. In a double-blind, crossover trial, twelve healthy male volunteers were given the following drug combinations: ketorolac dummy/heparin dummy, ketorolac active/heparin active, ketorolac dummy/heparin active, and ketorolac dummy/heparin active. In addition to significantly extending the bleeding time,

ketorolac also prevented platelet aggregation and the production of platelet thromboxane. Heparin greatly extended the kaolin-cephalin clotting time but had no effect on bleeding time or platelet function. and elevated anti-X a levels over time. Anti-X a levels and the kaolin-cephalin clotting time were unaffected by ketorolac, and there was no interaction between the drug and heparin. Given that almost all subjects' bleeding times remained within the normal range, the slight prolongation of bleeding times with ketorolac is unlikely to have any significant clinical implications.However, patients with hemostatic disorders should use the medication with caution due to its antiplatelet properties.[43] **Resman-Thrgoff BH *et al.*, 1990** has analysed When injected intramuscularly to treat acute pain, ketorolac tromethamine, a pyrrolo-pyrrole nonsteroidal anti-inflammatory drug (NSAID), has strong analgesic properties. Ketorolac has a quick start of action and is well absorbed. The highest concentrations of plasma are met in 45–50 minutes, with the greatest analgesic effects occurring one to two hours after the intramuscular injection. The elimination half-life, which is roughly four to six hours, rises in older patients and renally impaired patients. In single-dose studies of patients with postoperative pain or renal colic, its analgesic effectiveness was comparable to or greater than that of morphine, meperidine, or pentazocine; in patients with chronic cancer pain, it was more effective than a placebo. The negative consequences are typically self-limiting, mild to moderate, and comparable to those observed with other prostaglandin suppressors. Platelet aggregation is reversibly inhibited by ketorolac. It can even result in parenterally administered gastric ulcerations due to dose-related reactions. A non-narcotic substitute for opioid analgesics, ketorolac is a potentially effective parenteral option to oral NSAIDs. To more precisely define its role in therapy, more multiple-dose studies are required.[44]

B). Role of ketorolac as an anesthesia.

Xi Zhang *et al.*, 2023. has determined to monitor the effects of remifentanil and ketorolac tromethamine on sedation and analgesia during the emergence of general anesthesia and the reduction of complications related to it. Techniques-Ninety patients underwent total or partial thyroidectomies at our hospital; these patients were randomly assigned to three groups, each containing thirty cases. For general anesthesia, endotracheal intubation was combined with routine general anesthesia; for skin suturing, alternative treatments were given. Groups K and R received intravenous injections of normal saline (2 mL) and remifentanil (0.1 mcg/kg/min) via micropump until awakening and extubation; Group K received an intravenous injection of ketorolac tromethamine (0.9 mg/kg) and an intravenous injection of normal saline (10 mL/h).

Intravenous injections of 0.5 mg/kg ketorolac tromethamine and 0.05 mcg/kg/min remifentanil via micropump are administered until the patient awakens and is extubated. Following surgery, every patient was admitted to the postanesthesia care unit (PACU) for scoring, extubation, and recuperation. A count was conducted on the frequency and state of different complications.Regarding the patients' general information and the length of their operation, there was no discernible difference (P >.05). Each group received the same kinds of general anesthesia induction medications, and the drug measurement did not differ significantly.[45] **Reuben*et al.*, 1995.** Nonsteroidal anti-inflammatory medications (NSAIDs) can be used in addition to postoperative pain relief to prevent the synthesis of inflammatory mediators.Wehypothesised that utilizing parenterally administered ketorolac (K), an NSAID, as part of intravenous regional.Intraoperative tourniquet pain would be reduced and postoperative analgesia would be improved with anesthesia (IVRA). Randomly and blindly, sixty patients were divided into three groups: IV K and IVRA 0.5% lidocaine, IV saline and IVRA 0.5% lidocaine with K, or IV saline and IVRA 0.5% lidocaine with K. With reduced verbal analog pain scores at 15 and 30 minutes following tourniquet inflation, the patients who received IVRA K reported much less intraoperative tourniquet pain. In the initial twenty-four hours, they also needed fewer analgesic tablets than the other two groups.As the only nonsteroidal anti-inflammatory drug (NSAID) authorized for parenteral use in the US, ketorolac (K) increases the analgesic effects of systemic or epidural opiates by interfering with the synthesis of inflammatory mediators.NSAIDs are assumed to work at peripheral nociceptors, possibly by obstructing the production and function of arachidonic acid-derived pain mediators.One safe and efficient method of administering anesthesia for is through intravenous regional anesthesia (IVRA).[46]

C). Ketorolac`s function in randomized controlled studies

FuxianCai *et al.*, 2023. has evaluated Regarding the management of renal colic pain, there is ongoing debate regarding the efficacy of ibuprofen versus ketorolac. For this reason, we are conducting this meta-analysis to evaluate the effectiveness of ibuprofen and ketorolac as analgesics for renal colic. Based on the heterogeneity, the random-effect or fixed-effect model was used to conduct this meta-analysis. For the pain associated with renal colic, ibuprofen has an analgesic efficacy that is comparable to ketorolac.ibuprofen, ketorolac, pain management, renal colic, randomized controlled trials.[47] **Johnson BA, *et al.*, 2022.** We evaluated the impact of ketorolac given at the time of stent removal in a prospective, randomized, double-blind, placebo-controlled study. Before having their stents removed,

patients were randomly assigned to receive either a placebo or 30 mg of intramuscular ketorolac. One or seven days following the removal of the stent, patients were contacted to evaluate pain, the need for opioids, visits to the emergency room or clinic, and the necessity of surgical or medical interventions. Ketorolac administration prior to stent removal lowers the risk of severe renal colic requiring ER or office visits, but it does not significantly reduce the overall subjective pain experienced after stent removal when compared to placebo. When having a stent removed, eligible patients may benefit from routine use of ketorolac injection.[48] **De Oliveira*et al.*, 2012.** It is acknowledged that the use of non-opioid analgesic strategies for preventive analgesia can enhance postoperative pain management while reducing the risk of opioid-related side effects. A common nonsteroidal anti-inflammatory medication used to treat postoperative pain is ketorolac. To avoid postoperative pain, systemic single dose ketorolac's ideal dosage and method of administration are not yet fully established. To assess the effectiveness of a single dose of perioperative ketorolac on postoperative analgesia, we conducted a quantitative systematic review. To find randomized controlled trials assessing the impact of a single dose of systemic ketorolac on opioid consumption and postoperative pain, a thorough search was conducted. Systemic ketorolac taken as a single dose works well as an adjuvant in multimodal regimens to lessen postoperative pain. Ketorolac was able to improve postoperative analgesia while also reducing postoperative nausea and vomiting. The most frequent unfavorable consequence for patients undergoing surgical procedures is postoperative pain. Postoperative pain not only hurts patients, but it also makes recovery take longer and lengthens hospital stays.[49]

D). Role of ketorolac in cancer

Allen T. Yu *et al.*, 2023. has revied on When a patient has jaundice and biliary blockage, biliary decompression is achieved through percutaneous transhepatic biliary drainage. Rarely, high drain output over 2000 millilitres per day might lead to electrolyte imbalances and dehydration in the absence of appropriate interventions. We report the first patient, to our knowledge, with malignant biliary obstruction from duodenal adenocarcinoma who responded to the analgesic ketorolac with progressive reduction in biliary output.[50] **Belinda Butcher *etal.*, 2021.** has approached The conventional approach to managing pain associated with cancer entails the coadministration of opioids and non-steroidal anti-inflammatory drugs (NSAIDs). An NSAID called ketorolac has been shown in other clinical settings to have opioid-sparing properties.The purpose of this systematic literature review was to examine the opioid-sparing effects of ketorolac in patients who were being treated

with opioids for chronic pain related to cancer. The total daily dose of opioids was the main outcome. Adverse events, the frequency of using "rescue" medication, and the frequency of opioid use were all considered secondary outcomes. Results were outlined and, when feasible, meta-analysed. CRD42019130894, PROSPERO registration number. Ketorolac may have an opioid-sparing effect, despite the significant heterogeneity. A single randomised controlled trial showed significant reductions in the total daily dose of morphinebut the differences between the before and after studies were not statistically significant. Data were inconsistent, but ketorolac was linked to a higher chance of totalpainrelief.[51] **Zhongqi Liu*et al.*, 2020.** has worked on Contrary to nonsteroidal anti-inflammatory medications (such ketolorac), which were linked to a lower rate of metastasis in TNBC, opioids were found to cause TNBC. These conflicting results call for more information about how postoperative ketorolac and morphine affect TNBC metastasis. A measurement was taken of the number of lung metastases three weeks following resection. In recurrent cancers, microvessel density, thrombospondin-1 (TSP-1) and c-Myc expression in recurrent tumors. MDA-MB-231 cells were treated in accordance with the above regimen, either with or without the addition of an AKT inhibitor, in order to investigate the activation of the PI3K/AKT/c-Myc pathway and shed light on the aforementioned phenomenon in vitro. Morphine increased TNBC metastasis and angiogenesis, lowered TSP-1 expression, and elevated c-Myc expression in mice; however, concurrent ketorolac administration dramatically corrected the aforementioned phenotypes ($p < .05$). Mechanistically, ketorolac increased TSP-1 secretion ($p < .05$) by inhibiting the PI3K/AKT/c-Myc pathway, while morphine inhibited TSP-1 secretion ($p < .05$) by activating the same pathway. According to our research, angiogenesis and TNBC metastasis were both increased by morphine, but these effects were inhibited by ketorolac. Mechanistically, this could be connected to the further deactivation of the PI3K/AKT/c-Myc pathway caused by the increase in TSP-1 synthesis following ketorolac administration.[52] **Venu K *et al*., 2018**. has reported Ketorolac (KT) is a NSAID, with multiple pharmacological activities having been reported. Aim To formulate chitosan nanoparticles of KT for assessing their potential in decreasing the growth of colon cancer cells. Chitosan nanoparticles of KT such as F1 and F2 have shown anticancer activity against SCC-29 cell lines. Furthermore, nanoparticles have been subjected to stability test at various pH, drug-release study, and in-vivo pharmacokinetics in Wistar rats. The nanoparticles were in the size range between 164 and 210 nm. The oral absorption of nanoparticles was relatively higher than the KT alone. The prepared nanoparticle formulations showed better activity than KT alone.[53] **Kotagal M *et al.*, 2016**. has studied on During colon surgery, nonsteroidal anti-inflammatory medications

can worsen wound healing and raise the possibility of anastomotic leaks. The sample size, lack of ability to detect confounding, and exclusive focus on colon surgery have limited the studies conducted thus far.[54] **Yuna Guo*et al.*, 2015.** has examined The R-enantiomer of ketorolac has been shown to inhibit the GTPases Rac1 and Cdc42, which are members of the Rho family. Rac1 and Cdc42 control processes related to cancer, such as the remodeling of the cytoskeleton required for tumor cell adhesion and migration. This study examined whether peritoneal distribution of R-ketorolac, target GTPase inhibition in cells recovered from the peritoneal cavity, and measurable effects on patient outcomes resulted from the administration of racemic (R,S) ketorolac following ovarian cancer surgery. Patients who met the eligibility criteria may have had primary peritoneal, fallopian tube, or advanced-stage ovarian cancer. When ovarian cancer was diagnosed and optimally debulked, an intraperitoneal port was implanted, and there were no contraindications to the administration of ketorolac, secondary eligibility was satisfied. GTPase activity was assessed in peritoneal cells, and R- and S-ketorolac levels were assessed in serum and peritoneal fluid. Perioperative ketorolac use and the specific survival of ovarian cancer patients were linked in a retrospective study.[55] **KINSELLA *et al.*, 1992** has worked on The analgesic efficacy and postoperative morphine requirements of four doses of intramuscular ketorolac (30 mg) given six hours apart were compared with a placebo in a double-blind study involving patients undergoing major or minor orthopaedic surgery. In the 24 hours following surgery.During the 2-hourly study period that started after surgery, patients were given 10 mg of morphine intramuscularly as needed, and their pain levels were monitored every 4 and 24 hours. Following a major following surgery, patients who received ketorolac consumed a median of 10 mg of morphine over a 24-hour period, while patients who received a placebo consumed 30 mg (P = 0.008).from mild to severe discomfort 24 hours following surgery. Patients who received ketorolac in addition to opioids experienced an improvement in analgesia. But we didn't observe a corresponding decline in the negative effects of opioids, like nausea and vomiting. This might be the result of research using too small of sample sizes, making it difficult to identify variations in the frequency of opioid-related adverse effects. High dosages, prolonged therapy (>5 days), and invulnerable patients increase the risk of adverse events when using ketorolac. were not, however, statistically different at 24 hours between the groups. The two groups of patients who had major surgery were similar in terms of their overall pain assessment. Patients in the minor surgery groups consumed 0 mg of morphine on average.who took ketorolac, as opposed to 10 mg for placebo-treated individuals (ns). Patients who received ketorolac had significantly lower visual analogue pain scores 24 hours

after surgery (P = 0.046) than those who received a placebo, and the ketorolac group also had better overall pain relief ratings (P = 0.0007). Ketorolac administration by mandate seemed to be beneficial for both major and minor orthopaedic surgery; the main benefits were better overall analgesia for minor surgery and a decrease in the need for additional morphine for major surgery.[56]

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Conficts of interest

None.

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