Comparing the Effectiveness of Perioperative Ketorolac to Opioids: A Scoping Review

Kruze Vanderford, Abbie Walter, & Anastasiya Woodard

University of Tennessee Health Science Center

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Dr. Bobby Bellflower

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Rationale

Opioid administration is the current mainstay for treating and preventing postoperative pain (Dastan et al., 2020). Opioids reduce pain effectively, but they bear the risk of unpleasant and even dangerous side effects. Opioids are known to increase the incidence of postoperative nausea and vomiting (PONV), constipation, respiratory depression, and addiction (Lytle et al., 2020). Adequate pain management positively affects patients' rehabilitation, morbidity, mortality, and overall patient experience following surgery. Thus, anesthesia providers must effectively manage their patients' pain without contributing further to the opioid crisis through opioid introduction (Dastan et al., 2020).

Ketorolac is a non-steroidal anti-inflammatory drug proven safe and efficacious in various surgical procedures such as thoracolumbar spinal fusions, mandibular fractures, and ankle fracture surgeries (Eftekharian & Ilkhani Pak**,** 2016; Lytle et al., 2020; McDonald et al., 2020). Routine inclusion of ketorolac can effectively manage pain while decreasing opioid use and their adverse side effects. While there is a substantial amount of current literature, there is little consensus on the route, dose, and patient populations to which ketorolac is best suited. We performed this scoping review to examine ketorolac's impact on postoperative pain and opioid consumption and discover where further research is needed.

Objectives

This review aims to answer the question: What does the existing literature say about the effectiveness of ketorolac versus opioids in the adult surgical population? Our specific objectives in performing this scoping review were examining the efficacy of ketorolac in the perioperative

period, its role in reducing opioid consumption, and whether there is an overwhelming consensus on the preferred dose and route of administration.

Methods

Eligibility Criteria

For inclusion in this review, sources had to evaluate the effectiveness of perioperative ketorolac administration on postoperative pain. Additionally, they had to be peer-reviewed journal articles published within the last ten years. Research had to be approved by the institutional review board and performed on human participants undergoing a procedure that required general anesthesia. Studies had to be in English and published in a medical or nursing journal. Meta-analyses, scientific studies, and evidenced-based practice reports were all deemed eligible for inclusion. These criteria ensured that we included only relevant, high-level information in our scoping review.

Information Sources

All members of the team performed a literature review between September 2020 and October 2021. One of the team members completed the final literature search on October 30, 2021. We performed a comprehensive literature search by searching the GoogleScholar ™, PubMed, Ovid, Cochrane Library, and the University of Tennessee Health Science Center (UTHSC) library databases for relevant articles. We acquired the sources not available in full-text online as an interlibrary loan through the UTSHC library.

Search

We performed our literature search using filters for peer-reviewed, English, full-text articles published within the last ten years to identify current, comprehensive research. We also

searched for articles without a time restriction. However, we did not include any articles greater than ten years old in our final review. We used the following Boolean operators in our search: “ketorolac” AND “opioid” OR “narcotic” AND “intraoperative” OR “perioperative period.” We also queried the trade name for ketorolac, “Toradol.” We used the search terms “narcotics,” “operative,” and “surgical” to find gray literature undiscovered during our initial search.

Selection of sources of evidence

After completing our comprehensive literature search, as detailed in the following section, 28 articles were deemed worthy of further review. The articles were distributed equally between our three team members for closer examination and then presented to the group with recommendations for inclusion or exclusion. We excluded all reports that did not meet the criteria after a rapid critical appraisal (RCA). Each member reviewed the remaining articles to increase consistency between reviewers, and the group collectively decided to include 15 high-quality entries in the final analysis. We constructed and frequently updated a synthesis table to display the articles’ level of evidence, methods, and outcomes. No disagreements about which articles met inclusion criteria occurred.

Data charting process

The initial synthesis table was constructed in February 2021 by all group members. This table indicated the literature’s level of evidence and visually demonstrated the results of study outcomes. One team member made a more comprehensive Excel document to organize pertinent information during the final scoping review. The Excel sheet used as our data-charting form includes the article year, level of evidence, study time frame, interventions, and primary outcomes. All three team members reviewed and annotated the chart and held a team meeting to discuss chart results.

Data items

We examined each source for the type of surgery and type of anesthesia performed, dose and route of ketorolac administration, as well as timing of ketorolac administration (preoperative, intraoperative, upon incision closure, immediate postoperative, or late postoperative). The following primary outcomes were extracted: morphine equivalents (ME) administered postoperatively and pain scores on a visual analog scale (VAS) in the early and late postoperative periods. We also extracted any tertiary outcomes such as adverse effects, length of stay (LOS), and time to rescue analgesics. We did not require each article to include all these data points for consideration in the scoping review. The results of our scoping study include both qualitative and quantitative data.

Synthesis of results

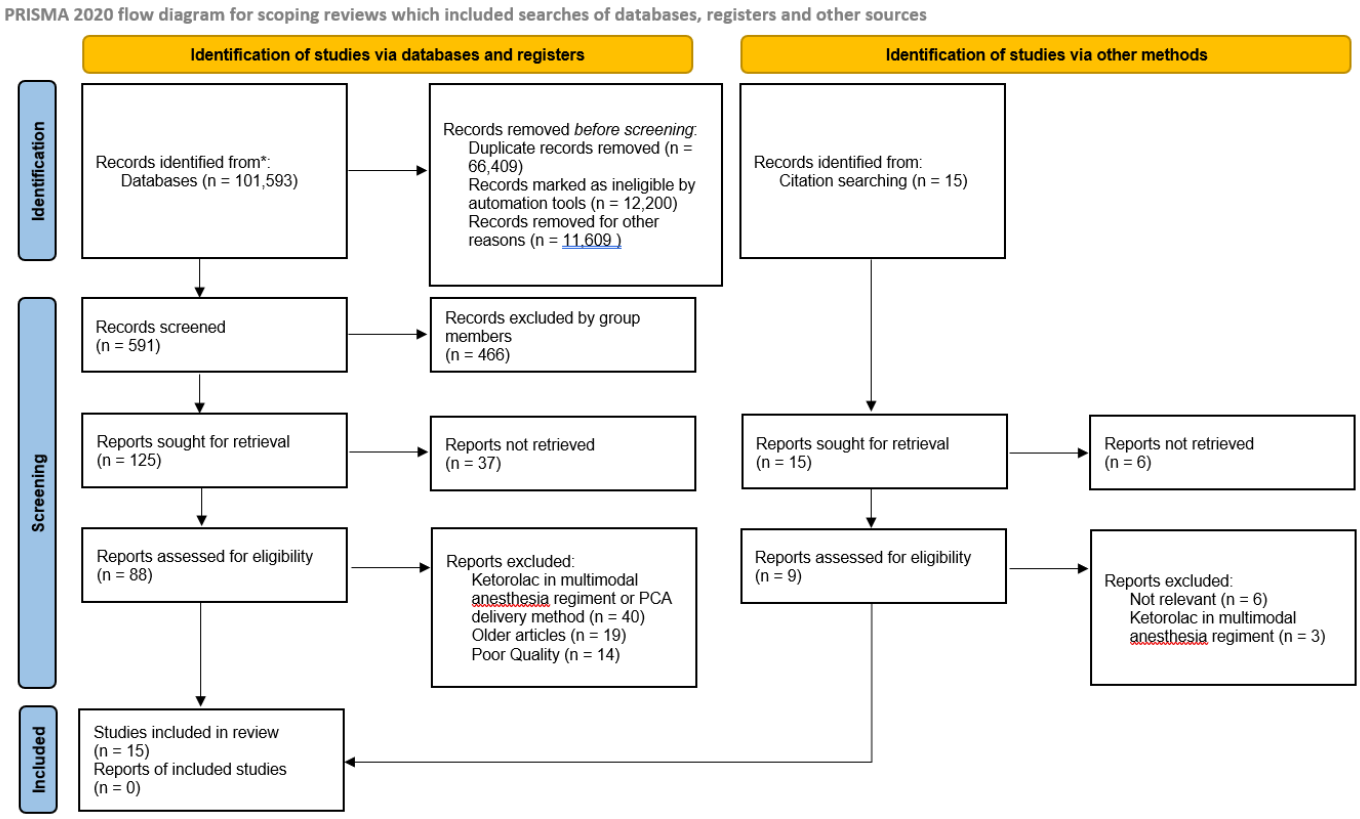
We grouped the evidence by the results of the primary outcomes. We constructed a final synthesis table to visually demonstrate whether postoperative opioid consumption and pain scores were increased, decreased, or stayed the same with the inclusion of ketorolac. The specific intervention, level of evidence, and timing of ketorolac administration were listed on the table. See Appendix 1 for the final synthesis table.

Results

Selection of sources of evidence

Our initial search strategy yielded over 100,000 article results from the PubMed, CINAHL, Google Scholar, Ovid, and Cochrane databases. We focused the search on adult surgical patients between 18-65 years old, articles less than ten years old, and those with free text or links to the paper through UTHSC library access, which resulted in about 600 potential

sources. Our group further excluded entries that did not meet the inclusion criteria after reviewing individual abstracts. Finally, we excluded sources that listed ketorolac as part of a multimodal anesthesia regiment instead of comparing its effects with an opioid-only course of treatment. Through this process, we arrived at 28 potential articles, which were later subjected to rapid critical appraisal (RCA). We determined that 15 peer-reviewed journal articles met all inclusion criteria. Six were level I meta-analyses and systematic reviews, seven were level II randomized clinical trials, and two were level IV retrospective cohort studies. The flow diagram of our search process is below.



Characteristics of sources of evidence

The journal articles we selected for this review represent a well-rounded and extensive sample of available literature on the topic of perioperative ketorolac use. Randomized control

trials (RCTs) (n=6) and systematic reviews and meta-analyses (n=6) represent the chosen articles equally. Additionally, we included high-quality retrospective cohort studies (n=3). The relevant data we charted and used for this scoping review were total postoperative opioid consumption, postoperative pain scores, the incidence of adverse effects, and time to first rescue analgesic request.

The systematic reviews and meta-analyses analyzed a total of 181 RCTs, comparing perioperative use of ketorolac to control groups receiving either a placebo or intravenous opioids. Several meta-analyses compared a variety of ketorolac dosing regimens, administration times (preoperative, intra-operative, and postoperative), and administration routes (intravenous (IV), intramuscular (IM), and would infiltration). They also reviewed ketorolac use in various surgical cases ranging from complex orthopedic surgeries to simple gynecologic procedures. All the studies included in this review involved adult surgical patients with a wide range of ages from 18-65.

One of the RCTs we selected analyzed postoperative pain severity at rest via the visual analog scale rating (VAS) in patients undergoing video-assisted thoracoscopic surgery (VATS) (Dastan et al., 2020). The study featured three separate groups, each receiving postoperative IV bolus injection of morphine, ketorolac, or paracetamol, respectively, followed by an infusion of the same drug during the first 24 hours. Four RCTs compared the use of IV ketorolac bolus to a control group that received no additional pain medication. (Eftekharian & Pak, 2017; Gutta et al., 2013; Wladis et al., 2019, 2020). One RCT analyzed postoperative opioid consumption and VAS pain scores in 106 adult patients undergoing open reduction and internal fixation (ORIF) of an acute ankle fracture. Patients received postoperative intravenous ketorolac with an opioid medication (treatment group) or opioids alone (control group) (McDonald et al., 2020).

The retrospective cohort studies all had varying approaches to analyzing the effects of ketorolac on postoperative pain. Hariri et al. (2019) compared postoperative opioid consumption in bariatric surgery patients who either received IV ketorolac in addition to opioids (treatment group) or opioids alone (control group). Lytle et al. (2020) reviewed the efficacy of intraoperative 30 mg of ketorolac injection in the "musculocutaneous tissue adjacent to the operative bed" (p. 295) on postoperative VAS pain scores and cumulative opioid consumption in adult patients undergoing thoracolumbar spinal fusions. Finally, Nguyen et al. (2020) analyzed the inpatient narcotic use and the LOS in implant-based breast reconstruction patients. The treatment group received IV ketorolac intraoperatively followed by additional doses on an as-needed basis every six hours for up to five days. They were also able to receive acetaminophen, opioids, or both as needed for postoperative pain. The control group did not have ketorolac as part of their postoperative pain treatment regimen.

Results of individual sources of evidence

Out of the articles we reviewed for this scoping review, the most common outcomes assessed were postoperative opioid consumption, postoperative VAS pain scores, time to first rescue analgesic request, and incidence of postoperative adverse events. The studies analyzed a wide variety of negative outcomes, including postoperative nausea and vomiting (PONV) (Dastan et al., 2020; De Oliveira et al., 2012; Lytle et al., 2020; Martinez et al., 2019; Wan et al., 2020; Wladis et al., 2020), urinary retention (Secrist et al., 2016), abnormal bleeding (Dastan et al., 2020; De Oliveira et al., 2012; Hariri et al., 2019), pruritis (De Oliveira et al., 2012; Martinez et al., 2019), and postoperative sedation (Fillingham et al., 2020). Two studies examined the effects of perioperative ketorolac use on LOS. (Hariri et al., 2019; Nguyen et al., 2020).

Nine articles, including three meta-analyses, found a statistically significant reduction in postoperative opioid consumption when patients received an IV bolus of ketorolac in the perioperative period compared to placebo or opioids alone. Furthermore, 11 of the articles we examined found a reduction in postoperative VAS pain scores of patients treated with IV and IM doses of ketorolac compared to the patients who received a placebo or opioids alone. Five of the six systematic reviews and meta-analyses we reviewed supported this finding. Martinez et al. (2019) found no statistically significant difference in postoperative pain scores.

Three meta-analyses showed no difference in adverse postoperative outcomes in study groups treated with ketorolac (De Oliveira et al., 2012; Fillingham et al., 2020; Martinez et al., 2019) while one showed a statistically significant reduction in the ketorolac group (Secrist et al., 2016).

Lastly, of the studies that we analyzed, most showed no difference between study groups in the time to the first analgesic request (Gutta et al., 2013; Eftekharian & Pak, 2017; Lytle et al., 2020), while Wan et al. (2020) concluded that there was a modest increase in how long ketorolac treated patients waited before requesting the first dose of postoperative analgesic.

For details of individual article findings, please see the table in Appendix 1.

Synthesis of results

Our analysis of the charted data revealed that most of the literature reports an observable decrease in postoperative opioid consumption for surgical patients treated with ketorolac in the perioperative period. Additionally, most of the studied literature shows a statistically significant reduction in postoperative pain scores for a diverse group of patients undergoing various surgical procedures. Finally, most studies concluded the use of ketorolac as part of the analgesic regimen

does not increase the incidence of postoperative adverse outcomes and shows a marked reduction in PONV.

Discussion

Summary of evidence

Nine studies showed decreased opioid consumption in the perioperative period, while the remaining six showed no difference in opioid consumption following ketorolac administration. Eleven studies showed a decrease in postoperative VAS scores. However, four studies showed no significant difference between the control and intervention groups. Three studies showed no significant difference in time to first analgesic request, while one showed an increase in time to first analgesic request between the control and intervention groups. Most of the literature in this scoping review reveals that perioperative ketorolac administration reduces postoperative opioid consumption and postoperative VAS pain scores in adult patients undergoing a variety of surgical procedures. Additionally, the literature concluded that perioperative ketorolac significantly reduced the incidence of PONV and had no significant effect on postoperative outcomes in adult surgical patients.

Limitations

Several of our articles, including the surveyed metanalyses, recognized that the studies in their reviews were heterogeneous in the dosage regimens, routes of administration, administration timing, and outcome assessments. Because of the numerous study groups, authors of systematic reviews had to contend with sample sizes much smaller than initially anticipated. One article stated that the heterogeneity between studies and the lack of standardization in pain assessments directly affected the authors' ability to do a metanalysis (Blanton et al., 2017). Ultimately, we had to include a variety of surgical procedures, patient populations, and

procedures to maximize the homogenous data and provide a meaningful output supporting the objectives of this scoping review.

Conclusions

We met the general objective of this scoping review: we analyzed the current literature regarding the effectiveness of perioperative ketorolac compared to opioids in the adult surgical population. However, we identified significant heterogeneity in the current data, which makes giving specific recommendations to anesthesia providers surrounding the use of ketorolac difficult. More extensive, homogenous studies should be performed. In general, ketorolac administration during the perioperative period provides sufficient, opioid-sparing analgesia without the adverse effects of narcotics. Ketorolac administration can be a valuable adjunct in multimodal analgesia. It should be considered an alternative to perioperative opioids to improve postoperative patient outcomes and combat the opioid pandemic in America.

Appendix 1

									Results		
Study	Year	Level of Evidence	Type	Intervention	Administration Timing	Outcome 1	Outcome 2	Outcome 3	O1	O2	O3
Blanton	2017	I	Meta	various	various	Post-op opioid consumption	post-op VAS pain score		—	↓	
Dastan	2020	II	RCT	IVK vs IV opioid vs tylenol	post-op	Post-op opioid consumption	post-op VAS pain score		—	—	
De Oliveira	2012	I	Meta	IV and IM K (30mg and 60mg) vs. placebo	"perioperative"	Post-op opioid consumption	post-op VAS pain score	adverse effects	↓	↓	—
Eftekharian & Pak	2017	II	RCT	IVK (30 mg) or none (control)	post-op	Post-op opioid consumption	post-op VAS pain score	time to 1st analgesic request	↓	↓	—
Fillingham	2020	I	Meta	various	various	Post-op opioid consumption	post-op VAS pain score	adverse effects	↓	↓	—
Gutta	2013	II	RCT	IVK (30 mg) or none (control)	pre-op	Post-op opioid consumption	post-op VAS pain score	time to 1st analgesic request	—	—	—
Hariri	2019	IV	retro cohort	ketorolac + opioid vs. opioids alone	various	Post-op opioid consumption	LOS		↓	↓	
Lytle	2020	IV	retro cohort	IMK 30mg vs none (control)	intra-op	Post-op opioid consumption	post-op VAS pain score	time to 1st analgesic request	—	—	—
Martinez, L.	2019	I	Meta	IVK (30 mg) + opiod or none (control) + opioid	"perioperative"	Post-op opioid consumption	post-op VAS pain score	adverse effects	↓	—	—
McDonald	2020	II	RCT	IVK (30 mg) + opiod or none (control) + opioid	intra-op	Post-op opioid consumption	post-op VAS pain score		↓	↓	
Nguyen	2020	IV	retro cohort	IV K (15mg vs. 30mg)	intra-op	Post-op opioid consumption	LOS		↓	↓	
Secrist	2016	I	Meta	various	various	Post-op opioid consumption	post-op VAS pain score	adverse effects	—	↓	↓
Wan	2020	I	Meta	IV K (30mg and 60mg) vs. placebo	"perioperative"	Post-op opioid consumption	post-op VAS pain score	time to 1st analgesic request	—	↓	↑
Wladis	2019	II	RCT	IVK or none (control)	pre-op	Post-op opioid consumption	post-op VAS pain score		↓	↓	
Wladis	2020	II	RCT	IVK (15 or 30 mg) or none (control)	pre-op	Post-op opioid consumption	post-op VAS pain score		↓	↓	

SYMBOL KEY

↑ = Increased, ↓ = Decreased, — = No Change

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