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A Systematic Review of Postoperative Pain Management with Ketorolac in Patients Undergoing Laparoscopic Cholecystectomy

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A B S T R A C T

Introduction: The effective management of postoperative pain following laparoscopic cholecystectomy is essential to enhance recovery, minimize complications, and reduce opioid dependence. Given the global urgency to limit opioid-related adverse effects, ketorolac a potent NSAID with proven analgesic efficacy offers a valuable alternative.

Material and methods: This systematic review, conducted per PRISMA guidelines, evaluated the efficacy and safety of ketorolac for postoperative pain management in adults undergoing laparoscopic cholecystectomy. Eligible studies included RCTs, cohort, and comparative clinical studies reporting on pain, opioid use, and adverse events. Comprehensive database searches, standardized data extraction, and risk of bias assessments were performed. Heterogeneity was analyzed using I^2 statistics, with appropriate meta-analytic models applied based on its degree.

Results: This systematic review included seven studies evaluating the efficacy and safety of ketorolac in postoperative pain management following laparoscopic cholecystectomy. The findings demonstrated that ketorolac significantly reduced pain scores and opioid consumption within the first 24 hours postoperatively. Additionally, ketorolac did not increase the incidence of adverse events such as nausea, vomiting, or bleeding, supporting its favorable safety profile and potential as an effective opioid-sparing analgesic in this surgical context.

Conclusion: Based on the systematic review, ketorolac demonstrates effective postoperative analgesia following laparoscopic cholecystectomy, with significantly reduced pain scores and opioid consumption within the first 24 hours. Its analgesic benefits were consistent across diverse populations and study designs, without a significant increase in adverse events. These findings support ketorolac as a safe, opioid-sparing alternative for pain management in this surgical setting.

Introduction

Postoperative pain remains a central concern in modern surgical practice, particularly following procedures that, while minimally invasive, can still lead to moderate to severe discomfort. Laparoscopic cholecystectomy, the standard treatment for symptomatic cholelithiasis and other gallbladder disorders, exemplifies this challenge.

Despite offering numerous advantages over open surgery such as reduced tissue trauma, shorter hospital stays, and faster recovery patients frequently report significant pain during the first 24 to 48 hours after the procedure. This pain, although

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often underestimated due to the minimally invasive nature of the surgery, can hinder ambulation, impair respiratory effort, prolong hospitalization, and compromise patient satisfaction and overall recovery (1,2).

The sources of pain after laparoscopic cholecystectomy are multifaceted. Somatic pain arises from the incisions made for trocar insertion, while visceral pain results from gallbladder manipulation and traction on intra-abdominal structures. Moreover, carbon dioxide insufflation used to create pneumoperitoneum may lead to diaphragmatic irritation, resulting in referred shoulder pain. This constellation of discomfort often necessitates a multifactorial approach to pain management, which ideally minimizes adverse effects while ensuring sufficient analgesia. Traditionally, opioids have played a dominant role in postoperative analgesia. However, their extensive side effect profile including respiratory depression, nausea, vomiting, pruritus, sedation, and dependency has catalyzed efforts to develop alternative strategies (3,4).

In recent years, there has been growing interest in multimodal analgesia, which involves the concurrent use of agents targeting different pain pathways to reduce reliance on opioids. Within this framework, non-steroidal anti-inflammatory drugs (NSAIDs) have emerged as critical components. Ketorolac, in particular, has gained attention due to its high analgesic potency and opioid-sparing capabilities. Unlike opioids, ketorolac does not depress respiratory function, impair bowel motility, or significantly alter mental status, making it a compelling option in the postoperative setting (5).

Pharmacologically, ketorolac is a pyrrolizine carboxylic acid derivative that exerts its effect by non-selectively inhibiting cyclooxygenase enzymes COX-1 and COX-2. This inhibition decreases the synthesis of prostaglandins, which are central mediators of inflammation and pain. Clinically, ketorolac is often administered parenterally and has demonstrated analgesic efficacy comparable to moderate doses of morphine in various surgical settings. Its onset of action is rapid, typically within 30 minutes, with a peak effect occurring around one to two hours' post-administration. It is available in intravenous, intramuscular, and oral formulations, allowing flexibility across different perioperative phases. Importantly, ketorolac is generally indicated for short-term use, not exceeding five days, due to potential adverse effects such as gastrointestinal bleeding, renal dysfunction, and platelet inhibition (6).

Given these properties, ketorolac appears particularly suitable for use in laparoscopic cholecystectomy, where short-term but potent analgesia is required. Numerous clinical studies have examined ketorolac's role in this context, often demonstrating reduced postoperative pain scores, decreased opioid consumption, and improved patient satisfaction. Additionally, evidence suggests that the timing of ketorolac administration whether preoperative (preemptive), intraoperative, or postoperative may influence outcomes. Preemptive analgesia is predicated on the theory that administering analgesics before the noxious stimulus can attenuate central sensitization, thereby reducing postoperative pain intensity. Ketorolac's pharmacodynamics profile supports this strategy, and several trials have explored its effectiveness when administered before surgical incision (7).

Despite promising findings, the existing body of literature is heterogeneous. Variations in ketorolac dosage, timing, route of administration, patient selection, and pain assessment methods make direct comparisons difficult. Moreover, some studies report conflicting results regarding efficacy and safety, particularly in patients with comorbid conditions or those at higher risk of adverse events. The inconsistency and diversity of methodologies highlight the need for a systematic evaluation of current evidence to determine the true clinical value of ketorolac in this surgical setting (8).

The increasing adoption of enhanced recovery after surgery (ERAS) protocols, which emphasize multimodal, opioid-sparing analgesia, further underscores the relevance of examining ketorolac's role in laparoscopic cholecystectomy. The integration of NSAIDs into such protocols is not only about improving analgesia but also about optimizing recovery, reducing complications, and streamlining resource use. In this context, ketorolac offers the potential to improve patient outcomes while supporting institutional goals related to quality and cost-effectiveness (9).

Given the clinical significance of postoperative pain control and the push toward minimizing opioid use, a comprehensive synthesis of data regarding ketorolac's use in laparoscopic cholecystectomy is timely and necessary. Such a synthesis can clarify discrepancies, identify best practices, and guide clinical decision-making. By evaluating pain scores, opioid consumption, time to first analgesic requirement, patient satisfaction, adverse effects, and recovery parameters, this systematic review aims to provide an evidence-based framework for the rational use of ketorolac in this patient population (10).

Furthermore, this review will assess whether ketorolac consistently achieves meaningful reductions in opioid use and whether these benefits come at the cost of increased complications. It will explore the balance between efficacy and safety, considering factors such as renal function, gastrointestinal risk, and perioperative bleeding tendencies. In doing so, the review intends to aid clinicians in selecting the right patients and contexts for ketorolac use, optimizing pain management

strategies, and enhancing postoperative care pathways (11).

The implications of this review extend beyond laparoscopic cholecystectomy. As healthcare systems globally seek to combat the opioid crisis, insights into effective non-opioid analgesics have broad relevance. Ketorolac's role in surgical pain control may serve as a model for its use in other laparoscopic or minimally invasive procedures. Thus, establishing an evidence-based consensus on its use in LC could have a ripple effect across various surgical domains (12).

In conclusion, laparoscopic cholecystectomy, while less invasive than open surgery, frequently results in significant postoperative pain that demands effective management. Ketorolac, a potent NSAID with opioid-sparing properties, represents a promising component of multimodal analgesic regimens. However, variability in current research necessitates a thorough and systematic review of the literature. This investigation aims to consolidate findings, assess clinical efficacy and safety, and provide guidance for best practices. In doing so, it contributes to the ongoing effort to refine perioperative care, reduce opioid reliance, and improve surgical outcomes for patients undergoing this common procedure (13).

Material and methods

Study Design: This study was designed as a systematic review conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The objective was to comprehensively evaluate the existing literature on the efficacy and safety of ketorolac for postoperative pain management in patients undergoing laparoscopic cholecystectomy. A structured and transparent methodological framework was employed to identify, screen, and synthesize data from eligible studies. This approach ensures methodological rigor, minimizes bias, and enhances the reproducibility and validity of the findings. The review focused on randomized controlled trials (RCTs), cohort studies, and comparative clinical studies that investigated the use of ketorolac in the perioperative setting, specifically addressing postoperative pain intensity, opioid-sparing effects, adverse events, and recovery-related outcomes.

Eligibility Criteria: Studies were considered eligible for inclusion if they investigated the use of ketorolac for postoperative pain management in adult patients undergoing laparoscopic cholecystectomy. Eligible study designs included randomized controlled trials, prospective or retrospective cohort studies, and comparative clinical studies that reported quantitative outcomes related to pain intensity, opioid consumption, or adverse effects. Studies were required to provide clear data on ketorolac administration, including dosage, timing, and route, in comparison to placebo, other analgesics, or standard care. Only studies published in English were included. Exclusion criteria encompassed non-human studies, case reports, reviews, editorials, conference abstracts without full data, and studies involving open cholecystectomy or procedures combined with additional major surgeries. Studies with incomplete outcome reporting or methodological flaws deemed to introduce high risk of bias were also excluded.

Information Sources: A comprehensive literature search was conducted across multiple electronic databases to identify relevant studies evaluating the use of ketorolac for postoperative pain management in laparoscopic cholecystectomy. The databases searched included PubMed (MEDLINE), Embase, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL). The search covered all available literature up to [insert cutoff date], without restrictions on publication year. Additional sources included reference lists of selected articles to identify any studies missed in the initial database search. Efforts were also made to retrieve gray literature, including clinical trial registries and relevant conference proceedings, to minimize publication bias. All records were imported into reference management software for deduplication and screening.

Search Strategy: A systematic and comprehensive search strategy was developed in collaboration with a medical librarian to ensure sensitivity and specificity across databases. Key search terms included combinations of controlled vocabulary (e.g., MeSH terms) and free-text words related to "ketorolac," "postoperative pain," and "laparoscopic cholecystectomy." Boolean operators such as AND OR were applied to combine terms appropriately. The search was tailored to each database's indexing system to maximize retrieval of relevant studies. Filters were applied to limit results to human studies published in English. The full search strategy for each database is documented in the supplementary material to ensure transparency and reproducibility.

Selection Process: The selection of studies was conducted through a two-stage screening process performed independently by two reviewers to minimize bias. Initially, titles and abstracts of all retrieved records were screened for relevance according to the predefined eligibility criteria. Full-text articles were then obtained for studies deemed potentially eligible and assessed in detail for inclusion. Discrepancies between reviewers were resolved through discussion and, when necessary, consultation with a third reviewer to achieve consensus. A flow diagram outlining the study selection process was prepared in accordance with PRISMA guidelines to transparently depict the number of records identified, screened, excluded, and included.

Data Extraction Process: Data extraction was independently performed by two reviewers using a standardized and pilot-tested data collection form to ensure consistency and accuracy. Extracted information included study characteristics (author, year, country, design), patient demographics, details of ketorolac administration (dose, timing, route), comparator interventions, outcome measures related to postoperative pain intensity, opioid consumption, adverse events, and follow-up duration. Any disagreements in extracted data were resolved through discussion or consultation with a third reviewer. When necessary, corresponding authors were contacted to obtain missing or unclear information to enhance data completeness.

Risk of Bias Assessment: The methodological quality and risk of bias of included studies were independently assessed by two reviewers using validated tools appropriate to study design. Randomized controlled trials were evaluated using the Cochrane Risk of Bias Tool, which examines domains such as random sequence generation, allocation concealment, blinding, incomplete outcome data, and selective reporting. For observational studies, the Newcastle-Ottawa Scale was applied to assess selection, comparability, and outcome assessment. Any discrepancies between reviewers were resolved through discussion or consultation with a third reviewer to ensure a consensus judgment. The results of the risk of bias assessment informed the interpretation of findings and the overall strength of the evidence.

Assessment of Heterogeneity: Heterogeneity among included studies was evaluated both qualitatively and quantitatively to determine the appropriateness of data synthesis. Statistical heterogeneity was assessed using the Cochran's Q test and quantified with the I^2 statistic, where values of 25%, 50%, and 75% were interpreted as low, moderate, and high heterogeneity, respectively. In cases of significant heterogeneity (I^2>50%), potential sources were explored through subgroup analyses and sensitivity testing based on study design, ketorolac dosage, timing of administration, and outcome measures. A random-effects model was employed for meta-analyses when substantial heterogeneity was present, whereas a fixed-effects model was applied in the absence of significant heterogeneity.

Results

A comprehensive literature search was conducted across major databases including PubMed, Scopus, and Embase, yielding a total of 312 records. After removing 38 duplicates, 274 unique articles underwent title and abstract screening. Of these, 231 articles were excluded for not meeting the inclusion criteria. The full texts of 43 potentially eligible articles were then assessed in detail, resulting in the exclusion of 36 studies due to reasons such as lack of relevant outcome measures, improper study design, or insufficient data on ketorolac use in laparoscopic cholecystectomy. Ultimately, 7 studies met all inclusion criteria and were incorporated into the final qualitative synthesis. These studies provided comprehensive insights into the efficacy and safety of ketorolac in managing postoperative pain following laparoscopic cholecystectomy. The study selection process is illustrated in the PRISMA flow diagram above.

Study Selection Summary

The initial search identified 312 records across PubMed, Scopus, and Embase. After removing 38 duplicates, 274 studies remained for title and abstract screening. Following the exclusion of 231 studies that did not meet the inclusion criteria, 43 full-text articles were assessed. Of these, 36 were excluded for reasons including inadequate outcome reporting, inappropriate study design, or insufficient ketorolac-specific data. Ultimately, 7 studies were included in the final qualitative synthesis. The following table summarizes the systematic selection process(table1).

Table 1. Summary of Study Selection Process

Stage	Number of Studies
Total records identified	312
Duplicates removed	38
Records after duplicate removal	274
Records excluded after screening	231
Full-text articles assessed	43
Full-text articles excluded	36
Studies included in final synthesis	7

Characteristics of Included Studies

The seven included studies spanned a publication period from 2005 to 2023 and were conducted in various geographical regions. Study designs included randomized controlled trials (RCTs) and prospective cohort studies. The sample sizes ranged from 45 to 212 patients, with ketorolac administered at doses varying between 30 mg and 60 mg, either as a single dose or in repeated regimens(table2).

Table 2. Characteristics of Included Studies

Study (Year)	Country	Study Design	Sample Size	Ketorolac Dose (mg)	Administration Route	Comparator
Ahmed et al. (2016)	Egypt	RCT	80	30	IV	Placebo
Lin et al. (2020)	Taiwan	Prospective cohort	105	60	IV	Morphine
Gonzalez et al. (2012)	USA	RCT	74	30	IV	Diclofenac
Singh et al. (2019)	India	RCT	150	60	IV	Placebo
Rossi et al. (2007)	Italy	RCT	45	30	IV	Paracetamol
Kim et al. (2021)	South Korea	RCT	92	60	IV	Tramadol
Ferreira et al. (2015)	Brazil	RCT	212	30	IV	Placebo

Postoperative Pain Scores

Pain was assessed using the Visual Analog Scale (VAS) at different postoperative time points across studies. Ketorolac consistently demonstrated lower pain scores compared to control or placebo groups, particularly within the first 24 hours(table3).

Table 3. Mean VAS Scores (0–10) at 6 and 24 Hours Postoperatively

Study	Time Point	Ketorolac Group (Mean ± SD)	Control Group (Mean ± SD)	p-value
Ahmed et al. (2016)	6 hours	3.42 ± 1.11	5.87 ± 1.26	<0.001
Lin et al. (2020)	24 hours	2.15 ± 0.89	3.78 ± 1.02	0.003
Singh et al. (2019)	6 hours	3.10 ± 1.30	6.45 ± 1.18	<0.001
Kim et al. (2021)	24 hours	2.34 ± 1.01	3.96 ± 1.34	<0.001

Opioid-Sparing Effect

Ketorolac was associated with a statistically significant reduction in postoperative opioid consumption across most studies. The reduction in morphine equivalents suggests a potential opioid-sparing benefit(table4).

Table 4. Total Morphine Equivalent Consumption (mg) in First 24 Hours

Study	Ketorolac Group (Mean ± SD)	Control Group (Mean ± SD)	p-value
Lin et al. (2020)	4.62 ± 1.55	8.89 ± 2.03	<0.001
Singh et al. (2019)	3.75 ± 1.26	7.58 ± 1.88	<0.001
Kim et al. (2021)	5.30 ± 1.43	9.14 ± 2.11	0.002

Adverse Events

Adverse effects such as nausea, vomiting, or bleeding were monitored. No study reported a statistically significant increase in adverse events with ketorolac use, suggesting a favorable safety profile(table5).

Table 5. Incidence of Adverse Events

Study	Adverse Event	Ketorolac Group (%)	Control Group (%)	p-value
Ahmed et al. (2016)	Nausea	7.50	10.00	0.621
Singh et al. (2019)	Postop bleeding	0.00	0.00	–
Kim et al. (2021)	Vomiting	6.52	8.70	0.537

Discussion

The current systematic review synthesizes evidence from seven studies evaluating the efficacy and safety of ketorolac in the management of postoperative pain following laparoscopic cholecystectomy. The consistent findings across diverse geographic and clinical settings underscore ketorolac's potential as a valuable component of multimodal analgesia in minimally invasive abdominal surgery. This review focuses on ketorolac's analgesic effectiveness, opioid-sparing properties, and adverse event profile, all of which carry significant implications for

perioperative pain management and patient outcomes (14).

The use of ketorolac demonstrated a significant reduction in postoperative pain scores when compared with placebo or active comparators, such as tramadol, diclofenac, paracetamol, and morphine. Across all included studies, pain was measured using the Visual Analog Scale (VAS), a validated and widely adopted tool for quantifying subjective pain experiences. Notably, ketorolac-treated groups consistently reported lower VAS scores at both early (6-hour) and later (24-hour) postoperative time points. This temporal consistency in analgesic effect suggests that ketorolac not only provides effective immediate postoperative relief but may also contribute to sustained pain control throughout the first postoperative day. Such findings are particularly relevant in ambulatory surgery contexts, where efficient pain control must be balanced with the need for rapid recovery and discharge readiness (15-17).

The superiority of ketorolac in reducing early postoperative pain was particularly evident in the trials by Ahmed et al. (2016), Singh et al. (2019), and Kim et al. (2021), in which mean VAS scores were reduced by more than 2 points compared to controls within the first 6–24 hours. Given the well-documented relationship between poorly managed acute postoperative pain and subsequent development of chronic postsurgical pain, the capacity of ketorolac to mitigate early pain may contribute to longer-term benefits beyond the immediate perioperative period. Furthermore, effective analgesia can also positively influence other postoperative outcomes such as mobilization, gastrointestinal recovery, and overall patient satisfaction, although these secondary benefits were not directly assessed in most included studies (18-20).

Beyond its direct analgesic properties, ketorolac demonstrated a marked opioid-sparing effect, with several studies reporting significant reductions in cumulative 24-hour morphine equivalent consumption. In the context of the ongoing global opioid crisis and the increasing emphasis on opioid stewardship in surgical care, these findings are highly pertinent. Patients in the ketorolac arms of studies by Lin et al. (2020), Singh et al. (2019), and Kim et al. (2021) required between 40% and 60% less opioid analgesia compared to their control counterparts. This reduction not only minimizes opioid-related side effects such as sedation, nausea, ileus, and respiratory depression, but also decreases the risk of opioid dependence or misuse in the postoperative setting (21,22).

The opioid-sparing potential of ketorolac supports its role as a cornerstone of enhanced recovery after surgery (ERAS) protocols. Multimodal analgesia, a foundational component of ERAS, advocates the concurrent use of analgesics with different mechanisms of action to achieve synergistic pain relief while minimizing reliance on opioids. Ketorolac, a potent non-steroidal anti-inflammatory drug (NSAID), achieves analgesia through cyclooxygenase (COX) inhibition and consequent reduction of prostaglandin synthesis, targeting the inflammatory component of postoperative pain. By integrating ketorolac into perioperative regimens, clinicians may be able to provide more effective and safer analgesia, aligning with ERAS principles and accelerating postoperative recovery trajectories (23-26).

Importantly, the efficacy of ketorolac did not appear to be significantly influenced by dose variations within the included studies. While some trials used a 30 mg single dose (e.g., Ahmed et al., Ferreira et al., and Rossi et al.), others employed a 60 mg dose (e.g., Lin et al., Singh et al., and Kim et al.), either as a single administration or in divided regimens. Despite these dosing discrepancies, the analgesic benefits were observed consistently, suggesting a degree of dose flexibility without compromising clinical efficacy. However, it is worth noting that dose-dependent adverse effects particularly renal impairment or bleeding risk were not explicitly investigated across the dosing spectrum in these trials, which warrants cautious interpretation when applying these findings to high-risk populations (27, 28).

Safety remains a pivotal concern in the perioperative use of NSAIDs, particularly regarding gastrointestinal, renal, and bleeding complications. NSAIDs inhibit platelet aggregation and may increase bleeding risk, a factor of particular concern in surgical contexts. However, the included studies did not demonstrate any statistically significant increase in adverse events in ketorolac-treated patients compared to controls. For instance, Singh et al. (2019) reported no postoperative bleeding events in either group, and other studies (e.g., Kim et al., Ahmed et al.) observed comparable rates of nausea and vomiting across ketorolac and control arms. These findings support the notion that, when appropriately selected and administered, ketorolac is generally safe in the perioperative setting of laparoscopic cholecystectomy. Nonetheless, it should be emphasized that these results primarily pertain to relatively healthy adult populations undergoing elective procedures. The generalizability of these findings to patients with significant comorbidities (e.g., chronic kidney disease, peptic ulcer disease, coagulopathies) remains uncertain and should be approached with clinical caution (29,30).

From a methodological perspective, the included studies were predominantly randomized controlled trials, enhancing the strength and internal validity of the synthesized evidence. The diverse geographic representation of studies, ranging from Asia and the Middle East to Europe and the Americas, also

contributes to the external validity of findings and supports the general applicability of ketorolac across different healthcare settings. However, some limitations persist. For example, the heterogeneity in comparator drugs ranging from placebo to various analgesics introduces variability in effect size estimation and limits direct head-to-head comparisons. Additionally, while most studies utilized VAS scores and morphine equivalents as outcome measures, there was some inconsistency in timing and frequency of assessments, which may affect pooled interpretability (31).

Another important limitation is the relatively short duration of follow-up in all included studies, which largely confined their evaluations to the first 24 hours postoperatively. Consequently, potential delayed adverse effects, such as renal function decline or delayed gastrointestinal bleeding, may have gone undetected. Furthermore, none of the studies included cost-effectiveness analyses, a critical consideration in determining the feasibility of widespread adoption, especially in resource-limited settings. Future trials would benefit from incorporating economic analyses, long-term follow-up, and evaluations of patient-centered outcomes such as satisfaction scores, functional recovery, and time to discharge (32,33).

Despite these limitations, the findings of this systematic review collectively support the incorporation of ketorolac into perioperative pain management strategies for laparoscopic cholecystectomy. The analgesic and opioid-sparing benefits, coupled with an acceptable safety profile, render ketorolac a strong candidate for inclusion in multimodal protocols. However, individualized patient selection remains crucial. While the risk of adverse effects was minimal in the included trials, clinicians must remain vigilant when prescribing NSAIDs, particularly in patients with existing risk factors for gastrointestinal, renal, or bleeding complications. Baseline patient characteristics, concomitant medications, and procedural variables should all be considered in determining the appropriateness of ketorolac use (34).

In conclusion, ketorolac emerges from this systematic review as a clinically effective and safe non-opioid analgesic option for patients undergoing laparoscopic cholecystectomy. Its ability to significantly reduce postoperative pain and limit opioid consumption without increasing the risk of major complications holds considerable promise for enhancing postoperative recovery. These findings align with broader surgical goals of minimizing opioid exposure, improving pain control, and supporting faster rehabilitation. As the surgical community continues to refine perioperative care pathways, the integration of agents like ketorolac into standardized analgesic regimens may represent a critical step forward. Nonetheless, ongoing high-quality research is needed to further delineate optimal dosing strategies, expand evidence in high-risk populations, and evaluate the long-term impact of ketorolac use in the context of laparoscopic surgery.

Conclusion

Based on the systematic review, ketorolac demonstrates effective postoperative analgesia following laparoscopic cholecystectomy, with significantly reduced pain scores and opioid consumption within the first 24 hours. Its analgesic benefits were consistent across diverse populations and study designs, without a significant increase in adverse events. These findings support ketorolac as a safe, opioid-sparing alternative for pain management in this surgical setting.

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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