

Clinical Benefits of Ketorolac in Postoperative Pain Control Management: A Comprehensive Review

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Abstrak

Sebanyak 70% kunjungan ke instalasi gawat darurat disebabkan oleh nyeri, sekitar 80% pasien bedah mengalami nyeri akut pasca operasi, lebih dari 38% pasien dirawat kembali setelah operasi karena nyeri yang hebat. Nyeri pasca operasi merupakan salah satu keluhan yang paling sering ditemukan, karena nyeri merupakan efek samping pasca operasi yang sulit dihindari. Sekitar 77% pasien pasca operasi tidak memperoleh manajemen nyeri pasca operasi yang adekuat, sebanyak 71% pasien dilaporkan terus mengalami nyeri pasca manajemen dan pasien yang masih merasakan nyeri sedang hingga berat sebanyak 80%. Terdapat beberapa penelitian terdahulu yang dilakukan baik di dalam maupun luar negeri telah menunjukkan manfaat ketorolac dalam manajemen nyeri pasca operasi. Tujuan penulisan artikel ini untuk mengetahui secara mendalam potensi ketorolac sebagai agen farmakologis dalam manajemen nyeri pasca operasi. Metode yang digunakan secara *narrative review* dengan mengambil literatur melalui artikel penelitian dan pedoman internasional. Diperoleh 230 pustaka yang memenuhi kriteria, setelah dipelajari didapatkan 27 pustaka untuk menyusun artikel. Ketorolac memiliki profil keamanan yang baik dan beberapa kontraindikasi yang harus diwaspadai oleh dokter sebelum memberikan pengobatan kepada pasien. Studi menyarankan pemberian ketorolac dalam waktu dua jam setelah operasi, dengan durasi pengobatan dua hingga lima hari. Ketorolac telah terbukti memiliki potensi yang baik dalam manajemen nyeri pasca operasi pada berbagai penelitian.

Kata Kunci: ketorolac; nyeri pasca-operasi; kontrol nyeri, narrative review, manajemen nyeri

Abstract

Pain accounts for about 70% of visits to emergency rooms, approximately 80% of surgical patients experience acute postoperative pain, more than 38% of patients are readmitted following surgery due to severe pain. Up to 77% of post surgical patients received insufficient pain treatment, following treatment 71% of patients reported continuing to experience pain and 80% said they were still experiencing moderate to severe pain. Previous studies conducted both domestically and internationally have demonstrated the benefits of ketorolac and its usefulness in managing postoperative pain. This article's goal is to provide a comprehensive understanding of the potential of ketorolac as a pharmacological agent in the management of post-operative pain. A narrative review method was employed, utilizing research articles and international guidelines to gather literature. Around 230 libraries were found to meet the criteria and studied, 27 libraries were used in order to create this article. Ketorolac has a good safety profile and there are a few contraindications in patients that clinicians must be aware. Studies suggest that administering ketorolac within two hours after surgery for a treatment duration of two to five days. Numerous studies have demonstrated the potential of ketorolac in the therapy of postoperative pain.

Keyword: ketorolac, postoperative pain, pain control, narrative review, pain management

Introduction

Pain is defined as a miserable emotional and sensory experience connected to an injury, like possible tissue damage or symptoms that indicate tissue damage, by the International Association for the Study of Pain (IASP). The IASP definition has been accepted globally by

health workers, researchers, and has been recognized by governments and non-governmental health organizations, including the World Health Organization (WHO). Pain is an important stimulus for living creatures. It has unique characteristics because, in addition to causing suffering to the subject, pain has a role as an impulse in the self-protection response mechanism of living creatures (1).

Acute and chronic pain are commonly distinguished by the timing of the event, the intensity of the pain, and the frequency of the pain, the distinction between the two types of pain is based on the mechanisms underlying the two categories. The peripheral nervous system detects and sends noxious stimuli to the central nervous system, then modulated as acute pain (2). Chronic pain can persist for a long period because it is associated with pain signal processes that do not follow universal mechanisms, leading to mistakes in the body's response to pain. The precise global prevalence of pain is extremely difficult to ascertain, but rough calculations suggest that around 70% of emergency room visits are due to pain, acute pain is the main reason why patients seek medical attention, acute pain is experienced during treatment by many hospitalized patients. Acute post-operative pain affects about 80% of surgical patients, and acute pain accounts for more than a third (38%) of readmissions following surgery (3).

Pain is experienced by post-operative patients because of tissue discontinuity, surgical wounds from incisions made during the surgical process. Damage to tissue (noxious stimulus) causes inflammation, which in turn causes inflammatory cells to emerge and be picked up by pain receptors known as nociceptors. These receptors are directly linked to free nerve endings, which are typically composed of two types, delta-A and C fibers (4). Postoperative pain needs to be managed right once since it might have an indirect negative impact on the patient by causing damage and issues via the spinothalamic and spinoreticular pathways, which connect to the spinal cord and ultimately the brain (5).

Around fifty percent of patients undergoing elective surgery report postoperative pain, which is a significant issue globally for healthcare services. This is a major problem for health systems worldwide. This will increase the number of cases of chronic pain and lower patient satisfaction with healthcare (6). One of top five complaints in hospitals is postoperative pain. Up to 77% of post surgical patients received insufficient postoperative pain management. Following treatment, around 71% of patients reported continuing to experience postoperative pain and 80% patients were still experiencing moderate to severe pain (7).

Physicians' knowledge of managing patients' pain is still growing, but managing pain following surgery is still difficult and frequently encountered in day-to-day practice. Patient complaints drive physicians to use opioid anti-pain medications inappropriately, creating new issues (8). Opioids cause patients to have negative side effects, such as addiction to intoxication, the current opioid epidemic has forced medical professionals to lower opioid use before and after surgery in an effort to prevent patients from continuing to use them (9). It is necessary to make the best use of already available, safer pharmacological medicines in order to position them as the primary means of addressing patient concerns and lowering the usage of opioid medications (10).

Ketorolac is one pharmacological agent that can be used effectively and efficiently. It is a flexible agent because it comes in different dosage forms, such as oral, nasal spray, IV, or IM. Ketorolac can be used postoperatively for pain management. It can significantly reduce the requirement for opioids and lower the incidence of opioid side effects, like decreased gastrointestinal motility and vomiting. Ketorolac is equally as effective as opioid analgesics in pediatric population. Ketorolac may be a good primary or additional pain management option for children or adults experiencing acute postoperative pain (11).

Through this article, it is hoped that knowledge of the pharmacological profile of ketorolac, its advantages over other analgesic agents, general side effects that should be avoided, indications and dosage for wise administration, benefits when combined with opioids, and patient satisfaction with postoperative pain management will be indirectly increased. The goal of writing this article is to convey in detail the benefits and advantages of ketorolac as a pharmacological agent in postoperative pain management.

Methods

The benefits of ketorolac in post operative pain management are the subject of this paper, which employs a narrative research style and draws its literature from research journal articles and international guidelines. The writing process is organized into the following steps: a) Identifying the primary goal of the writing, which is to improve medical knowledge to enable the best possible care for post operative pain patients; b) searching the Pubmed, NCBI, Google Scholar, and ScienceDirect portals from 2013 to 2023 using the keywords "postoperative pain," "pain control," and "ketorolac"; c) Including articles that explain the advantages of ketorolac and research that employs the RCT method. Articles that did not fully

discuss ketorolac pharmacological therapy in patients with post operative pain or that were not uploaded in full were excluded. d) Review the literature to help with writing preparation and delivery. e) Begin preparing written work by using multiple supporting resources and drawing a conclusion without deviating from the main idea. f) Proofread the final draft to make sure it is clear and well-written.

Research Results

The search yielded 2,012 libraries in both Indonesian portal and English from the Pubmed, NCBI, Google Scholar, and ScienceDirect portals. The author then conducted a selection process to eliminate duplicates and irrelevant articles, leaving 230 references in total, of which 27 references were used to compile the entire article.

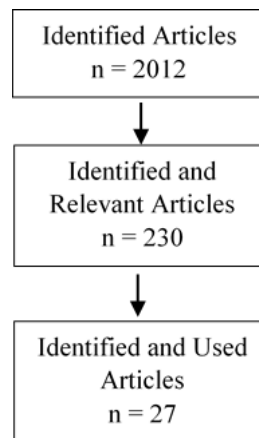


Image 1. Paper selection algorithm

Discussion

Ketorolac Overview

Ketorolac inhibits both cyclooxygenase-1 and cyclooxygenase-2. Research indicates that ketorolac is more potent than most other NSAIDs. It has been shown in a number of recent trials to be able to manage cancer-related pain, albeit the evidence for this is still insufficient (12). Generally speaking, the mechanism of action of ketorolac is non-selective cyclooxygenase (COX) inhibitor, COX is an enzyme that turn arachidonic acid (AA) into precursors of inflammatory mediators. Inhibition of COX enzyme indirectly reducing the production of inflammatory mediator precursors and reduces pain (13).

Ketorolac is easily absorbed when taken orally and completely absorbed by intramuscular (IM) or intravenous (IV) injection. It takes different time to reach peak plasma

concentration. It takes 45 minutes to reach peak plasma concentration by oral, around 2 minutes via IV, around 30 minutes via IM and around 45 minutes via nasal (14). The use of ketorolac has been shown in several studies to reduce the consumption of opioids to treat postoperative pain. Ketorolac has poor penetration into cerebrospinal fluid (CSF). Ketorolac is metabolized in the liver through conjugation with glucuronic acid and hydroxylation. Ketorolac excretion through urine is approximately 94% and feces is approximately 6%. Ketorolac has an average half-life of about 5 hours (2-9 hours) (15).

Why Ketorolac?

In research by Eftekharian et al., the aim is to determine the effect of IV ketorolac in treating acute pain after mandibular fracture surgery. The study was conducted in a randomized, double-blind manner, with a placebo as the control group. A total of 50 patients with mandibular fractures who underwent surgery were divided into two groups, with one group of 25 people randomly receiving IV ketorolac at a dose of 30 mg right at the end of the operation and the other 25 people being given the placebo. According to the results of the study, patients on placebo required significantly higher analgesic use than the ketorolac group (72% vs. 28%; $p=0.002$). Ketorolac significantly reduced pain intensity 30 minutes after surgery ($p<0.001$) and no significant side effects were reported (16).

Based on a study conducted by Stone and Sadie to determine ketorolac's efficacy and safety in managing postoperative pain in neonates and infants. Researchers used eight reports that included 239 babies under six months of age who met the inclusion criteria. Most patients were given ketorolac at a dose of 0.5 mg/kg every six hours for 48–72 hours. The effect was assessed using the Neonatal/Infant Pain Scale Scores; there was a significant reduction and no serious side effects were found (17).

Ketorolac versus Other Analgesics

In 2020, research was conducted in Iran to determine the analgesic effect of ketorolac compared with paracetamol in patients after coronary artery bypass graft (CABG) surgery. A randomized clinical trial (RCT) with sixty CABG patients was conducted by researchers in response to the hypothesis that there are no effective analgesic agents in patients following CABG surgery, making post operative pain management a burden. Researchers carried out the intervention by randomly dividing patients into two groups, after meeting specified inclusion criteria such as heart failure, complex surgery, history of seizures, etc. Researchers provided treatment, the first group was given ketorolac at a dose of 0.5mg/kg dissolved in

100cc of normal saline (NS) given every six hours, and the second group was given paracetamol at a dose of 10mg/kg dissolved also in 100cc of NS given every six hours. Evaluate results by comparing Visual Analog Scale (VAS) scores and hemodynamic parameters. Results were recorded when the patient was extubated, at 6, 12, 24, and 48 hours. This study showed significant changes in VAS scores, where the paracetamol group had a greater VAS score at 24 and 48 hours compared to the ketorolac group. Hemodynamic parameters between the two groups did not differ significantly and were classified as free from dangerous side effects. Hemodynamic parameters did not significantly change among the two groups, no harmful side effects were observed (18).

According to Gopalraju's research in 2014, patients were divided into two groups randomly and treated with ketorolac 30 mg or tramadol 50 mg before surgery for pain management after the third molar surgery. Patients were evaluated with VAS every hour for twelve hours. Patients in the ketorolac group had significantly lower VAS scores and were administered fewer postoperative analgesics. Researchers concluded that intraoperative administration of ketorolac can be part of postoperative pain management. After surgery, the mean number of analgesics taken in the tramadol and ketorolac groups was 10.2 vs. 6.8 with a standard deviation of 1.76 and 1.67 ($p < 0.001$). Using VAS scores over 12 hours, the mean VAS scores in the tramadol and ketorolac groups were 5.46 and 3.29 respectively, and were statistically significant ($p < 0.003$) (19).

Postoperative pain management is rarely discussed in urogynecology research. Many post-urogynecologic surgery patients complain of inadequate postoperative pain management. Based on these problems, Dwarica's research in 2019 aimed to compare the effects of ketorolac with ibuprofen as the best analgesic choice for managing postoperative pain. Around 224 patients were included in this study. Patients were divided into two groups randomly given IV ketorolac and the other IV ibuprofen. Researchers compared the results of evaluating VAS scores, patients satisfaction, and opioid consumption. The difference was not significant, except for the VAS score in post-laparotomy patients and patient satisfaction. Ketorolac is a better analgesic than ibuprofen (20).

Table 1. VAS score, Satisfaction, and Opioid Consumption (Ketorolac vs. Ibuprofen)

Variables	Ketorolac	Ibuprofen
VAS at rest	2,3	2,7
VAS at ambulation	3,4	3,6

VAS (laparotomy patients)	2,8	4,9
Satisfaction	Higher	Lower
Hydromorphone consumption (average in mg.)	3,68 mg	4,04 mg

Research conducted by Anand in 2013 analyzed the effects of ketorolac and acetaminophen on post-operative pain in patients undergoing parathyroidectomy under general anesthesia. The study involved randomly selecting patients and administering either IV acetaminophen or IV ketorolac. Pain was measured using the VAS score every 15 minutes until the patient was discharged from the PACU. The results showed that the IV administration of ketorolac was more effective in reducing postoperative pain compared to acetaminophen. Additionally, the incidence of adverse events was significantly lower in the ketorolac group (3.4%) than in the acetaminophen group (14.6%). In both groups, some patients received additional morphine (21).

There was a study in 2019 in Indonesia that compared the efficacy of ketoprofen with ketorolac in managing postoperative pain in cesarean section (C-section) patients. In this study, 24 patients were given ketoprofen, and 26 patients were given ketorolac. The pain level of patients undergoing C-section surgery was measured using VAS. This research is an analytical observational study, and data collection was carried out prospectively. Patients who received ketorolac had a mean VAS score lower than patients who received ketoprofen, but not significantly ($p = 0.593$) (22).

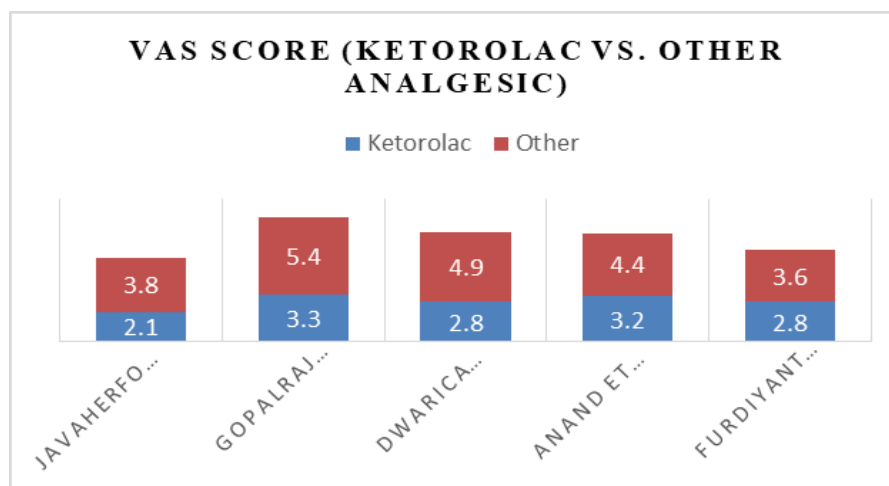


Image 2. VAS score based on previous research (lower indicates more effective analgesic effect)

Safety Considerations

The safety of using ketorolac in patients experiencing postoperative pain was the subject of a study by Maslin et al. The evaluation method used was an analysis of the available supportive data regarding the safety of ketorolac in postoperative pain management. The evaluation results show several points that need attention. First, the use of ketorolac at normal doses does not inhibit the bone healing process, so its use in orthopedic trauma (fracture) patients is not contraindicated. Numerous studies support the use of ketorolac as a potent post operative pain management, however few discuss the profile of using ketorolac in patients and recommendations for using ketorolac to obtain maximum benefits and minimal side effects (23).

It has been determined that the administration of ketorolac in post operative management is generally safe and effective; however, a thorough patient evaluation, such as obtaining a history of allergies, is still needed, and multidisciplinary evaluation and collaboration are still recommended to obtain maximum safety. Secondly, the use of ketorolac must be used with caution in patients who have comorbid kidney, heart, and liver diseases (24).

Ketorolac Dosage Recommendation

The recommended dose of ketorolac for pain management follows established recommendations. IV or IM administration, the initial dose for short-term management of acute pain is 10 mg, followed by 10–30 mg every four to six hours as needed. Ketorolac can be given within the first two hours as an initial postoperative treatment. The maximum dose of ketorolac is 90 mg/day, with a maximum administration duration of two days. In patients weighing under 50 kg and the elderly (≥ 65 years), dose adjustment is required; the maximum dose is 60 mg/day with a maximum administration duration of two days. Therapy can be changed to oral preparations if possible (25).

In adult patients with oral administration, in cases of pain management or as a continuation of therapy after parenteral administration of drugs, an initial dose of 20 mg (single dose) can be given, and every four to six hours, 10 mg can be given as needed. In patients weighing under 50 kg, 10 mg can be given every four to six hours as needed. The main principle of management is to use the lowest effective dose for the shortest possible time. The maximum allowable dose is 40 mg/day, and the maximum treatment duration is five days. In elderly patients, in cases of short-term pain management, as a continuation of therapy after administration of parenteral drugs, an initial dose of 10 mg every 4–6 hours can be given. The

highest dose that can be given is 40mg/day and the maximum duration of treatment is five days (26).

A randomized double-blind trial with 240 patients, age 18-65, who presented to an Emergency Department was conducted by Lyon et al. (2019) to evaluate the effectiveness of three different IV ketorolac doses for acute pain. Patients were assigned at random to receive 10, 15, or 30 mg of IV ketorolac in 10cc of NS. Every 15, 30, 60, 90, and 120 minutes, pain VAS score, vital signs, and adverse effects were recorded. Each three groups have similar baseline VAS scores (7.5-7.8). The mean VAS score of 10- and 15-mg groups were 5.1 (4.5-5.7 and 4.5-5.6, 95% CI), and the mean pain score 30-mg group was 4.8 (4.2-5.5, 95% CI). The research mentioned above shows that all doses of ketorolac significantly decreased pain, with no significant difference and adverse effects among the three different doses. It should be noted that the most widely available injection preparation is 30 mg/ampoule (27).

Conclusions and Suggestions

In general, ketorolac has a good safety profile as long as it is used according to the recommended dosage and there are a few contraindications in patients that they must be aware of before treatment. Several studies suggest administering ketorolac within two hours post surgery for a treatment duration of two to five days. Prior studies have demonstrated the benefits and possible uses of ketorolac in the treatment of postoperative pain and the reduction of postoperative opioid usage.

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