REVIEW ARTICLE

Ketorolac Tromethamine – Routes and Clinical Implications

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■ **Abstract:** Opioids have long been used for analgesic purposes for a wide range of procedures. However, the binding of these drugs to opiate receptors has created various challenges to the clinician due to unfavorable side effect profiles and the potential for tolerance and abuse. In 1989, ketorolac became an approved nonsteroidal inflammatory drug (NSAID) for injectable use as an analgesic. Over the last 20 years, numerous studies have been conducted involving ketorolac. These studies have provided additional information about various routes of administration and their effect on the efficacy and the side effect profile of ketorolac. Moreover, ketorolac has been compared with several widely used analgesics. This review evaluates both the potential benefits and potential drawbacks of ketorolac generally, and specifically discusses routes of administration, including their advantages and disadvantages when compared to several traditional analgesics in both inpatient and outpatient settings. ■

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INTRODUCTION

Moderate-to-severe acute pain occurs commonly following ambulatory procedures and in patients following surgery. Controlling moderate-to-severe acute pain adequately in the emergency room setting is also a challenge. Conventionally, the central acting opiates have been the keystone of postoperative analgesia; however, the adverse effect profile of opiates, such as respiratory depression, psychomotor disturbances, ataxia, sedation, constipation, tolerance, and dependence, has led some clinicians to avoid repeated dosing of opioids. This led to the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in conjunction with opioids to provide adequate postoperative analgesia and minimize the adverse drug effects of opioids.

Long-term exposure to ketorolac has been correlated with an enhanced risk of gastrointestinal bleeding and with renal insufficiency in chronic kidney disease.[1] The use of ketorolac with or without opioids in the immediate postoperative period results in improvement in the

quality of analgesia, with a decrease in opioid-related side effects. Studies have shown that restricting the dosage and duration of exposure (5 days or less), as well as use in patients younger than 65 years old, significantly reduces adverse effects.[2] Moderate-to-severe acute pain in the emergency room setting is often controlled by intravenous agents, such as opioids like butorphanol, or intravenous NSAIDs, including diclofenac (not available in the US) and ketorolac. This review will discuss the use of ketorolac in inpatient and in outpatient settings, its properties, and its advantages and disadvantages as an analgesic.

CHEMICAL STRUCTURE AND PHARMACOLOGY

Chemical formula of Ketorolac- (+)-5-benzoyl-2,3-dihydro-1Hpyrrolizine-1-carboxylic acid, 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1).

Ketorolac belongs to the heteroaryl acetic acid nonselective COX inhibitor group. It possesses a chiral center and is composed of (+)R and (-)S enantiomers in equal proportions. The pharmacological (analgesic and COX inhibitory activity) is retained almost exclusively in the S-enantiomer.[3] It is commercially available as a tromethamine salt which augments its water solubility.[4] According to Jamali and Mroszczak, the analgesic efficacy of ketorolac depends on the racemic mixture concentrations of S and R enantiomers.[5,6]

Preparations

Ketorolac tromethamine [Toradol®] was the first NSAID commercialized in the United States for parenteral use in March 1990; later, oral tablets were approved in 1991. Ketorolac tromethamine is highly water soluble, and it is the only NSAID that can be delivered via intranasal route owing to its solubility profile. Sprix®, an intranasal formulation of ketorolac, was introduced in May 2010. Another topical form of ketorolac, called Acular®, is being used as an analgesic and anti-inflammatory agent for ocular conditions.

Clinical Pharmacology

Absorption and Bioavailability. Ketorolac is rapidly absorbed following oral and intramuscular administration. The presence of food in the stomach delays the rate of absorption. The tromethamine component of the drug enhances its solubility that helps in absorption.[7]

The bioavailability of ketorolac is approximately 80% to 100% following oral, intramuscular and intravenous administration.[8] The bioavailability of intranasal ketorolac compared with IM administration is about 67% to 75%.[7]

Analgesic Onset of Action. Ketorolac has a rapid onset of action with effects beginning within 10 minutes following IM and IV route of administration, and peak analgesia achieved at 75 to 150 minutes. Intranasal ketorolac has a faster onset of action, and the time required for peak effect is about 45 minutes[7] (Table 1).

Oral administration has a much slower onset, occurring 30 to 60 minutes following consumption of the drug, with peak analgesia at 1.5 to 4 hours. This must be taken into consideration, especially when treating postoperative pain. The total duration of action following oral, intramuscular and intranasal administration is about 6 to 8 hours.

The half-life is 5 to 6 hours in adults and 3.8 to 6.1 hours in pediatric patients.[8] It is prolonged in the presence of renal impairment up to 9 to 10 hours.[9] Hepatic impairment does not affect half-life significantly.

In a study conducted in geriatric subjects, a single IM injection of 30 mg ketorolac tromethamine was given. This was succeeded by an oral dose of 10 mg ketorolac following a 1-week washout period. It was found that the half-life was prolonged for both routes of administration (4.7 to 6.1 and 4.5 to 7 hours for oral and IM route, respectively), and oral plasma clearance was decreased in comparison with younger adult subjects ($P < 0.001$). Hence, the elderly require a lesser dosage and frequency of intramuscular and oral ketorolac administration to maintain similar plasma levels.[10]

The recommended dosage of ketorolac tromethamine (oral, IM, IV) for subjects aged > 65 years is half of the dosage used for patients aged < 65 years of age (typi-

Table 1. Comparative Pharmacokinetics and Pharmacodynamics of Ketorolac Routes of Administration[7]

Pharmaco-Kinetics	Oral	Intra Muscular	Intra Nasal	Intra Venous
Bioavailability	80–100%	100%	67–75%	100%
Onset of action (minutes)	30–60	10–20	10–20	10–15
Peak analgesia (minutes)	90–240	75–150	45	75–150
T_{max} (min)	30–53	45–50	45–50	5
Half-life (hours)	5.3 (3.5–9.2)	5.3 (2.4–9.0)	5.24	5.6 (4–7.9)

cally 30 mg for single doses), and a total daily dose should not exceed 60 mg when multiple doses are used.[11] Ketorolac is not recommended for use in pediatric patient age group.

Distribution. Ketorolac is highly protein bound (> 99%) and has limited distribution in the extravascular tissues including its penetration across the blood–brain barrier.[8] However, it crosses the placenta and is also excreted into milk.[3,8] Hence, it should not be used during the final trimester of pregnancy due to the danger of premature closure of the *ductus arteriosus* in the newborn and is classified as a category C drug. It is also contraindicated in women who nurse due to risk of exposure to infants.

Metabolism. It is metabolized in the liver via glucuronidation and parahydroxylation[3] with 96% of the circulating drug in the form of the active parent drug, ketorolac, and the remainder in the form of its inactive metabolite, p-hydroxy ketorolac.

Elimination. Approximately 90% of the consumed drug is eliminated in urine, and around 6% to 8% is eliminated in the feces. Nearly 60% of the drug excreted in the urine represents the parent drug, approximately 12% of the drug is excreted as p-hydroxy ketorolac, and approximately 28% is in the form of glucuronide conjugates of ketorolac metabolized by the liver.[3]

MECHANISM OF ACTION

Ketorolac inhibits the enzyme cyclooxygenase that converts arachidonic acid to thromboxane, prostacyclin, and prostaglandins. Prostaglandins secreted at the site of injury/inflammation augment the sensitization of afferent nerve endings.[1] However, there are some grounds to confirm that NSAIDs may have a central mechanism of action due to its effect on the hypothalamic prostaglandin system. In addition, central (serotoninergic, beta-endorphin, and monoaminergic) pathways involved in nociception may also be affected by the NSAIDs.

In order to analyze the CSF penetration of ketorolac, Rice et al.,[12] conducted a study on 29 patients to establish the ratio of ketorolac tromethamine in cerebrospinal fluid (CSF) to the plasma concentration following a single IM dose of 90 mg. The results showed that the amount ketorolac in the CSF was about 1,000 times lower than that of the plasma. This confirms the limited entry of ketorolac and its active metabolites into CSF, indicating that the central prostaglandin synthase inhibition is not significant. However, there still remains the possibility of a central mechanism of action due to lack of data regarding the sensitivity and amount of drug required for inhibition of the central prostaglandin system and central pathways of nociception.

Nitric oxide also plays a significant role in the mechanism of action of ketorolac. A study tested the role of nitric oxide on rats utilizing the "pain-induced functional impairment model." Animals were either injected with a nitric oxide synthase inhibitor such as NG-nitro-L-arginine methyl ester, or saline intra-articularly into a joint which was subjected to prior injury by uric acid. They were then administered either dipyrone, ketorolac, or no drug. It was observed that ketorolac and dipyrone brought about a substantial antinociceptive effect, which was diminished by prior treatment with the nitric oxide synthesis inhibitor, but not with saline. Thus, it was reasoned that the antinociceptive effect of ketorolac requires the synthesis of nitric oxide.[13]

ADVERSE EFFECTS

The adverse effects of ketorolac are similar to other NSAIDs. Clinically important adverse effects include gastrointestinal bleeding, peptic ulceration, renal failure, or hematological dysfunction due to inhibited platelet aggregation with thromboxane inhibition.[4]

The association of serious adverse events with ketorolac usage has decreased since the implementation of new dosages and short-term exposure (5 days or less) guidelines.

DRUG INTERACTIONS AND PRECAUTIONS

IM/IV and oral/intranasal ketorolac should not be given concurrently or with aspirin, or other NSAIDs. Ketorolac must be administered with precaution in geriatric patients or those with a history of peptic ulcer disease, gastrointestinal (GI) bleed, renal disease, patients on ACE inhibitors or diuretics, and patients on anticoagulant therapy.

Ketorolac potentiates the risk of serious GI bleeding when used along with warfarin, heparin, other NSAIDs, and pentoxifylline due to their synergistic action. It is recommended that the use of ACE inhibitors/angiotensin II receptor antagonists and diuretics along with ketorolac be limited due to an increase in the risk of renal impairment. Also, ketorolac interferes with the natriuretic effect of furosemide and thiazides.

Other significant drugs that need to be used with caution are probenecid, as it significantly increases the half-life of ketorolac by decreasing the clearance and the volume of distribution of ketorolac. Similarly, ketorolac can enhance the toxicity of drugs such as lithium and methotrexate by decreasing their renal clearance.[4]

CLINICAL STUDIES

Effective postoperative pain management is critical to early recovery and discharge of patients. Opioids are commonly used to achieve pain control, but cause sedation, nausea, vomiting, respiratory depression, delayed recovery of bowel function including paralytic ileus, constipation, difficulty in voiding, "narcotic bowel syndrome", tolerance, dependence, and addiction.[14] Certain short-acting opioid analgesics such as alfentanil and remifentanil, which are popularly used intra-operatively due to reduced residual adverse effects, are not appropriate for postoperative pain due to their rapid excretion and development of acute tolerance.[15]

An alternative or adjunct to opioids should possess similar analgesic efficacy, fewer adverse effects, an alternative mechanism of action, and compatibility with multiple routes of administration. Ketorolac meets all these requirements and thus is an effective morphine-sparing drug. Single- and multiple-dose clinical trials on postoperative pain in surgical patients have shown an analgesic efficacy of ketorolac similar to opioids such as morphine and pethidine and other NSAIDs with fewer adverse effects.[14,16,17] There is evidence that ketorolac can reduce the opioid (morphine) analgesic requirement by nearly 30% to 50%.[17] The onset of analgesic action may be slightly delayed compared with opioids but often persists for a longer duration. It decreases the occurrence of adverse effects such as respiratory depression, hemodynamic changes, and addiction.[14,18] Studies have shown that ketorolac use reduces the duration of hospital stay and facilitates faster recovery of postoperative paralytic ileus due to reduced opioid requirements and alterations in bowel motility.[19,20] Of late, multimodal or balanced analgesia involving a combination of nonopioid analgesics, such as NSAIDs, acetaminophen, ketamine, steroids, beta blockers, and alpha-2 agonists and regional analgesic techniques with opioid analgesics, has become popular due to advantages such as morphine-sparing and better postoperative analgesia.[21]

The dose-sparing effect of NSAIDs, cyclooxygenase-2 (COX-2) inhibitors (COXIBs), or acetaminophen administration on systemic administration of opioids was supported by the American Society of Anesthesiologists Task Force on Acute Pain Management. It has been suggested that all patients take an "around-the-clock" individualized dosing regime of NSAIDs, COX-IBs, or acetaminophen along with opioids to experience fewer adverse effects.[22]

EFFICACY OF KETOROLAC COMPARED WITH OPIOIDS

A number of studies have been conducted comparing the analgesic efficiency of ketorolac to opioids.

Initial reports indicated that NSAIDs possessed pain-relieving properties comparable to opioids.[23–25] In one of the older studies on 221 patients with moderate-to-severe pain by Wong et al., patients were administered IV ketorolac (30 g) twice, then 10 mg IV every 30 minutes as required (up to 6 doses) to produce analgesia, followed by 10 mg oral ketorolac every 4 to 6 hours up to 7 days following surgery; another group received 50 μg of IV fentanyl at similar time intervals as the ketorolac group, succeeded by 60 mg codeine and 600 mg acetaminophen (C+A) orally given 4 to 6 hourly; and another group received 10 μg fentanyl per dose in a similar fashion.[26] During the first 15 minutes of study, 50 μg fentanyl provided better analgesia; however, the analgesic efficacy of 30 mg IV ketorolac was comparable to that of fentanyl in the remainder of the 4-hour study period. Ketorolac was comparable with the codeine and acetaminophen combination, and 10 mg oral ketorolac was linked with a decreased occurrence of nausea ($P < 0.009$) and somnolence ($P < 0.0261$), and a speedy return of bowel function when compared to the other groups. The study concluded that ketorolac is a reliable and efficacious antinociceptive agent in an ambulatory surgery setting, especially when used in an IV and subsequent oral sequence.

Another similar study by Ding et al. also demonstrated that the postoperative analgesia provided by ketorolac was comparable to that of fentanyl with fewer adverse effects such as nausea and sedation. Bowel function returned sooner following ambulatory surgery.[27]

A study by Yee et al.[25] defined a dosage of intramuscular ketorolac that can achieve pain relief similar to that of morphine. Subjects were divided into 5 treatment groups: ketorolac tromethamine 10 mg, 30 mg, 90 mg and morphine 6 and 12 mg. Pain intensity and analgesia were assessed for 6 hours using standard verbal ratings

and visual analog scales (VAS). The results showed that during the 6-hour study period, ketorolac 10 and 30 mg were as effective as morphine 12 mg and that ketorolac 90 mg was more effective than morphine 12 mg ($P < 0.05$).

A systematic review conducted compared analgesic efficiency and side effects of single-dose meperidine with ketorolac and found comparable efficacy between ketorolac 30 mg, morphine 10 mg, and meperidine 100 mg following intramuscular administration. Ketorolac 30 mg IM had relatively less adverse effects compared with the others.[28]

OPIOID-SPARING EFFECTS OF KETOROLAC

A study was conducted in living liver donors undergoing partial hepatectomy. The goal of the trial was to assess and compare the efficiency and dosage requirements of IV patient-controlled analgesia (PCA) morphine (80 mg; 1 mg/mL) vs. morphine supplemented with ketorolac (80 mg morphine + 150 mg ketorolac; 1 mg/mL morphine and 1.87 mg/mL ketorolac) to delineate any opioid-sparing effect.[29] Rescue medication with IV fentanyl 25 μg was given to both groups. Efficacy was evaluated using a pain VAS. The daily consumption of morphine, the frequency, and dosage of the rescue drug fentanyl, and the adverse effects were also assessed. The results showed that both regimes produced satisfactory pain control with similar daily VAS scores of < 3, similar daily total morphine consumption, and similar adverse effects of pruritus, nausea, vomiting, and dizziness. However, the frequency and the total dosage of rescue drug fentanyl were higher in the group taking only morphine, demonstrating an opioid-sparing effect of ketorolac.

To directly compare ketorolac and morphine, Cepeda et al.[30] conducted a double-blind, randomized trial involving 1,003 adult patients who received 30 mg ketorolac or 0.1 mg/kg morphine intravenously. The number of patients who achieved at least a 50% decrease in pain intensity at 30 minutes was used to assess analgesic efficacy of the 2 drugs. Patients with pain intensity more than 5 of 10 received 2.5 mg morphine every 10 minutes until the intensity of pain reduced to 4 or less. Half of the patients in the morphine group achieved analgesia compared with 31% in the ketorolac group. The ketorolac–morphine group required less morphine (difference between the 2 groups: 6.5 mg; $P < 0.00001$) and had a reduced incidence of adverse effects (by 11% $P < 0.007$) compared with the morphine group. It was concluded that opioids have better analgesic efficacy than NSAIDs. However, adding ketorolac to opioids reduces morphine requirements and opioid-associated adverse effects in the initial postoperative period.

In another study by Myers et al., ketorolac was given by continuous subcutaneous infusion along with diamorphine at concentrations up to 4 g diamorphine/10 mL and 120 mg ketorolac/10 mL to 36 patients suffering from advanced cancer pain. Enhancement in analgesia was noted in 80% of the patients. The dose of concomitant opioid was reduced in 76% of the patients, and a decrease in opioid-associated side effects was observed in 73% of patients. Infusion was well supported for duration of up to 115 days (mean 21 days; median 15 days; range 3 to 115 days). Four patients had gastrointestinal bleeding, but no other clinically important side effects were noted.[31]

A phase 3, double-blind, randomized study conducted by Gan et al. on patients with moderate-to-intense pain (defined as ≥ 50 mm on a 0 to 100 mm visual analog scale), within 6 hours postabdominal or pelvic surgery, compared analgesic efficacy and morphine-sparing properties of ketorolac with diclofenac. Patients were administered HPβCD diclofenac (a new formulation of diclofenac that can be given as an IV bolus) at 18.75 or 37.5 mg; ketorolac tromethamine 30 mg; or placebo as an IV bolus injection given 6 hourly until discharge. Rescue analgesia (IV morphine) was made accessible throughout the study up to a maximum of 7.5 mg over 3 hours. The aggregate pain intensity differences from 0 to 48 hours following drug administration were measured. Both HPβCD diclofenac and ketorolac resulted in substantial reductions in the intensity of pain over placebo (all $P < 0.05$), and a substantial reduction in the requirement of rescue analgesic (morphine) when compared to placebo ($P < 0.0001$).[32]

Additionally, ketorolac is more efficacious than COX-2 inhibitors in minimizing postoperative pain as shown in the study by Ng et al. comparing 30 mg IV ketorolac with 40 mg IV parecoxib given intra-operatively at the time of induction of anesthesia during laparoscopic sterilization.[33] Similarly, Lenz and Raeder concluded that when 30 mg of ketorolac was given IV after the induction of general anesthesia, it had superior analgesic efficacy and resulted in reduced consumption of opioids during the first 4 hours after surgery in comparison with 120 mg etoricoxib (long-acting COX-2 inhibitor) given immediately before surgery.[34]

Ketorolac is also considered to be more efficient than corticosteroids. Thagaard et al.[35] demonstrated that 30 mg of ketorolac given IV resulted in better analgesia when compared to the glucocorticosteroids betamethasone and dexamethasone in patients undergoing hernia repair.

EFFECT ON MORPHINE-ASSOCIATED SIDE EFFECTS

In a meta-analysis by Marrett et al. studying the effects of NSAIDS on morphine-associated adverse drug effects, it was concluded that NSAIDs decreased the morphine-associated side effects of vomiting by 32%, postoperative nausea and vomiting by 30%, sedation by 29%, and nausea by 12%. It was noted, however, that respiratory depression, urinary retention, and pruritus were not significantly diminished by NSAIDs.[36]

Similar analgesic efficacy, combined with a decreased incidence of respiratory depression, has been shown when comparing ketorolac to morphine in a study by Krimmer et al. This group hypothesized that ketorolac causes effective analgesia, similar to opiates, without producing any respiratory depressant effects. A study was conducted in patients having abdominal/vascular surgery to compare the analgesic and respiratory effects of ketorolac and morphine. Eligible patients had moderate or intense pain on a Verbal Rating Scale (VRS) within 2 hours after emergence from anesthesia. They were randomized to receive ketorolac 10 mg, ketorolac 90 mg, or morphine 10 mg. Pain intensity was determined by a 5-point VRS and a 100 mm VAS for 4 hours following administration of the study medication. Respiratory function in all patients was assessed on a continual basis by supervising transcutaneous carbon dioxide pressure ($TcPCO_2$). The study showed that all 3 treatment groups had comparable duration of analgesia, without significant differences in the time required for next dose of analgesic. The ketorolac group displayed decreased CO_2 levels, thus suggesting improved ventilation; the morphine group had a slight increase in CO_2 levels. Similar analgesic efficacy has been obtained with ketorolac compared with opiates with lesser respiratory depression.[37]

Operative Site Bleeding

In a prospective, randomized, placebo-controlled, double-blind study by Cassinelli et al., 25 patients undergoing lumbar decompression were randomly received either ketorolac or placebo. Patients received intravenous morphine for rescue analgesia following surgery. Morphine requirement was recorded immediately following surgery, and at 6, 12, 24 hours postoperatively. Postoperative pain was assessed by VAS. There were no substantive disparities in the intraoperative blood loss, or postoperative wound drain output between the study groups. Similar to other studies, lesser morphine equivalent requirements and the overall hospital morphine requirement along with lower visual analog pain scores were found to be associated with patients randomized to receive ketorolac.[38]

KETOROLAC COMBINED WITH LOCAL ANESTHETICS AND OTHER NONOPIOID ANALGESICS

Ketorolac can be combined with other nonopioid analgesics such as paracetamol, local anesthetics, and other NSAIDs to achieve better pain relief.

Anorectal Surgery

In a study by Colona M et al., patients were divided into 3 groups: They received 2 mL of saline IV and infiltration of 2 mL of saline combined with the local anesthetic solution (placebo group), 2 mL of 60 mg ketorolac IV and 2 mL saline combined with the local anesthetic solution (IV ketorolac group), or 2 mL saline IV and 2 mL (60 mg) of ketorolac IV (local ketorolac group) before the start of surgery. Propofol, 50 to 100 μg/kg/min IV, was also given. Lidocaine gel 2% was then administered topically to the anodermal area with a large cotton applicator. Fentanyl 25 μg IV, 3 to 5 minutes was administered as boluses intraoperatively to relieve patient discomfort. The local anesthetics used included mixtures containing lidocaine 1% and bupivacaine 0.25% with epinephrine 1:200,000. It was found that smaller number of patients belonging to the IV and local ketorolac groups suffered pain (37% vs. 6% and 6%, respectively) and required oral analgesic medication (20% vs. 3% and 0%, respectively) compared with the control group. The time required for discharging patients was significantly shorter in the group receiving surgical infiltration of ketorolac in comparison with the control group ($P < 0.05$). Ketorolac 60 mg administered IV or locally achieved better postoperative analgesia and earlier recovery with reduced requirement for postoperative oral analgesics.[39]

Paracervical Block

Similarly, ketorolac can be combined with a local anesthetic agent in deep paracervical block for ambulatory endometrial ablation procedures. Chapa et al. carried out a double-blind, randomized, placebo-controlled trial in which 40 patients were either given sublingual ketorolac (30 mg/mL) along with mepivacaine-only paracervical injection (standard group) or sublingual saline and a ketorolac (30 mg/mL)-mepivacaine paracervical block (ketorolac group). Sublingual ketorolac or saline was administered 20 minutes before the procedure. Pain control was assessed using a 100 mm VAS. Although there was no substantial difference noted statistically in the overall intra-operative VAS score ($P = 0.81$), there was a substantial reduction in postoperative VAS ($P = 0.01$) in the ketorolac group along with diminished postoperative analgesic use in the initial 24 hours ($P = 0.02$), and higher patient satisfaction.[40] Ketorolac when combined with regional anesthesia can result in better postoperative pain recovery.

ANALGESIC EFFICACY COMPARED WITH NONOPIOIDS

Studies Comparing Analgesic Efficacy of Ketorolac with Paracetamol

In a randomized, controlled trial involving 164 patients with moderate-to-intense pain following total hip/knee replacement procedures, IV infusion of propacetamol (2 g), ketorolac (15 or 30 mg), or placebo (saline) were administered. The median time of analgesic onset with propacetamol (8 minute) was shorter than the other 3 patient groups. There were no substantial dissimilarities observed between propacetamol and ketorolac 15 or 30 mg in analgesic efficacy.[41] Thus, ketorolac and paracetamol have similar analgesic efficacy. Another double-blinded study was conducted on patients following gynecologic surgery, where they were divided into 2 groups: One received IV paracetamol 2 g (2 doses) and the other received ketorolac 30 mg. Morphine consumption was compared in both the groups. The study demonstrated that the total requirements of morphine were not significantly distinct between the propacetamol (10.6 ± 4.8 mg) and ketorolac (10.2 ± 4.4 mg) groups. Thus, propacetamol (2 g) and ketorolac (30 mg) possess a similar morphine-sparing effect when used with IV PCA.[42] Hence, ketorolac can be combined with paracetamol as both have similar analgesic efficacy due to diverse mechanism of actions and lack of additive adverse effects.

COMPARATIVE ANALGESIC EFFICACY OF IM OR IV KETOROLAC AND ORAL KETOROLAC

A single dose of ketorolac has been proved to be effective in preventing early postoperative pain. Oliveira et al. conducted a meta-analysis of 13 randomized placebo-controlled, double-blind trials with 782 surgical patients based on a single perioperative ketorolac administration. The authors concluded that 1 dose of ketorolac is efficient in reducing postoperative pain. Ketorolac 60 mg given via the intramuscular route was found to be better in decreasing early postoperative pain, along with nausea and vomiting, with better opioid-sparing effects compared with a 30 mg dose. They also suggested that IM ketorolac has more analgesic efficacy compared with its IV form when given intra-operatively as they observed a longer time to peak concentration with the 60 mg IM injection (30 to 50 minutes) in comparison with that of 30 mg IV dose (3 to 5 minutes). Also, the clearance of the active enantiomer of the drug following IM administration is believed to be slower than the IV administration.[3] No significant increase in adverse effects related to ketorolac usage such as gastrointestinal bleeding or renal failure was found based on observations from studies by Chin et al., Vitale et al., and Agarwal et al.[43–46] However, single-dose ketorolac is less efficacious as a postoperative analgesic due to the short half-life of the drug (5 hours) and also due to a lack of potent anti-inflammatory properties as suggested from studies by Sinha et al. and Mather et al.[47,48]

Smith et al. showed that similarity existed in analgesic efficacy between ketorolac 10 mg oral and 30 mg IM. However, 10 mg oral ketorolac was associated with more adverse effects compared with IM ketorolac. Oral ketorolac was as effective as its intramuscular form and other injectable opioids although it had a higher association of adverse effects. Thus, it was also concluded that oral ketorolac can be used as a useful alternative in postoperative analgesia, whenever patients are capable of oral intake.[28]

Recently, compression-coated tablets of ketorolac tromethamine using hydroxypropyl methylcellulose (HPMC) that release the drug slowly in the colonic region, while preventing drug release in the stomach and small intestine, have been developed. HPMC is a synthetic compound that retards the release of a drug and is useful for making extended release formulations.

This gel-forming regulated release property allows ketorolac to be a suitable agent for use in colon-targeted compression-coated tablets. A colonic delivery system for ketorolac might reduce the adverse effects associated with regular intake of ketorolac such as gastric ulceration and bleeding and provide optimal therapeutic efficacy, with possibly better patient compliance.[49]

INTRANASAL KETOROLAC

The recommended intranasal (IN) dosage for adult subjects < 65 years is 31.5 mg (one 15.75 mg spray in each nostril) given 6 to 8 hourly. The maximal daily dose is 126 mg. For subjects who are ≥ 65 years, patients with renal insufficiency and those weighing < 50 kg: 15.75 mg (one 15.75 mg spray in only 1 nostril) given 6 to 8 hourly. The maximal daily dose is 63 mg.

In a clinical trial conducted by Bullingham et al. to compare the pharmacokinetics of a single intranasal dose of ketorolac tromethamine 31.5 mg (15.75 mg per nostril) between adults > 65 years old and younger adults aged < 65 years, it was found that the mean plasma Cmax of ketorolac was 10% higher and the mean elimination half-life was prolonged by 37% in the older group. Also, the mean residence time was 36% higher in the > 65 years age group ($P = 0.003$). Therefore, the dose of intranasal ketorolac should be restricted to 15.75 mg (1 spray to 1 nostril) in the elderly age group.[50]

Intranasal ketorolac spray [Spirix®] provides 15.75 mg ketorolac tromethamine in every 100 μL spray. Each 1.7 g bottle contains about 8 sprays and must be discarded 24 hours after consuming the initial use. It should be used with caution in pediatric patients. Intranasal ketorolac is classified as pregnancy category C (risk cannot be eliminated from consideration) when administered before 30 weeks' gestation and category D (positive grounds of risk) when used > 30 weeks' gestation.[51]

A randomized, double-blinded, placebo-controlled study was carried out on 127 adult subjects suffering from pain with an intensity rating of 40 mm or more on 100 mm VAS. Those with an allergic reaction to NSAIDs (including ketorolac) or opioids, upper respiratory tract infectious conditions (which hinders the absorption of nasal spray), with active peptic ulcer disease, recent GI bleed/perforation (within 6 months), advanced renal insufficiency, a history of cocaine usage or usage of any intranasal product 24 hours prior to the study, and pregnant and lactating women were excluded from study. Patients received intranasal ketorolac 10 mg (5% solution), or 30 mg (15% solution), or placebo every 8 hours for 40 hours through a metered device. Patients had access to morphine PCA throughout the study. Of 127 subjects, 28 subjects (22.0%) withdrew from the trial. The average consumption of morphine throughout the initial 24 hours was 56.5, 54.3, and 37.8 mg in the placebo group, 10 mg ketorolac group, and 31.5 mg ketorolac groups, respectively. The difference was statistically significant ($P < 0.0013$) between the 31.5 mg ketorolac and the placebo groups. Common adverse effects reported were nausea, vomiting, pyrexia, anemia, tachycardia, pruritus, headache, dizziness, nasal passage irritation, somnolence, constipation, and hypotension. Of these, pyrexia and tachycardia were the most common, both occurring in 50.4% of the subjects. The ketorolac 31.5 mg group had a lower incidence of pyrexia (33.3%) due to its antipyretic effect, in comparison with the ketorolac 10 mg group and the placebo group (55.8% and 61.9%, respectively). The occurrence of tachycardia was 40.5% in the placebo group, while it occurred less frequently in the ketorolac 31.5 and 10 mg groups (19.0% and 16.3%). This dissimilarity between the ketorolac group (31.5 mg) and the placebo group was statistically significant ($P < 0.0317$). Pruritus, somnolence, and hypotension were less frequently associated with the ketorolac group when matched to the placebo group, although the disparities were not statistically significant. Nasal passage irritation was reported in 11.9% of placebo subjects, 14% of 10 mg subjects, and 16.7% in the 31.5 mg ketorolac group. Thus, ketorolac is also an effective antipyretic drug; intranasal ketorolac had better analgesic efficacy, as evidenced by significant reduction in pain intensity and morphine consumption, compared with the placebo group. Also, intranasal ketorolac has been reported to provide antinociceptive efficacy similar to other methods of parenteral administration such as IM or IV routes.[52] This study is consistent with previous studies that have shown that ketorolac has opioid-sparing effects and is beneficial in reducing the adverse effects associated with opioid usage.[53–55]

Intranasal ketorolac being self-administrable by patients is a convenient alternative to injectable formulations of ketorolac and can be prescribed even after discharge of the patient on outpatient basis.[56]

Similar findings were observed in another phase 3 double-blind, randomized placebo-controlled study by Moodie et al. which included 321 adults in the United States and New Zealand who underwent major abdominal surgery.[52] Patients were administered 31.5 mg

intranasal ketorolac as a 100 μL spray or placebo every 6 hours up to 48 hours, followed by repeated dosing up to 4 times a day. Intravenous morphine PCA was made accessible for up to 48 hours, followed by oral hydrocodone or acetaminophen. The intensity of pain was measured using the VAS, and only patients with a pain intensity more than or equal to 40 mm were given study drug. Analgesic efficacy was measured using 6-hour summated pain intensity difference [SPID6], and the pain intensity difference scores were computed by deducting the post-treatment VAS score from the baseline VAS score. The secondary efficacy measures were morphine usage in the first 72 hours, 4-SPID, peak relief scores, quality of pain relief, and global assessment of pain control. The SPID score was substantially superior in the ketorolac group when compared to the placebo group ($P < 0.032$). The mean pain intensity VAS scores decreased over time in both groups and were substantially lower in the ketorolac group at all the intervals measured. The use of morphine was reduced by 34% in the ketorolac group in comparison with the placebo group (82 vs. 121 mg) in the first 72 hours. Nasal irritation and discomfort were associated with the ketorolac. Thus, intranasal ketorolac had statistically and clinically significant benefits with pain relief compared with placebo and resulted in less opioid consumption. Patients on ketorolac required 21% less opioid in first 24 hours and 26% less over the next 48 hours.[52]

Another study conducted by Grant et al. also evaluated the safety and efficacy of intranasal ketorolac in those with bony impactions undergoing third molar extraction. As soon as the intensity of pain rating reached at least 50 on a 100 mm VAS, subjects were randomly assigned to either the ketorolac group (which received 31.5 mg intranasally) or the intranasal placebo group. Rescue analgesia was also provided to both the groups. Safety was assessed from the occurrence of adverse events up to 24 hours after dosing. Efficacy was assessed by VAS for pain and total pain relief for up to 8 hours after dosing. The analgesic efficacy of the IN ketorolac group was consistently superior to placebo. This significant pain relief began 20 minutes after dosing and was maintained for 6 to 8 hours (as with the IM ketorolac regimen). Apart from headache (which occurred in both the groups), there were no other significant adverse effects reported, such as postoperative bleeding or GI symptoms.[57] Use of NSAIDs has not been associated with increased perioperative bleeding in outpatient oral surgical procedures.[58] The above studies on intranasal ketorolac have shown that IN ketorolac 31.5 mg has superior analgesic efficacy and opioid-sparing properties compared with placebo. The incidence of adverse events was similar to that of placebo group. Notably, gastrointestinal bleeding was not associated with ketorolac group.[11]

Bioadhesive in situ nasal gel forms can be used as an alternative to nasal spray for intranasal administration of the drug. Chitosan and pectin-based bioadhesive gelling systems have been shown to have better deposition, retention, and prolonged release in nasal applications with significantly less nasal irritation.[59]

KETOROLAC USE IN CANCER PATIENTS

A case series in 10 acutely ill cancer patients with pain reported complications of terminally advanced ailment, metastasis, and adverse drug effects of opioids. All patients were receiving morphine, which was given as a continuous intravenous infusion supplemented by "rescue" doses. Patients suffering from intense pain in spite of increasing morphine dose, or those who developed opioid-associated bowel syndrome were started on ketorolac in an attempt to reduce opioid load in this palliative care setting. Ketorolac 20 mg IV was administered every 6 hourly along with IV morphine and an intravenous H2 blocker (famotidine 20 mg IV given 12 hourly). When good pain control was achieved, IV morphine was converted to oral morphine given q4 hourly (IV:PO relative milligram potency ratio 1:3). Intravenous ketorolac was also changed to oral dosing and was given q6 hourly. No gastrointestinal adverse effects (including bleeding) were observed, and none of the patients developed renal dysfunction as assessed by blood urea nitrogen and creatinine measurements, suggesting that ketorolac can be given reliably by the IV route in large doses, even in debilitated geriatric patients with advanced cancer.[14]

KETOROLAC CAN BE USED AS AN ANTI-INFLAMMATORY AGENT

A prospective study was conducted by Solomon et al. to compare the efficacy of ocular ketorolac to ocular rimexolone as an anti-inflammatory agent following cataract surgery. Thirty-six patients undergoing small incision phacoemulsification with placement of a posterior chamber intraocular lens (IOL) were arbitrarily assigned to receive either ketorolac or rimexolone. The results showed that there were no statistically substan-

tial dissimilarities in subjective (lid erythema, conjunctival erythema, slit-lamp cell and flare, and ciliary flush) or objective measurements of inflammation between the ketorolac and rimexolone groups. Improvements in visual acuity and measurements were similar in both the groups.[60] Although the risk of causing elevated intraocular pressure with rimexolone is low when compared to prednisolone or dexamethasone, the other dangers of steroid usage such as aggravation of infection and impairment of wound healing are still present.[61,62]

The efficiency of ketorolac in limiting postsurgical inflammation was demonstrated by Flach et al. in 2 studies. The first was a double-masked paired comparison of 0.5% ketorolac tromethamine solution with vehicle placebo in patients undergoing extra capsular cataract extraction and posterior chamber IOL implantation. As measured by fluorophotometry, the results showed that prescribing 0.5% ketorolac tromethamine before and after surgery markedly decreased the disintegration of blood–aqueous barrier when compared with vehicle placebo and that it was well tolerated without affecting intraocular pressure.[63] The second study was a double-masked, parallel comparison of ketorolac with dexamethasone to study the efficacy of ketorolac in reducing postoperative inflammation. This study found no difference in the slit-lamp observations of postoperative anterior ocular inflammation between groups. Both ketorolac and dexamethasone solutions were well tolerated, and no additional corticosteroids were administered to any patient during the study.[64] These studies confirm that ketorolac ophthalmic solution can be used as a safe and effective alternative for corticosteroids as an anti-inflammatory agent for patients following cataract surgeries.

Pre-operative Intravenous Administration of Ketorolac

Chow et al.[65] conducted a study on 65 patients who received either 15 to 30 mg of ketorolac tromethamine IV given every 6 hours or placebo just prior to laparoscopic surgery. PCA morphine was used for rescue analgesia. Operative factors such as type and duration of surgery, and estimated amount of blood loss were registered. Postoperative factors such as analog pain score (range 0 to 10), opioid use, and duration of stay were assessed. The pain relief experienced by patients receiving ketorolac was higher than that of placebo ($P < 0.005$). The amount of morphine consumed was also less in the ketorolac group. Operative times ($P = 0.21$) and estimated blood loss ($P = 0.60$) were not substantially distinct between the 2 groups. Ketorolac did not impair renal function; serum creatinine changes were similar compared with patients receiving placebo ($P = 0.50$). Ketorolac administration, when given in the dose of 15 to 30 mg IV every 6 hours beginning pre-operatively in patients who are undergoing laparoscopic urologic surgery, resulted in adequate analgesia without adversely affecting blood loss or renal function when compared with the placebo treated group. Ketorolac has also been safely used in lumbar spinal surgery[38,66] and cardiac surgery.[67,68]

POSTOPERATIVE RETURN OF BOWEL FUNCTION AFTER KETOROLAC ADMINISTRATION USE

Ketorolac has been shown to be associated with early recovery of postoperative bowel function and possible early discharge from hospital with less treatment costs than other postoperative regimens. Stahlgren et al. reported that patients receiving IM ketorolac 30 and 10 mg subsequently every 6 hours after abdominal hysterectomy or cholecystectomy procedures had early postoperative recovery with significantly less time required for first bowel movement after oral fluids; the response was better functioning compared with patients receiving meperidine 100 mg IM prior to acetaminophen/codeine (600 mg/60 mg per os).[69]

In a double-blind, randomized study by Chen et al. involving 102 patients who underwent elective colorectal resection surgeries, subjects randomly received IV PCA morphine or IV PCA morphine with ketorolac. Patients in the group receiving ketorolac with morphine received 18.3% less morphine than those receiving morphine alone over the initial 72 postoperative hours. The maximal opioid-sparing effects of ketorolac appeared at 12 to 24 postoperative hours. Initial bowel movement and passage of flatus were earlier in the ketorolac group. The morphine group showed a 5.25 times increased risk of postoperative ileus, a result similar to the morphine with ketorolac group in colorectal surgery patients. The addition of ketorolac to IV PCA morphine resulted in opioid-sparing and shorter duration of bowel immobility.[70]

In a retrospective study on 154 patients who had undergone partial nephrectomy for renal cortical tumors, analgesic relief, postoperative recovery, and effects on renal function were studied in 2 groups: one receiving ketorolac and opioids and the other receiving opioids alone. Patients who received ketorolac demonstrated superior recovery during the postoperative

period with a quicker return to solid diet and a more rapid discontinuance of PCA without any increase in acute renal failure.[71]

KETOROLAC ADMINISTRATION AND POSTOPERATIVE STAY

In a retrospective analysis by Gora-Harper et al. conducted on 559 patients who had either undergone an orthopedic spine or total joint procedure showed that patients who received both ketorolac and opioids for postoperative analgesia achieved postoperative recovery goals such as time to first bowel movement, first oral intake, and first independent ambulation sooner than with opioids alone. The ketorolac group also had a shorter mean length of postoperative stay of 2.8 days compared with the opioid subjects at 3.78 days ($P = 0.01$) and were discharged 1 day earlier. Total cost of treatment for each patient was 32% greater in the group receiving opioids due to longer duration of hospitalization.[72]

In another retrospective analysis conducted by Turner et al. on patients who underwent lumbar laminectomy surgery with or without fusion, comparable findings were demonstrated. A substantial improvement in postoperative ambulation was manifested in the ketorolac group. A decrease in the duration of hospitalization by one-half day was noted for patients on ketorolac.[66]

KETOROLAC IN CHILDREN

A prospective trial was conducted by Gupta et al. in infants and children who underwent congenital heart surgery requiring cardio-pulmonary bypass. The study was intended to assess the risk of bleeding complications when ketorolac was used to treat postsurgical pain. The subjects were randomized to receive morphine and/or fentanyl as either continuous infusion or bolus doses (Group 1) or IV ketorolac 0.5 mg/kg/dose 6 hourly in addition to morphine and/or fentanyl (Group 2). The occurrence of bleeding complications was evaluated by chest tube drainage, GI bleeding, and wound bleeding. The results showed that the amount of chest tube drainage was diminished in those subjects who received the ketorolac regime vs. those who received morphine alone. In this study, short-term use of ketorolac (< 48 hours) did not result in a significantly increased risk of postoperative bleeding. However, caution must be used with those patients with greater than usual risk for early postoperative bleeding or with renal dysfunction.[73]

Postoperative pain management poses a significant challenge in young children, as they cannot articulate their analgesic needs. Thus, "as needed" administration of analgesics is often ineffective. Rather pain management in very young children should use preventive strategies with fixed interval dosing of potent analgesics with low toxicity.[74] Use of opioid analgesics is a significant concern due to the adverse effect profile including respiratory depression, ileus, urinary retention, and prolonged emesis. The authors of one study speculated that the usage of ketorolac postoperatively in healthy pediatric surgical patients might reduce opioid requirement without causing an increase in morbidity. Hence, they conducted a case-control clinical trial in which the pediatric surgical cases were given morphine or morphine with ketorolac. The study found that patients receiving morphine plus ketorolac required substantially less morphine, and there was no significant increase in nephrotoxicity or bleeding.[75]

Ketorolac in Retinopathy of Prematurity

In a study by Medardo et al. to determine the effectiveness and safety of topical ketorolac in preterm newborns with birth weight < 1,250 g or a gestational age of < 30 weeks, subjects admitted to neonatal intensive care unit were treated with topical ketorolac (0.25 mg every 8 hours to each eye). The comparison group was comprised of 53 preterm newborns, with the same inclusion criteria. The 2 groups were similar in terms of weight distribution, Apgar score at 5 minutes, the incidence of sepsis, intraventricular hemorrhage, and necrotizing enterocolitis. Oxygen therapy was administered for a substantially longer duration in the control group. This suggests that ketorolac in the form of an ophthalmic solution can reduce the danger of developing severe ROP in very preterm newborns, without producing substantial adverse effects.[76]

USE OF KETOROLAC IN OBSTETRICS

A trial was conducted by Lowder et al. to assess whether administration of ketorolac postcaesarean section reduces pain and opioid use. Forty-four women were recruited for the study and were randomized into 2 groups. One group received ketorolac 30 mg IV and the other received placebo. All of the participants also received opioid PCA (morphine/hydromorphone/meper-

idine) for pain control. Pain control was assessed using visual analog scales. The number of PCA attempts, PCA dosages administered, and time to discharge was also assessed. Those with bleeding tendencies, renal disease, asthma, peptic ulcer disease/GI bleeding, allergy to NSAIDs, and lactating mothers were excluded from the study. The study primarily showed that both the VAS scores measured up to 24 hours postoperatively and the usage of postoperative opioids were substantially lower in patients receiving ketorolac than the placebo group.[77]

In another randomized study, 90 patients scheduled for elective caesarean section were studied. The effects of pre-operative ketorolac on the surgical stress response and postoperative analgesic ingestion were examined. An increased sympathetic response and surge in corticosteroid level in response to laryngoscopy, tracheal intubation, and surgical stimulation have previously been well documented. Stress may reduce the placental perfusion and uterine blood flow by 20% to 35%.[78] Opioids mitigate the sympathetic response, but at the expense of causing neonatal respiratory depression.[79] Their study postulated that ketorolac given prior to induction of anesthesia would diminish the maternal stress response and postoperative analgesic consumption. Women with a prior history of allergy to NSAIDs, bleeding tendency, peptic ulcer, bronchial asthma, hepatic/renal disease, placenta previa, pregnancy-induced hypertension, placental abruption, and evidence of any fetal abnormality or intra-uterine growth restriction were excluded from study. Inclusion criteria included ASA I and II, those aged 20 to 35 years, and those with uncomplicated singleton pregnancies of at least 36 weeks gestation who were undergoing elective caesarean section. The subjects were randomly allocated into the placebo group and the ketorolac group in a blinded fashion. Heart rate, systolic pressure, and mean arterial pressure were noted prior to and also following intubation, after delivery, and postextubation. The stress response was assessed by changes in the plasma cortisol concentration. The severity of postoperative pain was evaluated using a VAS. The results showed that changes in heart rate, mean arterial pressure, and systolic pressure from baseline were significant in the placebo group, with higher serum cortisol concentrations 5 minutes after intubation and 1 hour after delivery. The patients of the placebo group had higher VAS scores following surgery; the time to the initial tramadol (rescue medication) request was also significantly shorter than the ketorolac group. The APGAR scores were comparable between groups, and no occurrence of untoward cardiovascular events, premature closure of the *ductus arteriosus*, or evidence of pulmonary hypertension were noted in either group. In patients undergoing elective caesarean section, pre-induction intravenous ketorolac was efficacious in attenuating the maternal stress response and also improved the quality of postoperative analgesia without apparent adverse effect on neonatal outcome.[80]

KETOROLAC USE IN NONSURGICAL SETTINGS

In addition to treating postoperative pain, ketorolac can also be used in the emergency setting for sickle cell crisis, musculoskeletal pain, migraine headache, or renal colic and is usually as effective as commonly used opioids, such as pethidine, morphine, and other NSAIDs and analgesics.

In a review article by Taggart et al. involving 8 RCTs with a total of 321 patients comparing ketorolac with other conventional therapies of migraine, it was found that ketorolac was associated with analgesia when used to treat acute migraines in adult patients and could be used as a second-line drug in the ED in combination with the standard commonly prescribed drugs. Ketorolac (60 mg IM) has similar efficacy in treating migraines compared with meperidine (dosage ranging from 50 to 100 mg in various studies) and is preferred due to lack of addictive properties. It is also more effective than nasal sumatriptan, although evidence regarding its comparison with other routes of sumatriptan remains inconclusive. Phenothiazines, DHE, and metoclopramide were found to be more effective than ketorolac.[81]

A randomized, double-blind, controlled trial was conducted by Olsen et al. involving 46 emergency department (ED) patients presenting with abdominal pain thought to be due to biliary colic. Patients received either ketorolac 30 mg IV ketorolac or butorphanol 1 mg IV. Pain level was evaluated using a VAS before and 15 and 30 minutes following infusion of study medication. Adverse effect profiles and the need for rescue analgesic medication were also evaluated. The mean pain score in the butorphanol group reduced from 7.1 ($\pm$1.7) to 2.1 ($\pm$2.2) after 30 minutes. The average pain score in the ketorolac group decreased from 7.4 ($\pm$2.0) to 3.1 ($\pm$3.3) after 30 minutes. Both butorphanol and ketorolac groups had comparable rescue analgesia requirements. The study concluded ketorolac along with butorphanol can be considered as effective alternatives to other opioids in the emergency management of biliary colic, especially in patients who undergo

HIDA scan, as opioids are known to interfere with the scan.[82]

ADVERSE EFFECTS

To assess the chances of GI and surgical site bleeding linked with the use of parenteral ketorolac, a postmarketing surveillance cohort study involving 20,000 patients was conducted in 35 community-based hospitals in suburban and urban settings and urban tertian care centers.[1] All identified patients who received intravenous and intramuscular ketorolac during the study period were enrolled in the exposed group. GI bleeding was noted in 4% of ketorolac group and in 3.6% of opiate group. While clinically significant GI bleeding occurred in 2.1% and 1.9% of courses, respectively, clinically serious GI bleeding (life threatening, causing death, residual disability, or prolonged hospitalization) was seen in 1.3% and 1.0%, respectively. Bleeding from the surgical site occurred in 39.6% of the ketorolac-exposed patients and 38.6% of unexposed patients. However, clinically threatening bleeding from the surgical site was uncommon, occurring in 1.5% and 1.8% of ketorolac-exposed subjects and opiate-exposed subjects, respectively. There was no apparent enhanced risk of operative site bleeding with ketorolac vs. opiates in subjects taking anticoagulants. To evaluate the effects of age on GI bleeding, subjects were analyzed in 4 age groups: < 15 year, 15 to 64 year, 65 to 74 year, > 75 year. An increase in the incidence of GI bleeding with age was noted in both the ketorolac group and the opiate group, but the incidence increased further in the ketorolac group than the opiate group. The overall danger of bleeding from the surgical site increases markedly with age, more so with the ketorolac subjects than with the opiate group ($P < 0.02$). However, no effect of age on ketorolac-associated clinically serious bleeding was noted ($P = 0.47$). Subjects that received higher doses of ketorolac had significantly more GI bleeding than those who received lower doses. The effect of dose was even more marked when studying clinically important and clinically serious GI bleeding. The patients at highest risk for gastrointestinal bleeding were older patients who received higher doses of ketorolac. The analysis of the effects of duration of the treatment on gastrointestinal bleed revealed an increased risk of GI bleed as therapy was prolonged, especially as it prolonged beyond 5 days. This risk was different from those in whom it was used for < 5 days ($P = 0.04$ for comparison of Odds Ratios). The same does not hold true for operative site bleeding in which no duration response relationship could be demonstrated ($P = 0.59$). Thus, compared with opioids, the use of ketorolac was linked with a small enhanced risk of GI bleeding. This risk was increased in the elderly, with use exceeding 5 days and with dose higher than 105 mg/day. Use in those younger than 65 years of age, at an average dose of lower than 105 mg/day, and for 5 or fewer days did not correlate with a detectable enhanced risk of GI bleeding. Ketorolac use was also linked with a slightly enhanced risk of bleeding from the surgical site, but only in elderly or those on higher-dose therapy.[2]

OPERATIVE SITE BLEEDING

As surgical hemostasis is achieved through platelet function, the initial dose of ketorolac should be administered near the end of surgery or at least after the surgeon has achieved hemostasis. There have been no reports of higher incidence of blood loss when the recommended doses of ketorolac were administered at the end of surgery or in the early postoperative period.[83,84]

Few studies have shown higher risk for bleeding with ketorolac administration. In one of the older studies, Rusy et al. found that blood loss was significantly higher in tonsillectomy patients receiving ketorolac 0.9 mg/kg (blood loss of 2.67 mL/kg) compared with the acetaminophen 30 mg/kg (blood loss of 1.44 mL/kg). It was reported that hemostasis was more difficult to attain during tonsillectomy procedure in patients receiving ketorolac.[85] Marrett et al., in their meta-analysis of 7 randomized, double-blind, controlled trials studied the effect of postoperative NSAIDs on bleeding in patients which included children < 16 years of age and adults who had tonsillectomy with or without adenoidectomy. The necessity for surgical electrocautery to stop bleeding and postoperative bleeding calling for a change in postoperative management, readmission to the hospital, or blood transfusion were used as criteria to assess the bleeding. They demonstrated that NSAID therapy used postoperatively enhanced the risk of postoperative bleeding necessitating intervention to control bleeding and the chance of reoperation by about 2.4% to 7%.[86]

Similar findings have been reported in studies that compared ketorolac with opioid analgesics.[87,88] In a retrospective cohort study by Chin et al.[44] involving patients undergoing thyroid surgery, the incidence of hematomas in patients receiving ketorolac (2.7% vs. 1.3%), which was not statistically significant.

A retrospective analysis involving 379 patients where intravenous ketorolac 15 or 30 mg was administered intra-operatively to patients undergoing reduction mammoplasty found that patients who received ketorolac had more than a threefold increase in the possibility of requiring surgical hematoma evacuation.[89] In contrast, another similar study found no difference in the incidence of hematoma formation following transverse rectus abdominis musculocutaneous (TRAM) flap breast reconstruction where ketorolac was administered postoperatively.[90]

Gupta et al. evaluated the occurrence of gastrointestinal or operative site bleeding after ketorolac administration and found no major risk of either and suggested ketorolac could be favorably used to bring about analgesia following congenital heart surgery.[73]

The safety of ketorolac use with respect to bleeding has been established in spinal surgeries. A prospective study by Chin et al. examined the danger of bleeding linked with the use of single intra-operative ketorolac 30 mg IV given after wound closure during single-level lumbar microdiscectomy. Group 1 comprised of 44 patients who were administered ketorolac, while Group 2 included 45 patients without ketorolac. There were no substantial changes in coagulation profile or surgical site bleeding in either of the group. The authors recommended single intra-operative dose of 30 mg ketorolac as it was associated with lower incidence of bleeding and renal dysfunction and suggested it might be associated with reduced postoperative inflammation around the nerve root.[45] Similarly, Munro et al. stated that ketorolac did not give rise to an enhanced rate of postoperative blood loss or transfusion requirements in adolescents undergoing posterior spinal fusion.[91]

EFFECT OF KETOROLAC ON BONE HEALING

The effect of ketorolac on spinal fusion was studied by Pradhan et al.[92] In this retrospective study, 405 patients who underwent primary lumbar posterolateral intertransverse process fusion were included. Of these, 228 patients were given ketorolac 30 mg IV every 6 hours for 48 hours. There were no substantial differences in the incidence of pseudarthrosis or nonunion ($P > 0.05$) between the 2 groups: 12 of 228 patients (5.3%) were prescribed ketorolac following surgery had nonunion in contrast to 11 of 177 patients (6.2%) in the control group who were not administered ketorolac after reviewing sequential radiographs and computed tomography. The authors recommended limiting the use of ketorolac after spinal fusion to 48 hours to decrease the effect on bone healing.

In another study, which was not retracted,[93] on 434 patients postspinal fusion surgery, the effect of ketorolac along with other NSAIDs and celecoxib and rofecoxib on spinal fusion when administered in the perioperative period was evaluated retrospectively. Patients administered NSAIDs, ketorolac (20 to 240 mg), celecoxib (200 to 600 mg), or rofecoxib (50 mg) 1 day prior to the surgery were compared with a control group where none were prescribed. The group receiving ketorolac had greater occurrence of nonunion 23/120 of patients (19.2%; $P < 0.001$) compared with the non-NSAID group, out of which only 3/50 patients (6%) receiving low-dose ketorolac (≤ 110 mg/day) experienced nonunion. This was not substantially distinct from non-NSAID users. Patients administered higher doses of ketorolac (120 to 240 mg/day) suffered from a higher incidence ($P < 0.0001$) of nonunion (20/70; 29%) when compared to non-NSAID users. This study also concluded that perioperative administration of low-dose ketorolac (≤ 110 mg/day) in the perioperative period had no substantial inhibitory effect on bone fusion.

In a retrospective study in a pediatric population by Kay et al.[94] on 221 children who underwent open reduction/internal fixation for fractures, 169 children were administered ketorolac perioperatively, while the control group did not receive the drug. There was no difference noted in the delayed union or nonunion rates between the 2 groups. Wound infection was also similar between the 2 groups, occurring in 1/52 (1.9%) patients in the nonketorolac group and in 4/169 (2.3%) patients in the ketorolac group. This study supports the findings of previous studies suggesting that perioperative ketorolac use does not enhance the risk of bone healing complications following operative fracture care in pediatric population ($P = 0.928$).

In a meta-analysis of retrospective studies by Li et al.[95] to determine the effect of perioperative nonsteroidal anti-inflammatory drugs (NSAIDs) on the incidence of adult spinal fusion, 5 retrospective comparative studies involving a total of 1,403 subjects who were administered NSAIDs for < 14 days postspinal fusion surgery were considered. Patients receiving high-dose ketorolac demonstrated a statistically significant deleterious effect on spinal fusion ($P = 0.001$), whereas normal-dose NSAIDs (ketorolac, diclofenac sodium, celecoxib, or rofecoxib) did not interfere with bone fusion compared with the non-NSAIDs group ($P = 0.30$).

In a retrospective study by Glassman et al.[96] involving 288 patients on whom instrumented spinal fusion surgery was performed, 167 patients were administered ketorolac postoperatively and the remaining 121 patients (control group) were not prescribed with any NSAID. It was found that ketorolac had a significantly deleterious effect with 5 nonunions in the nondrug group and 29 nonunions in the ketorolac group ($P > 0.001$). Nonunion was found to be approximately 5 times more likely after ketorolac consumption. This study differed from the other studies in that ketorolac at the usual doses used for postoperative analgesia was found to interfere with spinal fusion. This study also revealed that a shorter duration (< 14 days) of exposure to normal-dose NSAIDs (ketorolac, diclofenac sodium, celecoxib, or rofecoxib) was associated with lesser effects on bone fusion, whereas the use of high-dose ketorolac, even for shorter duration (< 14 days) may enhance the danger of nonunion.

In another retrospective study by Park et al.,[97] 88 consecutive patients diagnosed with spinal stenosis or spondylolisthesis who underwent spinal fusion with instrumentation and autologous bone graft (iliac crest) were examined. Patients were divided into 2 groups: 30 subjects received ketorolac 120 mg and fentanyl 900 μg via PCA for up to 3 days following surgery. The other 58 patients received only fentanyl 1,200 μg for the same duration of 3 days. The ketorolac group had significantly higher incidence of incomplete union or nonunion, and the relative risk was approximately 6 times higher than control group (odds ratio: 5.64).

The studies that used ketorolac in the postoperative period with a dosage > 110 mg found increased incidence of bone fusion complications including delayed union and nonunion. Although ketorolac has been considered to hinder bone healing, some evidence suggests that by limiting use to < 110 mg/day and to a duration < 14 days, the deleterious effects on bone healing might be reduced while simultaneously achieving postoperative analgesia.

ACUTE RENAL FAILURE

Acute renal failure is one of the common complications of NSAID use. NSAIDs inhibit the enzyme cyclooxygenase which decreases prostaglandin production which negatively affects glomerular filtration rate by causing afferent arteriolar constriction. However, normally, the GFR reduction caused by NSAIDs does not lead to renal failure. In patients with chronic kidney disease or following intravascular volume depletion in the postoperative period, prostaglandins play a vital role in maintaining GFR. Hence, NSAID use in such scenarios can lead to renal insufficiency. However, maintenance of adequate hydration through administration of intravenous fluids can mitigate the attenuating effects of ketorolac on glomerular filtration rate.[19]

Ketorolac does not have any higher risk of GI bleed or renal failure when compared to diclofenac or ketoprofen. A prospective, randomized multicenter trial ($n = 11,245$) compared the risks of allergic reactions, acute renal failure (ARF), bleeding from surgical site, GI bleeding, and death with ketorolac, diclofenac, and ketoprofen up to 30 days after surgery. Serious untoward events were seen in 1.38% patients, of which death and ARF constituted 0.17% and 0.09%, respectively, while 1.04% of patients suffered from surgical site bleeding and only 0.04% from GI bleeding. The results were comparable for ketorolac, diclofenac, and ketoprofen with regard to the bleeding outcomes.[98]

A literature review by Lee et al. involving 23 trials (1,459 patients) reviewed the impact of NSAIDs on kidney function. NSAIDs decreased creatinine clearance by 16 mL/min and also the output of potassium by 38 mmol/day on the first-day postsurgery in comparison with placebo. NSAIDs resulted in a fleeting decrease in renal function in the initial postoperative period in patients with optimal pre-operative renal function. Hence, NSAIDs should not be withheld from adults with normal kidney function.[99] Similarly, in a review of 14 trials specifically scrutinizing renal function, there was no evidence of renal failure when ketorolac was given for 5 days or fewer. However, when multiple doses are given for > 5 days, ketorolac may be associated with an enhanced rate of transient ARF.[84] Acharyaa and Dunning addressed the issue of increased risk of renal failure with use of NSAIDs following cardiac surgery. They concluded that NSAIDs, when administered at optimal doses in the initial postoperative period to low-risk patients following cardiac surgery, are not linked with an increased risk of renal failure.[67]

In a meta-analysis, 20 randomized controlled trials conducted by Bainbridge et al., there was no statistically significant increase in the incidence of renal failure associated with NSAIDs. Renal dysfunction was reported in 7 RCTs: about 5.5% in NSAID groups. The risk of renal failure did not increase with perioperative NSAID use in the low-risk surgical candidates, patients < 75 years of age, and in patients without

co-existing renal, hepatic, or congestive cardiac failure, diabetes mellitus, bleeding disorders, or prior history of peptic ulcer disease or GI bleed.[68]

These studies indicate when ketorolac is administered for 5 days or less within recommended dosage limits according to age and body mass index while considering patients' comorbidities, the risk of renal insufficiency is less and comparable with the other NSAIDs. Ketorolac is not associated with cardiovascular events commonly associated with the COX-2 and partial COX-1/2 inhibitors.[56]

CONCLUSION

Ketorolac tromethamine is a nonsteroidal anti-inflammatory drug (NSAID) that produces analgesia and decreases inflammation by inhibiting the enzyme cyclooxygenase, resulting in the decrease in formation of prostaglandins and sensitization to pain at sites of inflammation. Ketorolac tromethamine is highly water soluble and can be given via routes such as intravenous, subcutaneous, oral, and intramuscular and is the only NSAID currently available as a nasal spray. The adverse effect profile of opiates such as respiratory depression, postoperative ileus, and drug dependence can be reduced by concomitant use of ketorolac. The major side effects of ketorolac include enhanced risk of GI bleeding and renal insufficiency. Ketorolac provides sufficient postoperative analgesia after abdominal and pelvic surgery, such as hysterectomy, cholecystectomy, and cesarean sections. It has also been used effectively for analgesia in advanced cancer. Ketorolac has analgesic efficacy similar to that of morphine and possesses a different mechanism of action than that of opioids. This mechanism of action allows for multimodal analgesia when used with opioids as an adjuvant, making it an effective morphine-sparing drug by decreasing morphine requirements in the treatment of moderate-to-severe pain. Ketorolac has been used efficaciously in the ED in multiple conditions, such a biliary colic, migraines, in patients with opioid dependence, sickle cell crisis, and musculoskeletal pain.

The risk of renal insufficiency and GI bleed can be diminished by restricting its use to < 5 days and reducing the dosage in both geriatric patients and those with chronic renal disease. In spite of its adverse effects, its effectiveness via multiple routes and usefulness in a wide gamut of medical conditions make ketorolac a valuable analgesic in the armamentarium of healthcare providers treating pain.

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