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The efficacy and safety of ketorolac for postoperative pain management in lumbar spine surgery: a meta-analysis of randomized controlled trials

Jianbin Guan[1], Ningning Feng[3], Kaitan Yang[1,2], Haimiti Abudouaini[1*] and Peng Liu[1*]

Abstract

Background Ketorolac is widely utilized for postoperative pain management, including back pain after lumbar spinal surgery. Several trials have assessed the efficacy of Ketorolac alone and in combination with other analgesics such as bupivacaine, morphine, epinephrine, paracetamol, and pregabalin. However, the effects and safety profile of ketorolac in these contexts remain controversial.

Objective We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) to evaluate the efficacy and safety of Ketorolac administration, both as a monotherapy and in combination with other analgesics, for managing postoperative pain in adults undergoing lumbar spinal surgery.

Methods We searched PubMed, EMbase, Web of Science, EBSCO, CNKI, WanFang, VIP, and Cochrane library databases through July 2024 for randomized controlled trials (RCTs) assessing the analgesic efficacy of Ketorolac administration for postoperative pain of lumbar surgery. The meta-analysis was conducted following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statements. Data were extracted and analyzed using open-source meta-analysis software OpenMeta-Analyst, focusing on outcomes such as VAS pain scores, postoperative morphine requirements (PMR), length of hospital stay (LOS), and adverse effects, such as nausea, vomiting, pruritus, and constipation. The quality of evidence was assessed using the Jada scale.

Results Thirteen RCTs comprising a total of 938 patients were included. The methodological quality of the studies was high, with three studies scoring 5, six studies scoring 4, and four studies scoring 3 on the Jadad scale. Ketorolac significantly reduced pain compared to controls at 0–6 h, with a mean difference (MD) of − 1.42 (95% CI: − 2.03 to − 0.80; $P < 0.0001$), exceeding the Minimal Clinically Important Difference (MCID) of 1.2 to 2.0 points on the Visual Analog Scale (VAS), indicating clinically meaningful pain relief. During the 6–12-h period, the pain reduction was significant (MD = − 0.58; 95% CI: − 0.80 to − 0.35; $P < 0.0001$), though below the MCID threshold. In the 12–24-h period, Ketorolac continued to show significant pain reduction (MD = − 0.48; 95% CI: − 0.68 to − 0.28; $P < 0.0001$), but this reduction was also below the MCID. Heterogeneity was low in the 12–24-h period ($I^2 = 13\%$), indicating consistent results across studies. There was a significant reduction in PMR (SMD = − 1.83; 95% CI = − 3.42 to − 0.23; $P < 0.0001$),

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although with considerable heterogeneity among the studies ($I^2 = 93\%$, heterogeneity $P < 0.01$). Ketorolac administration also significantly reduced the LOS compared to controls (MD = −0.45 days; 95% CI = −0.74 to −0.16; $P = 0.0001$), though this reduction, which is less than a full day (0.45 days), may have limited clinical significance. The findings suggest that Ketorolac effectively reduces pain and opioid use postoperatively, supporting its role in multimodal analgesia for lumbar spinal surgery. The significant reduction in PMR indicates a beneficial opioid-sparing effect, crucial in the context of reducing opioid-related complications. The observed reduction in LOS, while statistically significant, may not translate into substantial clinical benefit due to its limited magnitude. No significant increase in common adverse effects was noted, indicating Ketorolac's safety profile.

Conclusion Ketorolac administration, either alone or in combination with other analgesics, effectively reduces postoperative pain and opioid consumption in adults following lumbar spinal surgery. And Ketorolac did not significantly increase the incidence of postoperative nausea and vomiting relative to other analgesics or placebos. While it also decreases LOS, the clinical relevance of this reduction is modest. However, the variability in study designs, dosages, and combination therapies contribute to significant heterogeneity in outcomes. Future research should focus on standardizing protocols and exploring optimal dosing strategies. Additionally, long-term safety and effectiveness studies are needed to better understand Ketorolac's role in postoperative pain management.

Keywords Ketorolac, Analgesia, Lumbar spine surgery, Opioid-sparing, Postoperative pai

Introduction

Lumbar degenerative diseases, such as disc herniation and spinal stenosis, often cause severe compression and damage to the lumbar nerve roots, leading to significant radicular pain [1]. When symptoms are severe, surgical interventions like fusion surgery and minimally invasive decompression are necessary to address the underlying issues. However, these surgeries disrupt physiological structures in the affected area, causing postoperative complications such as back pain and radicular pain [2, 3]. This pain can result from muscle dissection, muscle ischemia, and injury to spinal nerve branches during surgery [4]. Ineffective pain management can impede early postoperative mobility and rehabilitation, increasing the risk of complications like lower limb venous thrombosis and persistent spinal pain syndrome [5–7]. Current pain management strategies for postoperative care often rely heavily on opioids, which, despite their effectiveness, are associated with substantial adverse effects including nausea, vomiting, and the risk of long-term dependence [4, 8]. This opioid reliance poses a significant public health concern, especially amid the ongoing opioid crisis [9]. Research shows that using opioids for acute postoperative pain can inadvertently lead to long-term addiction [10]. Therefore, optimizing pain control while minimizing opioid use is crucial for improving postoperative outcomes.

Ketorolac, a non-steroidal anti-inflammatory drug (NSAID) known for its opioid-sparing properties, is widely used for postoperative pain management [11, 12]. Numerous randomized controlled trials (RCTs) have investigated the use of Ketorolac alone or combined with other analgesics like bupivacaine, morphine, and paracetamol for postoperative pain relief in lumbar surgery [13–17]. These studies report varying outcomes in pain reduction, opioid consumption, and adverse effects. Differences in study design, patient populations, and dosing regimens contribute to inconsistent findings, complicating the development of standardized pain management protocols. Current guidelines lack clear recommendations for incorporating Ketorolac into multimodal analgesic strategies for lumbar spinal surgery, underlining the need for a comprehensive synthesis of existing evidence.

This systematic review and meta-analysis aim to evaluate the efficacy and safety of Ketorolac for managing postoperative pain in adults undergoing lumbar spinal surgery. By comparing Ketorolac alone and in combination with other analgesics to standard postoperative pain management protocols, we seek to clarify its role and effectiveness. The analysis will focus on key outcomes such as pain scores, postoperative morphine requirements (PMR), length of hospital stay (LOS), and the incidence of adverse effects. Our findings will provide evidence-based insights to optimize postoperative pain management strategies and reduce opioid reliance, ultimately enhancing patient outcomes in lumbar spinal surgery.

Materials and methods

This systematic review and meta-analysis is performed based on the guidance of the Cochrane Handbook for Systematic Reviews of Interventions and reported accrediting to the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement [18, 19]. No ethical approval and patient consent are required because all analyses are based on previous published studies. Literature search, data extraction, data synthesis, and quality assessment were conducted by at least two

professional reviewers. The review protocols were registered on PROSPERO (International Prospective Register of Systematic Reviews, number CRD42023434438).

Literature search and selection criteria

We systematically search several databases including PubMed, EMbase, Web of science, EBSCO, CNKI, WanFang, VIP, Medline and the Cochrane library from inception to May 2023 with the following keywords combined with MeSH terms: "analgesia", "Ketorolac", "lumbar surgery", "spinal surgery","postoperative pain" and etc. The reference lists of retrieved studies and relevant reviews are also hand-searched and the process above is performed repeatedly in order to include additional eligible studies. The final search was performed in July 2024, ensuring that the review incorporates the most up-to-date available evidence at the time of the analysis.

The inclusion criteria are presented as follows: (1) study design must be a randomized controlled trial (RCT), (2) participants must be patients who underwent lumbar spinal surgery, and (3) intervention must include Ketorolac (either alone or in combination with other analgesics) compared to control interventions (other analgesics alone without Ketorolac or placebo, such as saline). In this analysis, Ketorolac was considered both as monotherapy and in combination with other analgesics. The decision to include these in a single analysis is based on the underlying mechanism of action of Ketorolac, which is primarily through its role as a nonsteroidal anti-inflammatory drug (NSAID). Whether used alone or in combination, Ketorolac's contribution to pain management remains consistent, targeting similar pathways of inflammation and pain relief. Including both monotherapy and combination therapy allows for a more comprehensive assessment of Ketorolac's efficacy and safety across various clinical contexts. Regarding the control groups, we combined studies using 'active' control treatments (e.g., other analgesics) with those using 'inactive' control treatments (e.g., saline) into a single control group. This decision was made to provide a broader comparison of Ketorolac's effectiveness and safety. While active controls may offer alternative analgesic effects, inactive controls serve as a baseline, allowing us to assess the full range of Ketorolac's efficacy compared to both no treatment and other therapeutic interventions. By combining these control types, we aim to capture the relative benefits and risks of Ketorolac across a diverse set of clinical scenarios.

Exclusion criteria were as follows: (1) studies with insufficient data to determine eligibility or to include in the meta-analysis (e.g., lacking essential outcome measures, unclear reporting of intervention details, or incomplete data on patient demographics), (2) animal studies, (3) studies with a sample size of fewer than 10 participants per group, (4) non-randomized studies, (5) papers were not published in English or Chinese, and (6) other topics that either focused on different patient populations (e.g., pediatric patients or those undergoing surgeries other than lumbar spine surgery) or evaluated different interventions (e.g., non-Ketorolac analgesics) and outcomes not relevant to this review.

The study selection process was conducted in a systematic and rigorous manner to ensure the inclusion of relevant studies. A total of 2 investigators (Jianbin Guan and Ningning Feng) independently screened the titles and abstracts of all identified articles. After this initial screening, the full texts of potentially eligible studies were retrieved and reviewed for inclusion by the same investigators. In cases where there were disagreements during the screening or full-text review process, the investigators discussed the discrepancies to reach a consensus. If consensus could not be reached, a third investigator (Haimiti Abudouaini) was consulted to resolve the conflict.

Data extraction and outcome measures

Baseline information is extracted from the original studies, and they include first author, country, sample size, age, sex, timing of administration, method of administration, type of surgery and duration of surgery in two groups. Data are extracted independently by two investigators (Jianbin Guan and Ningning Feng), and discrepancies are resolved by consensus. We have contacted the corresponding author (Haimiti Abudouaini) to obtain the data when necessary.

The primary outcome is VAS pain score after surgery 0 to 6 h, 6 to 12 h and 12 to 24 h, and postoperative morphine requirements (PMR). The VAS is commonly used to assess pain intensity, with patients marking their pain level on a scale from 0 (no pain) to 10 (worst imaginable pain). To interpret the clinical significance of changes in VAS scores, the Minimal Clinically Important Difference (MCID) is used as a threshold for determining whether a change in pain is meaningful to patients. According to previous studies, the MCID for the VAS in postoperative pain typically ranges from 1.2 to 2.0 points. A reduction of at least 1.2 points is considered the minimal threshold for patients to perceive a noticeable improvement in their pain. However, a change closer to 2.0 points is often regarded as more clinically significant, particularly in the context of acute postoperative pain management. This MCID value allows for better interpretation of the efficacy of interventions in terms of patient-centered outcomes. Secondary outcomes include length of hospital stay (days) and adverse effects, such as nausea, vomiting, pruritus, and constipation. The analysis focused on the most commonly reported adverse effects: nausea,

vomiting, pruritus, and constipation. These are the most prevalent and clinically relevant side effects associated with postoperative analgesic use, including ketorolac. They were consistently reported across the included trials and are crucial for patient management. While other adverse effects such as gastrointestinal complications, renal impairment, and cardiovascular events were occasionally noted, they were not reported consistently enough to allow for a comprehensive analysis.

Data for this review were primarily extracted from published sources. However, in certain cases, additional data not available in the public domain were provided directly by the original study authors. These data have been clearly marked in the corresponding tables and figures.

Quality assessment in individual studies

The methodological quality of each RCT is assessed by the Jadad Scale which consists of three evaluation elements: randomization (0–2 points), blinding (0–2 points), dropouts and withdrawals (0–1 points) [20]. One point would be allocated to each element if they have been conducted and mentioned appropriately in the original article. The score of Jadad Scale varies from 0 to 5 points. An article with Jadad score ≤ 2 is considered to be of low quality. The study is thought to be of high quality if Jadad score ≥ 3 [21, 22]. The decision to use the Jadad scale was based on several considerations. The Jadad scale is a widely recognized tool that is simple and efficient to apply, especially in cases where a large number of RCTs are included. Its straightforward scoring system allows for a quick assessment of key elements such as randomization, blinding, and withdrawal, which are crucial for evaluating study quality. And the Jadad scale focuses on critical components that are most likely to influence the internal validity of clinical trials, such as randomization and blinding. This makes it particularly useful for studies where these aspects are paramount. Moreover, the Jadad scale is frequently used in systematic reviews and meta-analyses of clinical trials. Using this scale allows for easier comparison with previous studies in the literature that may have also utilized the Jadad scale, ensuring consistency and comparability across reviews. Finally, given the types of studies included in this review, the Jadad scale was deemed to be a more appropriate tool for assessing the quality of evidence. The scale's focus on the methodological rigor of RCTs aligns well with the study designs evaluated in this meta-analysis. While the Cochrane Risk of Bias tool provides a more detailed and comprehensive assessment, the Jadad scale was selected to balance the need for thoroughness with practical considerations, such as ease of use and alignment with the study's objectives. This choice ensures that the quality of the included studies is assessed in a manner that is both rigorous and feasible given the scope of the review.

Statistical analysis, sensitivity analysis and publication bias

We assess mean difference (MD) and standard mean difference (SMD) with 95% confidence intervals (CI) for continuous outcomes, such as Visual Analog Scale (VAS) scores, length of stay, and postoperative morphine requirements. For continuous outcomes measured in different units or scales, we use SMD to ensure comparability across studies. For dichotomous outcomes, such as adverse effects, we calculate the risk ratio (RR) with 95% CI.

The choice of meta-analysis model was pre-specified based on the anticipated clinical homogeneity or heterogeneity of the included studies. Given the expected variability among studies in terms of design, population, interventions, and other factors, a random-effects model was primarily chosen to account for this inherent heterogeneity. A fixed-effect (common-effect) model was considered in cases where clinical homogeneity was anticipated across studies.

Statistical heterogeneity among the included studies was described using the Q-test and the I^2 statistic, with I^2 values of 25%, 50%, and 75% considered to indicate low, moderate, and high heterogeneity, respectively [23, 24]. In cases of significant heterogeneity, potential sources were explored through subgroup analyses or sensitivity analyses, including omitting one study at a time to assess its influence on the overall estimate. In this study, subgroup analyses were conducted based on the timing of administration and dosage of the medication to investigate the sources of heterogeneity. The timing of administration (preoperative, intraoperative, or postoperative) may influence the effectiveness of Ketorolac in managing postoperative pain and its impact on the length of hospital stay. Additionally, variations in dosage across studies could affect the drug's efficacy and side effect profile. By examining these factors, we aim to identify how different administration conditions and dosage levels contribute to the observed heterogeneity, thereby providing a clearer understanding of Ketorolac's effects in various clinical contexts.

Publication bias was assessed using Begg's test and Egger's test, and a funnel plot was constructed. However, publication bias was not evaluated for outcomes with fewer than 10 studies, consistent with standard practices due to the limited power of these tests in small samples. Statistical significance was defined as $P < 0.05$. All analyses were conducted using the open-source meta-analysis software OpenMeta-Analyst, which utilizes R as the underlying statistical engine [25].

Results

Search results

The electronic search identified 1312 studies from databases and conference abstracts. Despite our thorough search, no additional records were identified through the manual reference search. This might be due to the comprehensive nature of the initial database search, which captured the relevant studies available at the time. Additionally, the field of interest might have a limited number of eligible studies, further reducing the likelihood of finding unpublished or unindexed records. After duplicate removal, 625 papers were screened. Among them, 607 papers were excluded as not English or Chinese language, not RCTs, preclinical papers, or different topics. At the end of the selection process, thirteen studies fulfilled the inclusion criteria and were included in the meta-analysis [14, 26–37]. The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow chart summarizing the process of selection is shown in Fig. 1.

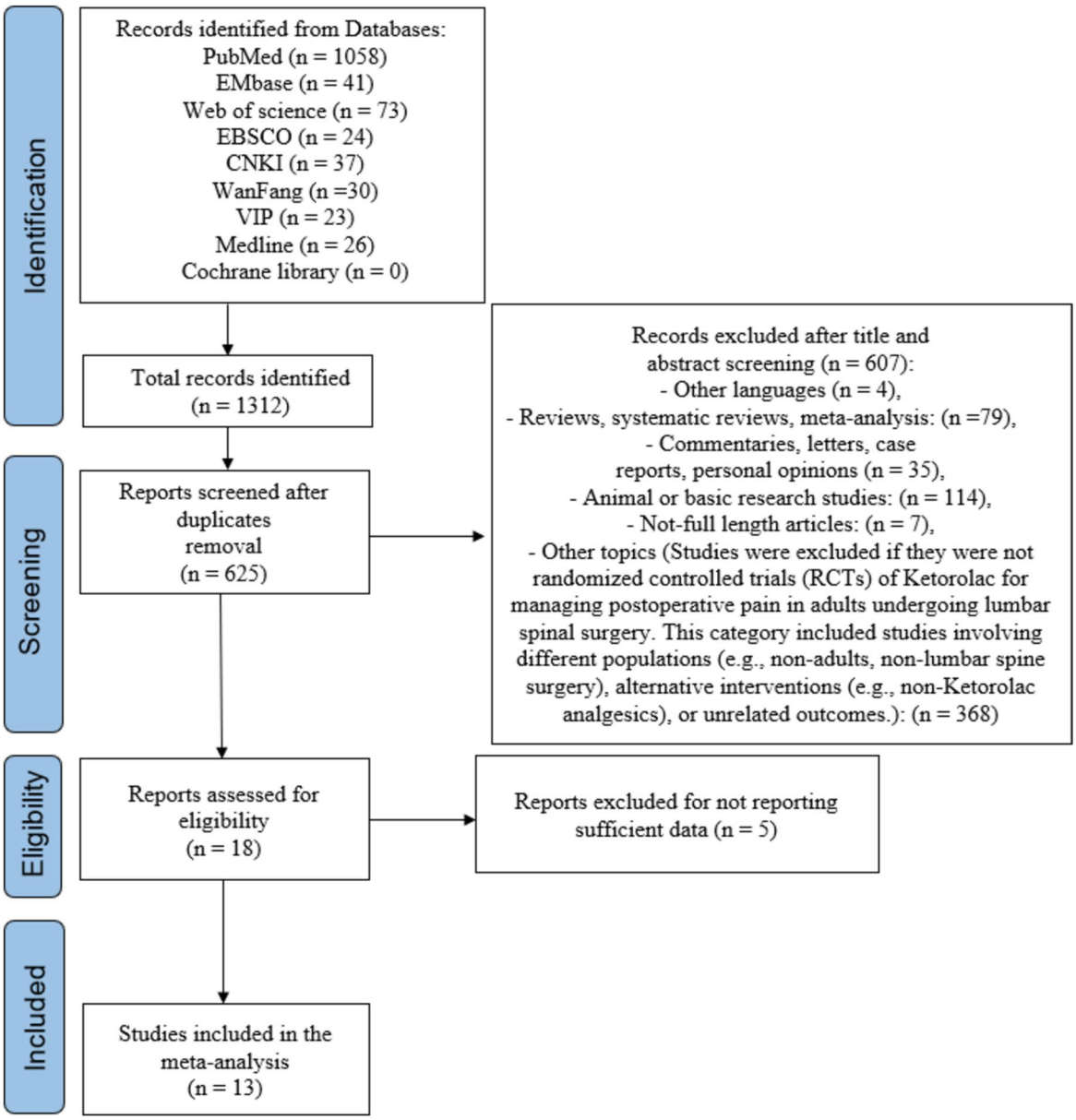

Fig. 1 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow chart of the selection process

Study characteristics and quality assessment

The baseline characteristics of thirteen included RCTs are shown in Table 1. These studies are published between 1997 and 2023, and the total sample size is 938. Among the included RCTs, Ketorolac is administered at the dose of 15 mg [26, 27, 30], 20 mg [32], 30 mg [14, 27–31, 33–37]. The routes of administration include intravenous injection [14, 26, 27, 29, 33–37], intramuscular injection [28, 30], intraoperative local infiltration [31], and oral administration [32]. Its adjunctive drugs include bupivacaine [31], morphine [31], epinephrine [31], paracetamol [31] and pregabalin [31]. The timing of administration includes preoperative [29, 32, 36], postoperative [14, 26–28, 33, 34, 37], and intraoperative periods [31, 35].

Among the thirteen included RCTs, seven studies report pain scores at 0–6 h [14, 27, 29–31, 36, 37], eight studies report pain scores at 6–12 h [27, 29, 31, 36, 37], six studies report length of hospital stay [26, 27, 31–34], ten studies report postoperative morphine requirements [14, 26–33, 36], eight studies report nausea [28, 35–37], six studies report vomiting [29, 30, 32, 35–37], four studies report pruritus [28–30, 35], and three studies report constipation [28, 29, 32]. Jadad scores of the four included studies vary from 3 to 5, and all thirteen studies have high-quality based on the quality assessment.

Back pain scores (visual analog scale)

Due to differences in race, administration methods, and timing of administration across the studies, the random-effect model was used for the analysis of postoperative pain scores. In this systematic review, all studies used the same scale for the primary outcome, such as the Visual Analog Scale (VAS) for pain, making the use of mean difference (MD) generally more intuitive and meaningful.

Back pain scores at 0–6 h after surgery

The results indicate that, compared to the control group, Ketorolac is associated with significantly lower postoperative pain scores within the first 0–6 h following lumbar spinal surgery. This is demonstrated by a mean difference (MD) of -1.42 on the pain scale, with a 95% confidence interval (CI) ranging from −2.03 to −0.80, indicating a statistically significant reduction in pain ($P<0.0001$). The studies show moderate heterogeneity with an I^2 value of 65% ($P<0.01$, Fig. 2), suggesting some variability in the effect sizes across the included studies. The reduction of −1.42 points on the VAS represents a notable improvement in pain relief. To provide context, the MCID for VAS pain scores is typically around 1.2 to 2.0 points. The observed reduction exceeds the lower end of this range, suggesting that the pain relief provided by Ketorolac is not only statistically significant but also clinically meaningful. However, it is important to note that there is moderate heterogeneity among the studies, with an I^2 value of 65% ($P<0.01$), indicating some variability in the effect sizes across the included studies.

Back pain scores at 6–12 h after surgery

The results find that compared to control group for postoperative pain of lumbar spinal surgery, Ketorolac is associated with significantly lower pain scores at 6–12 h (MD = −0.58; 95% CI = −0.80 to −0.35; $P<0.0001$) with low heterogeneity among the studies ($I^2=44\%$, Fig. 3). The reduction of −0.58 points on the VAS represents a moderate decrease in pain intensity. To provide context, the MCID for VAS pain scores is typically around 1.2 to 2.0 points. While the observed reduction of −0.58 points is statistically significant and indicates that Ketorolac provides effective pain relief compared to the control, it is below the threshold generally considered to be the minimal clinically important difference.

Back pain scores at 12-24 h after surgery

The results find that compared to control group for postoperative pain of lumbar spinal surgery, Ketorolac is associated with significantly lower pain scores at 12–24 h (MD = −0.48; 95% CI = −0.68 to −0.28; $P<0.0001$) with low heterogeneity among the studies ($I^2=13\%$, Fig. 4). The observed reduction of −0.48 points on the VAS indicates a moderate decrease in pain intensity. To contextualize this, the MCID for VAS pain scores is generally considered to be around 1.2 to 2.0 points. While the reduction of −0.48 points is statistically significant and demonstrates that Ketorolac provides effective pain relief compared to the control, it falls short of the MCID threshold.

Postoperative morphine requirements (PRM)

The analysis of PMR was conducted using a random-effects model. The results indicate that Ketorolac is associated with a significantly lower PMR compared to the control group after surgery (SMD = −1.83; 95% CI = −3.42 to −0.23; $P<0.0001$), though substantial heterogeneity was observed among the studies ($I^2=93\%$, Fig. 5).

There is significant heterogeneity in the PRM analysis. Therefore, we performed a sensitivity analysis to evaluate whether individual studies impacted the overall results. We found that when any one study was removed, the combined SMDs of the remaining studies all remained within the 95% CI of the combined SMDs from the meta-analysis (Fig. 6). The sensitivity analysis, which removed each study in turn, concluded that the pooled result was not significantly influenced by removing the extreme result from the Le Roux study, which is

Table 1 Baseline Characteristics of Thirteen Included RCTs

Authors	Year	Country	I/C*	Age (Mean ±SD or Mean) *	Male%*	Intervention	Control (Placebo)	Timming of administration	Method of administration	Type of surgery	Duration of surgery (min) *	J da scores
Claus CF et al [26]	2022	America	119/127	61.0±10.8/ 61.4±11.3	46.2/44.1	Ketorolac 15mg/6hours	Saline	post-operation	Intravenous	MIS TLIF	139.7±54.3/ 146.7±52.6	5
Cassinelli EH et al [27]	2008	America	13/12	62.3±10.0/ 65.9±10.1	N/A	Ketorolac 30mg/6hours	Saline	post-operation	Intravenous	MLD	179.7±31.5/ 179.4± 27.7	4
Le Roux PD et al [28]	1999	America	27/26	52.4 ± 14.3/ 48.7 ± 13.7	100/100	Ketorolac 30mg/6hours	Saline	post-operation	Intramuscular	LDe	N/A	3
Siribumrung-wong K et al [29]	2015	Thailand	32/32	58.2±9.5/ 55.6±14	28.1/40.6	Ketorolac 30mg	Saline	Pre-operation	Intravenous	LIF	157 ± 33.3/ 165.7± 46.7	4
Duttchen KM et al [30]	2017	Canada	25/25	54.0/53.0	68/68	Ketorolac 30mg	Saline	Post-operation	Intramuscular	LD	N/A	4
Singhatanadgige W et al [31]	2020	Thailand	40/40	66± 8/ 66±9	22.5/32.5	0.5% bupiv-acaine 92.5 mg Ketorolac30 mg morphine 5 mg epinephrine 0.5 mg	0.5% bupiv-acaine 100 mg morphine 5 mg and epinephrine 0.5 mg	Intraoperation	Local filtration	LIF	173±33/ 176±32	5
Raja SD et al [32]	2019	India	47/50	49.7±12.33/ 51.6±9.46	21.3/26	paracetamol 1gram Ketorola20mg pregabalin75mg	paracetamol 1gram and pregaba-lin75mg	Pre-operation	Oral	LIF	112.98±21.59/ 106.9±17.78	5
Ramirez-Gonza-lez M et al [33]	2023	America	43/45	59±11.51/ 54.1±15.1	33/43	Ketorolac 30mg/6hours	Saline	Post-operation	Intravenous	LIF	N/A	4
Turner DM et al [34]	1995	America	25/23	38.6/ 39.5	71.4/ 71.9	Ketorolac 30mg/6hours	Saline	Post-operation	Intravenous	Lumbar laminectomy	N/A	3
Mei YL et al [35]	2022	China	30/30	54.9±13.8/ 55.6±11.2	50/ 53.3	Ketorolac 30mg/6hours	None	Intraoperation	Intravenous	LIF	146.2±16.5/ 152.4±20.3	4
Zhao ZH et al [36] A	2016	China	12/12	51.02±4.26	N/A	Ketorolac 30mg	Saline	Pre-operation	Intravenous	LIF	N/A	3
Zhao ZH et al [37] B	2016	China	30/33	55.63±14.85/ 54.33±12.36	66.7/ 51.5	Ketorolac 30mg/24hours	Saline	Post-operation	Intravenous	LIF	154.47±35.9/ 146.83±38.65	3
Reuben SS et al [14]	1997	America	20/20	45±10/ 41±9	N/A	Ketorolac 30mg/6hours	Saline	Post-operation	Intravenous	LIF	266±45/ 277±44	4

LD Lumbar Decompression, *MIS TLIF* Minimally Invasive Transforaminal Lumbar Interbody Fusion, *LDe* Lumbar Discectomy, *LIF* Lumbar Interbody Fusion, *N/A* Not Applicable

*Data provided directly by the original study authors and not available in the public domain

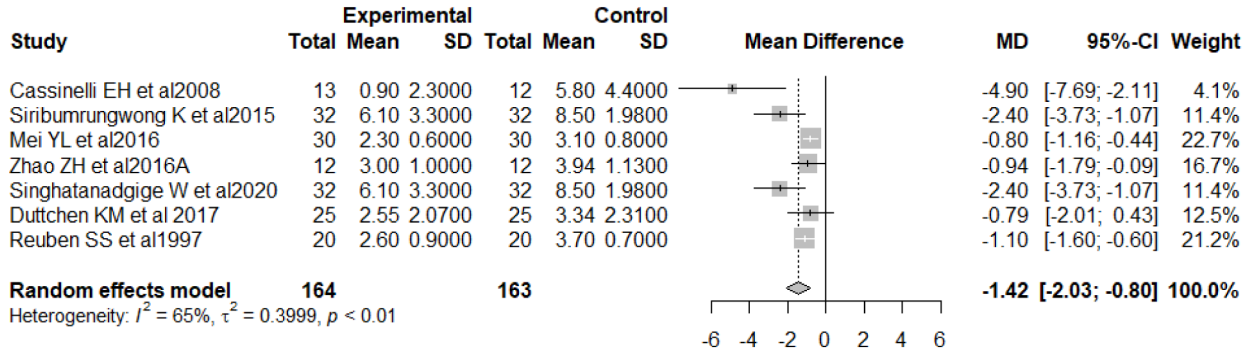

Fig. 2 Forest plot for the meta-analysis of pain scores at 0–6 h

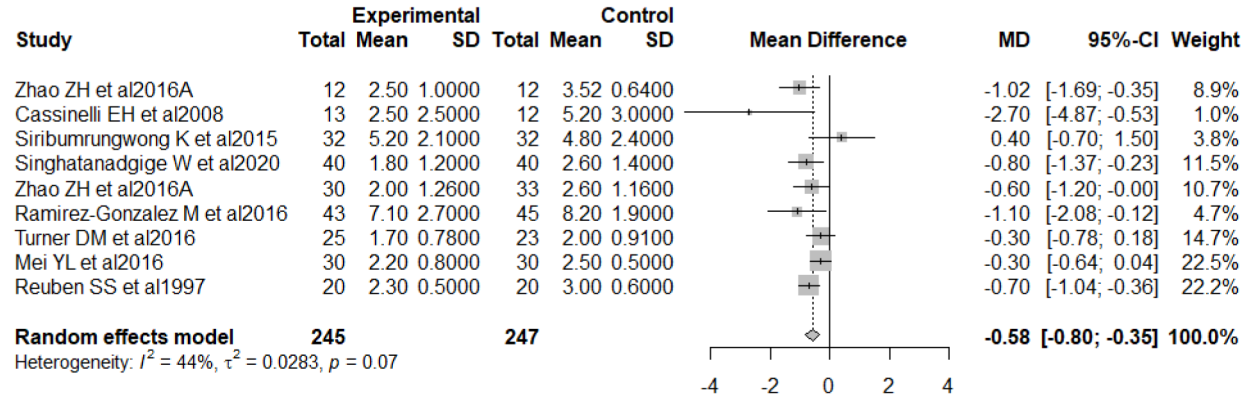

Fig. 3 Forest plot for the meta-analysis of pain scores at 6–12 h

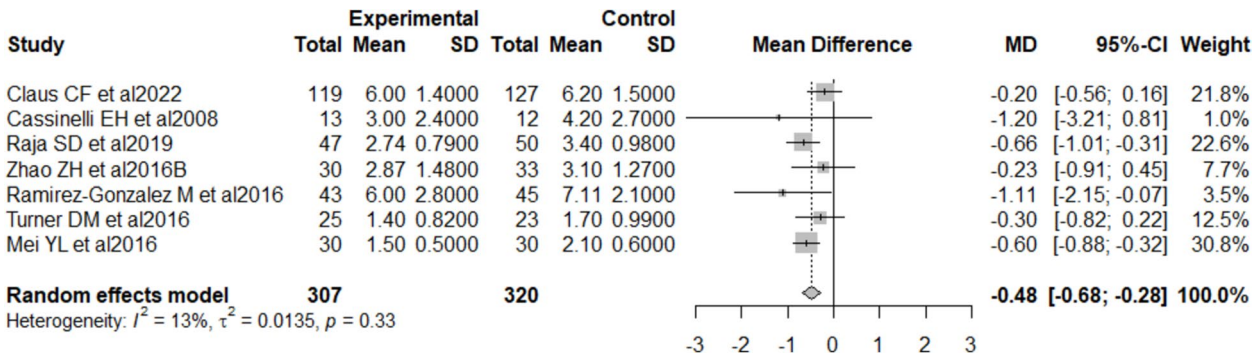

Fig. 4 Forest plot for the meta-analysis of pain scores at 12-24 h

clearly an outlier. Figure 6 shows that the pooled effect size was significantly reduced in both magnitude and imprecision. Therefore, excluding the Le Roux PD study is justified, as it increases the accuracy of this analysis. While very large SMD values between -1 and -2 may be plausible in small studies, extreme SMD values ranging from -9 to -10, as observed in certain studies, appear too extreme to be accurate. These outliers raised

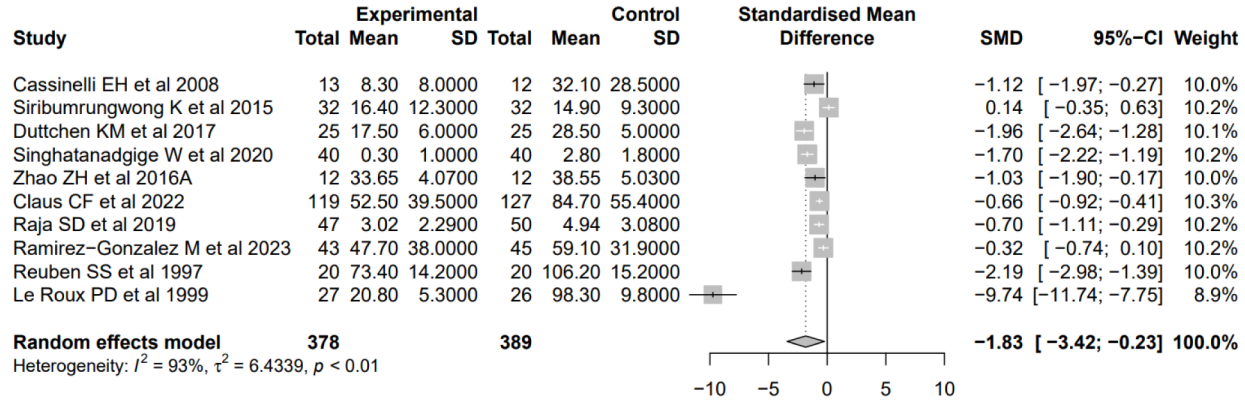

Fig. 5 Forest plot for the meta-analysis of postoperative morphine requirements

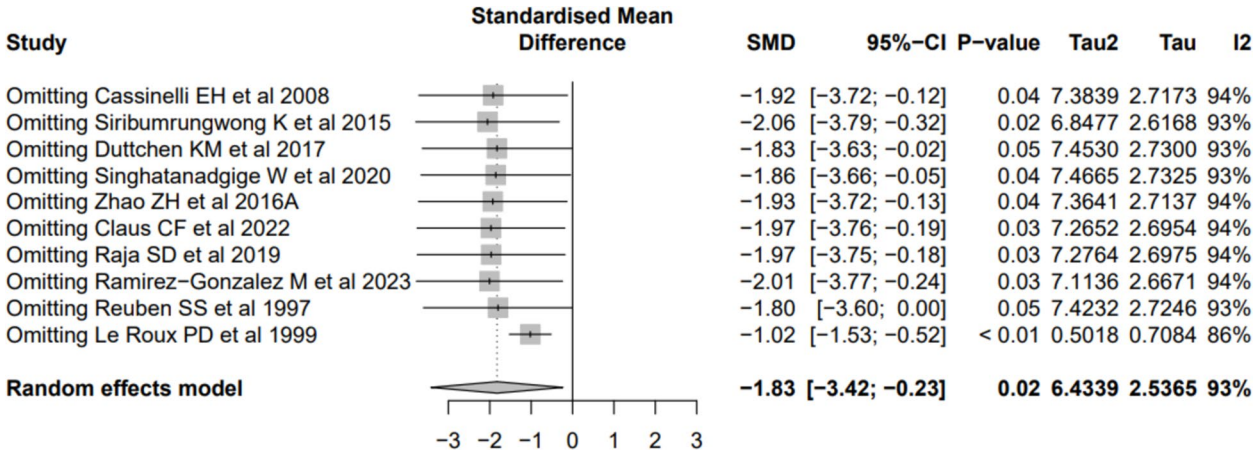

Fig. 6 Sensitivity analysis of PMR

concerns about potential data extraction errors, particularly in the Le Roux and Reuben SS studies. After excluding these two studies, the results became more consistent and reasonable, with the pooled effect size reduced to a more moderate level (SMD = −0.89; 95% CI = −1.37 to −0.40, Fig. 7).

Stratified by different dosage, subgroup analyses found that 30 mg (SMD = −0.98; 95% CI = −1.65 to −0.31; P < 0.0001, Fig. 8), 15 mg and 20 mg could significantly reduce the PMR after lumbar surgery. Stratified by different timing of administration, subgroup analyses found that postoperative administration (SMD = −0.97; 95% CI = −1.66 to 0.28; P < 0.0001, Fig. 9), preoperative administration (SMD = −0.48; 95% CI = −1.15 to 0.19; P < 0.0001, Fig. 9) and intraoperative administration could significantly reduce the PMR after lumbar surgery.

Publication bias

Through the funnel plot, we found that the included studies basically showed a symmetrical distribution. (Fig. 10) Quantitative analysis shows that after the combined SMD of PMR: Pr>|z| indexes are 0.15 and -1.43 (Begg test, Fig. 11), Pr>|t| indexes are 0.026 and -2.72 (Egger test, Fig. 12), therefore there was significant publication bias after the pooling of SMD for PMR.

Length of hospital stay (LOS)

The analysis of LOS was conducted using a random-effect model. The results indicate that, compared to the control group, Ketorolac is significantly associated with a shorter LOS following lumbar spinal surgery (MD = −0.45 days; 95% CI = −0.74 to −0.16; P = 0.0001), with no heterogeneity observed among the studies (I^2 = 0%, Fig. 13). This suggests that Ketorolac can reduce the average hospital stay by 0.45 days.

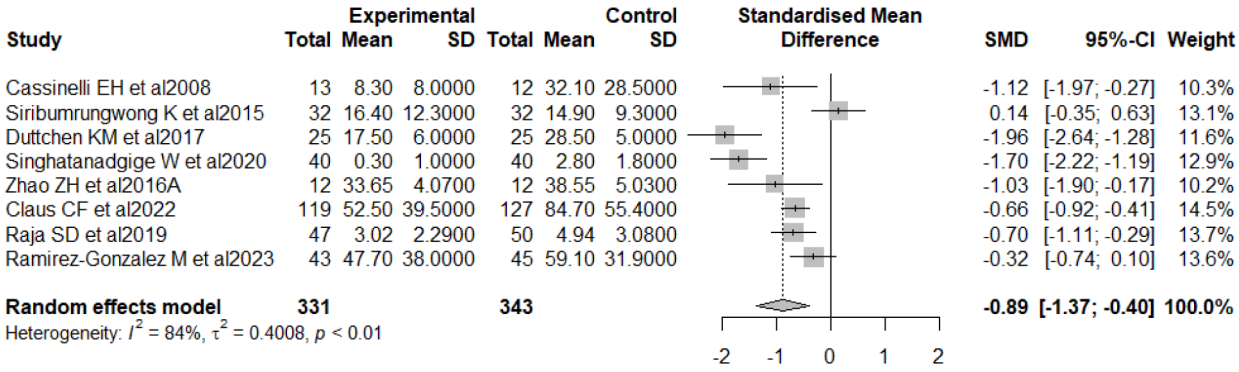

Fig. 7 Forest plot for the meta-analysis of postoperative morphine requirements excluding the Le Roux PD and Reuben SS studies

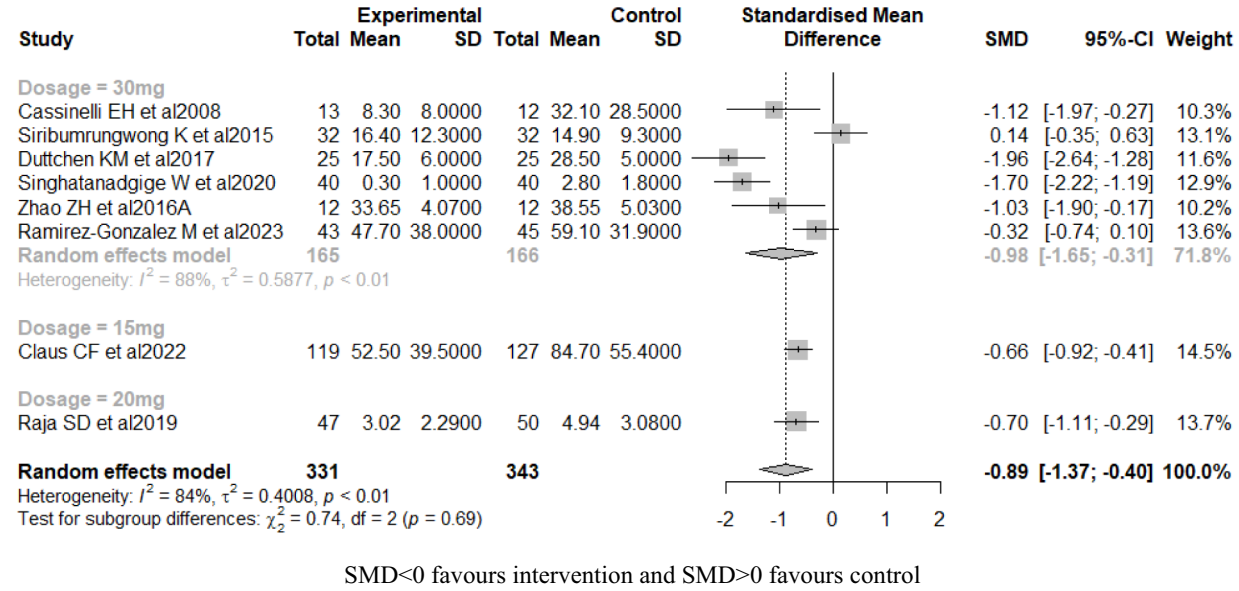

Fig. 8 Subgroup meta-analysis of postoperative morphine requirements

Adverse effect

In comparison with control group for postoperative pain of lumbar spinal surgery, demonstrates no impact on nausea (RR = 0.69; 95% CI = 0.33 to 1.45; P = 0.33, random-effect model, Fig. 14), vomiting (RR = 0.85; 95% CI = 0.55 to 1.30; P = 0.45, random-effect model, Fig. 15), pruritus (RR = 1.16; 95% CI = 0.33 to 4.13; P = 0.82, random-effect model, Fig. 16), or constipation (RR = 1.13; 95% CI = 0.61 to 2.10; P = 0.71, random-effect model, Fig. 17).

Discussion

In this study, we evaluated whether Ketorolac alone or in combination with other analgesics provides superior pain relief following lumbar spine surgery. By analyzing data from 13 randomized controlled trials involving 932 participants, we found that both Ketorolac and Ketorolac combinations effectively reduced pain scores 12 h postoperatively. Furthermore, regardless of dosage or timing, Ketorolac significantly decreased the need for postoperative morphine. Additionally, patients receiving Ketorolac

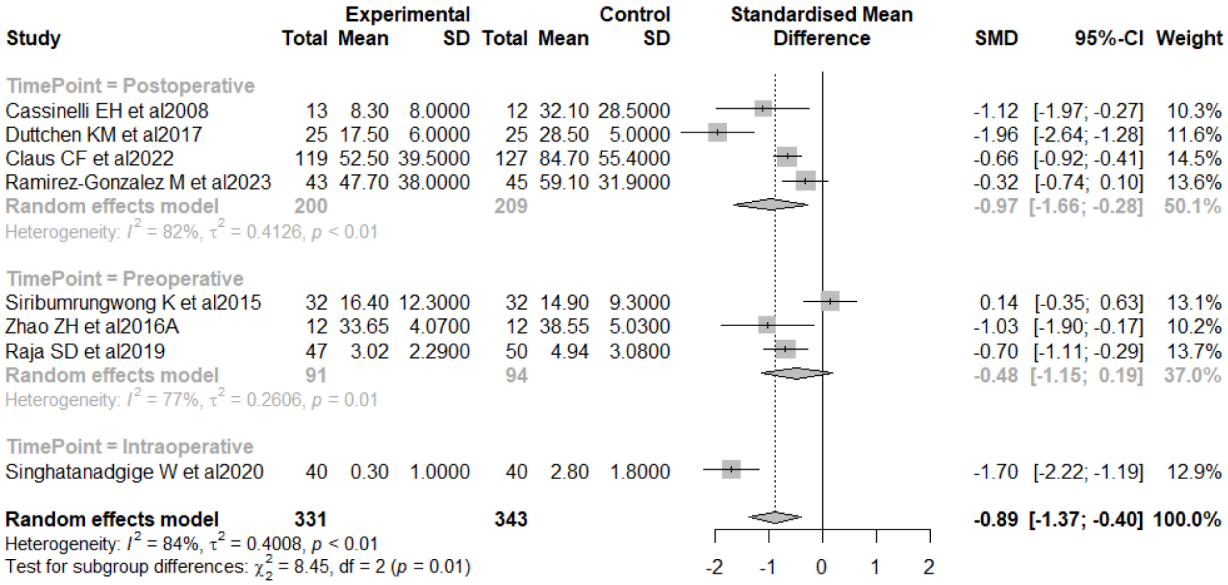

Fig. 9 Subgroup meta-analysis of postoperative morphine requirements

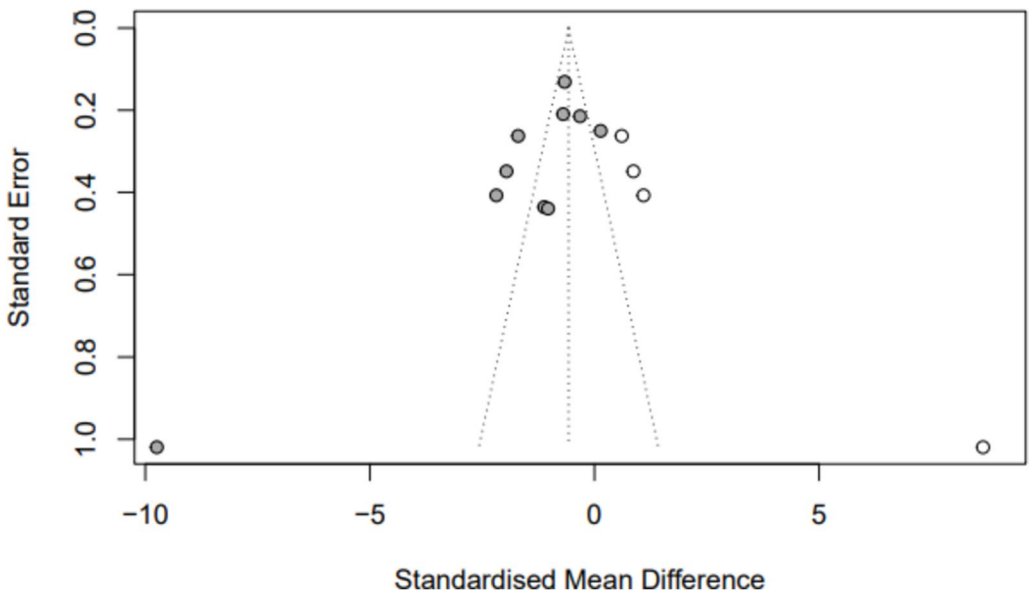

Fig. 10 Funnel plot of PMR

experienced faster discharge times without an increased risk of adverse effects.

Ketorolac has been used in patients with mild-to-severe pain following major surgical procedures in the different fields of surgery [38–41]. DeAndrade et al. revealed that intramuscular Ketorolac had a similar analgesic effect and reduced side effects when compared to conventional intramuscular meperidine dosages, and had a superior efficacy when compared to placebo in the immediate postoperative period after orthopedic surgery [38]. Our meta-analysis indicates that Ketorolac is an effective analgesic for managing postoperative pain within the first 12 h following lumbar spine surgery. Specifically, Ketorolac significantly reduced pain during

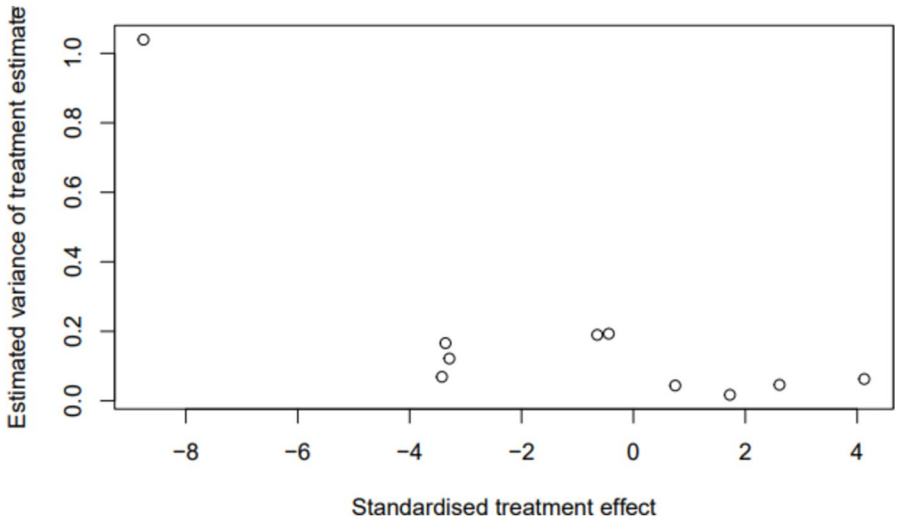

Fig. 11 Begg rank correlation of publication bias for Ketorolac administration and PMR

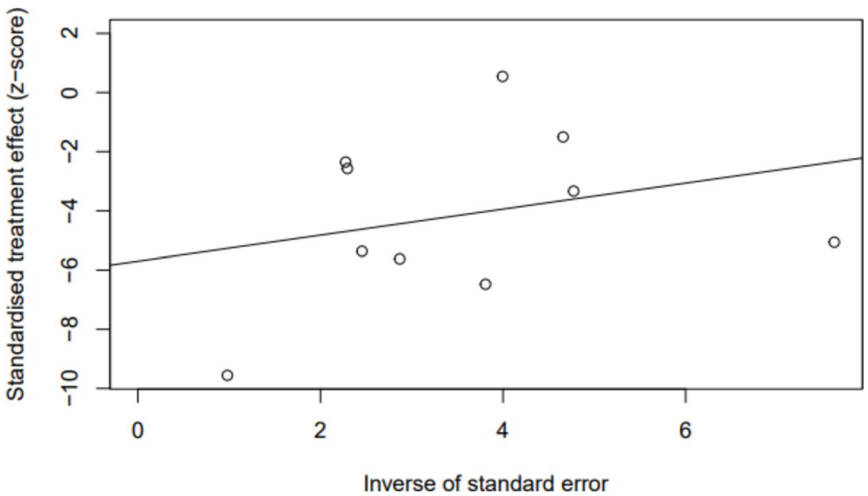

Fig. 12 Egger-weighted regression plot of publication bias for Ketorolac and PMR

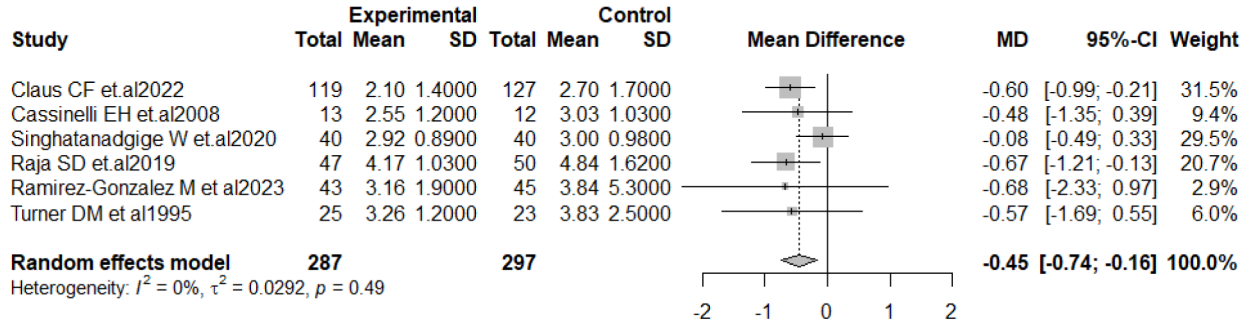

Fig. 13 Forest plot for the meta-analysis of LOS

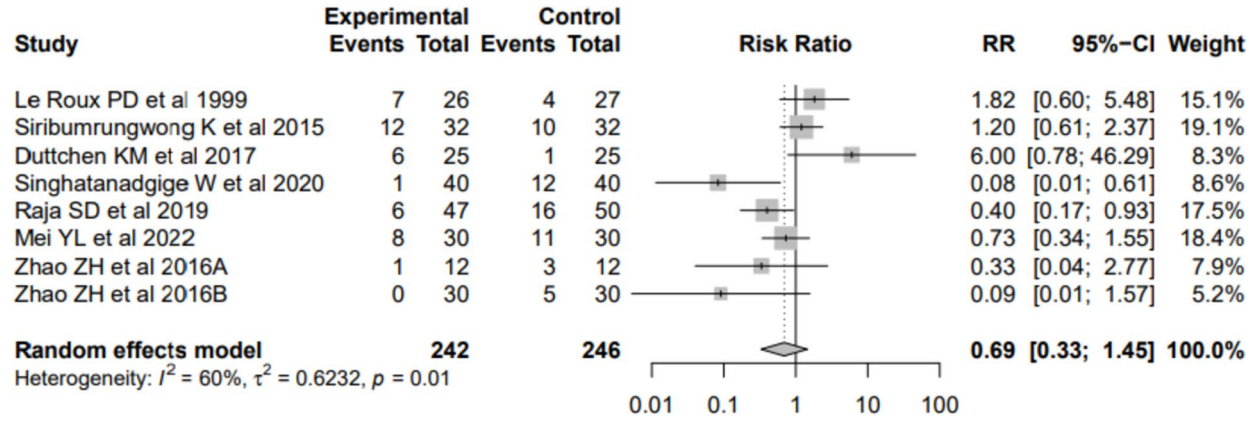

Fig. 14 Forest plot for the meta-analysis of nausea

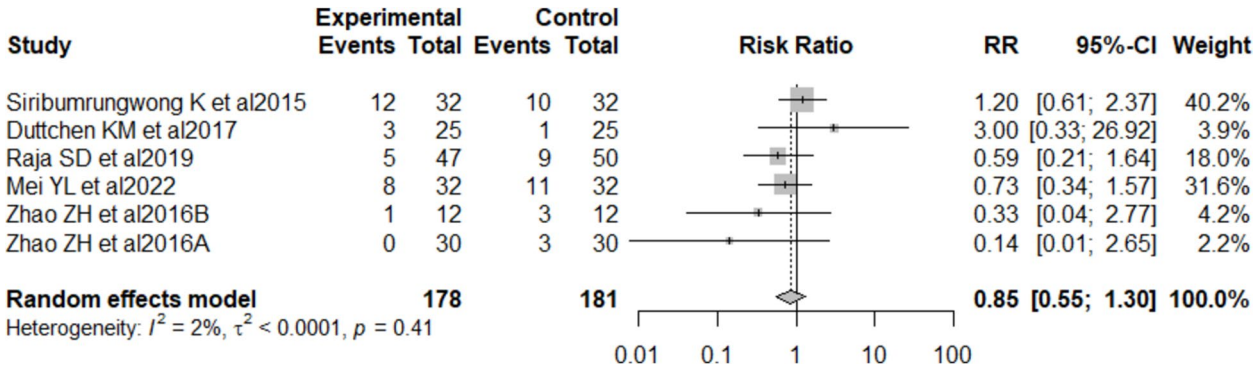

Fig. 15 Forest plot for the meta-analysis of vomiting

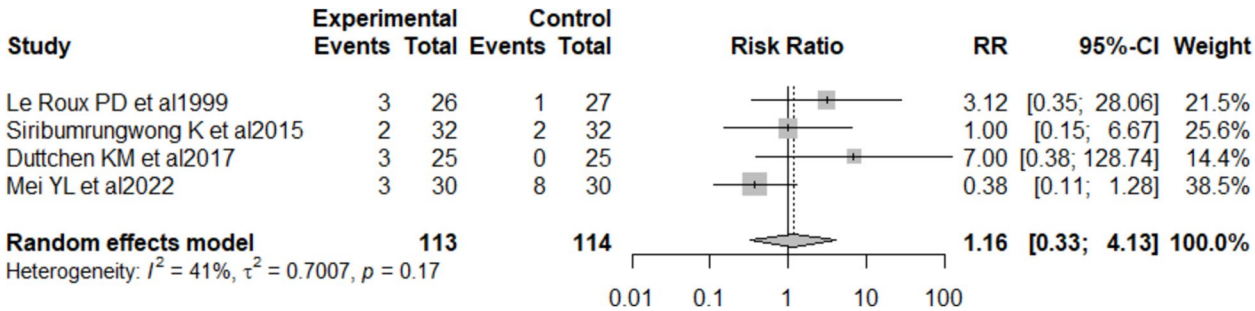

Fig. 16 Forest plot for the meta-analysis of pruritus

the 0–6-h period, with a MD of − 1.42 (95% CI: − 2.03 to − 0.80; $P < 0.0001$), which is above the MCID of 1.2 to 2.0 points on the VAS. This suggests that the observed reduction in pain is not only statistically significant but also clinically meaningful, providing substantial relief compared to control groups. Similarly, during the 6–12-h period, Ketorolac continued to show significant pain reduction, with an MD of − 0.58 (95% CI: − 0.80 to − 0.35; $P < 0.0001$). However, this reduction is below the MCID threshold, indicating that while the pain relief is statistically significant, it may not be perceived as clinically substantial by all patients. In the 12–24-h period, Ketorolac maintained significant pain relief compared to controls, with an MD of − 0.48 (95% CI: − 0.68 to − 0.28; $P < 0.0001$). Although this reduction is statistically significant, it is also below the MCID, suggesting that while Ketorolac continues to be effective, the clinical significance of the pain reduction diminishes over time. The

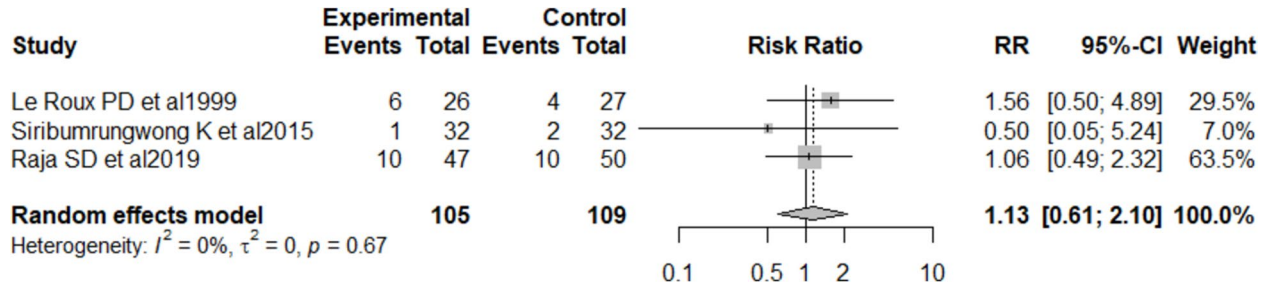

Fig. 17 Forest plot for the meta-analysis of constipation

low heterogeneity during this period ($I^2 = 13\%$) supports the consistency of these findings across studies. Overall, our findings suggest that Ketorolac is most effective in providing clinically meaningful pain relief within the first 6 h after lumbar spine surgery. The analgesic benefits continue to be significant up to 24 h, though they fall below the MCID in later periods. Given the limitations in the available data, especially beyond the first 24 h, further high-quality randomized controlled trials are needed to explore the long-term analgesic effects of Ketorolac and to address factors contributing to variability in pain outcomes.

PMR in the perioperative period remains a significant challenge for patients undergoing lumbar spine surgery [42]. Effective pain management is crucial, yet reliance on opioids like morphine can lead to adverse effects and dependence [42, 43]. This issue underscores the need for alternative analgesic strategies. In our meta-analysis, patients who received scheduled doses of Ketorolac during the perioperative period exhibited a significantly lower morphine requirement at all assessed time points compared to the control group. Our analysis demonstrated that Ketorolac reduced postoperative PMR with a SMD of −1.83 (95% CI: −3.42 to −0.23, $P < 0.0001$). However, substantial heterogeneity was observed ($I^2 = 93\%$, $P < 0.01$), raising concerns about variability across studies. To address this, we conducted sensitivity and subgroup analyses. The sensitivity analysis showed that the exclusion of certain outlier studies, particularly those by Le Roux and Reuben, greatly reduced heterogeneity and improved the precision of the pooled effect size (SMD = −0.89; 95% CI = −1.37 to −0.40). This justified the exclusion of these outliers, leading to more reliable results. Despite these adjustments, subgroup analyses stratified by dose and timing of administration did not substantially reduce the heterogeneity, though they consistently demonstrated that Ketorolac reduced PMR after lumbar surgery across different doses and administration routes. Specifically, significant reductions were noted for both 30 mg and lower doses, as well as for postoperative, preoperative, and intraoperative administration. This indicates that Ketorolac's opioid-sparing effect is robust across various perioperative regimens. While the heterogeneity remains a limitation, the consistent reduction in PMR across multiple analyses suggests that Ketorolac is a viable option for enhancing postoperative pain management in lumbar spine surgery. Its potential to reduce opioid consumption and related risks makes it a promising alternative in multimodal analgesia strategies.

LOS has significant impact on healthcare costs [44, 45]. Opioid use after lumbar fusion is closely linked to prolonged LOS, contributing to higher healthcare costs and increased incidence of surgical complications [46, 47]. The relationship between opioid dependence and LOS, however, remains debated, with available data showing inconsistent conclusions [48, 49]. For instance, while Walid et al. [48] reported no correlation between opioid requirements and LOS in 150 spinal surgery patients, Tank A et al. [47] found that opioid dependence was associated with a 2.11-fold increase in the likelihood of prolonged LOS. Given the complications associated with opioid use, NSAIDs are increasingly considered a viable alternative to perioperative opioid analgesics. However, it remains uncertain whether the perioperative use of NSAIDs, specifically in lumbar spine surgery, can effectively reduce LOS. In our study, we analyzed six studies that evaluated the use of Ketorolac, either alone or in combination, during the perioperative period. The results indicate that Ketorolac is significantly associated with a shorter LOS (0.45 days) following lumbar spinal surgery. This includes one study focused on intraoperative use, [31] one on preoperative use [32], and four on postoperative use [26, 27, 33, 34]. The reduction in LOS may be attributed to the decrease in PMR facilitated by Ketorolac. However, this reduction, which is less than a full day (0.45 days), may not lead to marked clinical improvement from a patient recovery perspective. The implications for hospital resource optimization and patient recovery require further exploration in future studies, considering longer follow-ups and

comprehensive assessments of patient outcomes. Furthermore, while the direct drug costs for patients receiving Ketorolac were higher compared to those for other analgesics, our analysis revealed that its use is associated with significant cost-saving benefits in the broader context of postoperative care. Ketorolac's efficacy in reducing PMR and its contribution to a shorter mean LOS in the hospital ultimately led to lower mean total hospital costs [34]. Specifically, by effectively managing pain and reducing the need for additional opioid analgesics, Ketorolac not only minimizes the costs associated with opioid-related side effects but also enhances recovery efficiency, leading to quicker patient discharge and reduced overall hospital resource utilization. Of course, these findings highlight the potential economic benefits of Ketorolac in postoperative settings; however, further RCTs are necessary to provide more granular insights and validate these observations. Future studies should aim to quantify the precise cost savings attributable to Ketorolac use, factoring in various surgical procedures and patient demographics to build a robust economic model. This specific analysis would help substantiate the role of Ketorolac in not only improving clinical outcomes but also in contributing to more cost-effective healthcare delivery.

Based on the results of our meta-analysis, we observed that Ketorolac, irrespective of the dose, significantly reduces perioperative morphine requirements (PMR) in patients undergoing lumbar spine surgery. However, the specific balance of efficacy and safety between different doses was not directly evaluated in our primary analysis, which focused on overall pain relief and opioid reduction rather than dose-dependent outcomes. While our findings suggest that Ketorolac is effective for postoperative pain management, recommendations for specific doses (such as 30 mg, 20 mg, or 15 mg) should be considered with caution and are primarily drawn from the broader body of literature. For instance, DeAndrade et al. [38] demonstrated that 30 mg of intramuscular Ketorolac provides analgesic effects comparable to intramuscular meperidine, but with fewer side effects. Similarly, evidence from other studies supports the efficacy of lower doses in patients with specific risk factors [50]. Our recommendations, therefore, should be interpreted in light of these external findings rather than exclusively from our meta-analysis results. Further research is necessary to evaluate the efficacy and safety of varying doses of Ketorolac within the context of lumbar spine surgery specifically.

Adverse effects are crucial evaluation indicators for analgesic drugs, playing a significant role in determining their overall suitability and safety for postoperative pain management [51, 52]. The analysis showed that Ketorolac did not significantly increase the incidence of postoperative nausea and vomiting relative to other analgesics or placebos. However, due to the substantial heterogeneity observed in the data related to nausea, we conducted a subgroup analysis to identify potential sources of variation. Despite this effort, the limited amount of included literature constrains the robustness of these findings. Therefore, additional research is required to validate the current results on nausea and to better understand the underlying factors contributing to the observed heterogeneity. Similar results were observed for pruritus and constipation, with Ketorolac not contributing to a higher incidence of these conditions compared to traditional analgesics or placebos. This suggests that Ketorolac is comparable to or even preferable over opioids in terms of minimizing these specific side effects, which are commonly associated with opioid use. Notably, Ketorolac may predispose patients to acute kidney injury, especially when used in individuals with pre-existing renal conditions or when administered at higher doses [53, 54]. Monitoring kidney function during the perioperative period is essential to mitigate this risk. Another critical concern is the risk of gastrointestinal bleeding, particularly in patients with a history of peptic ulcer disease or those concurrently using other medications that irritate the gastric mucosa [55, 56]. The use of Ketorolac should be cautiously considered in these patients, and prophylactic measures, such as co-administration of proton pump inhibitors (PPIs), may be warranted to protect the gastrointestinal tract. Although rare, anaphylaxis represents a severe allergic reaction that can occur with NSAIDs, including Ketorolac [57, 58]. Vigilance for signs of hypersensitivity reactions is crucial, particularly in patients with known allergies to NSAIDs or related compounds. Prompt recognition and treatment of anaphylactic reactions can prevent serious outcomes. In conclusion, Ketorolac does not appear to exacerbate the incidence of common postoperative adverse effects relative to other analgesic options. However, given the potential for serious complications such as AKI, gastrointestinal bleeding, and anaphylaxis, its use should be approached with caution, particularly in high-risk patient populations. Future studies should aim to expand the current evidence base, providing more comprehensive data on the safety profile of Ketorolac across diverse patient demographics and surgical contexts. This will enable more precise risk–benefit assessments and inform guidelines for the safe integration of Ketorolac into postoperative pain management protocols.

Limitations

The present Meta-analysis has certain limitations. Regarding PMR, we observed publication bias, primarily attributable to the limited sample size in certain studies.

As a result, the findings on the effectiveness of Ketorolac and its combination in mitigating postoperative PMR lacked precision. To ascertain the advantages of utilizing Ketorolac and its combination as compared to conventional postoperative analgesic treatment for reducing PMR, it is imperative to conduct additional RCTs with larger sample sizes in the future. Subsequent analyses incorporating effect sizes from these trials will help establish more conclusive evidence. Next, although subgroup analyses were performed, there is significant heterogeneity of PMR and adverse effect of nausea, different doses and combination methods of Ketorolac addition may have some effect on the pooling results. Finally, our analysis is based on only thirteen RCTs with small sample size, and more RCTs with large sample size should be conducted to explore this issue.

Conclusion

Ketorolac, whether administered alone or in combination with other analgesics, has proven effective in reducing postoperative pain and opioid consumption in adults undergoing lumbar spinal surgery. Furthermore, Ketorolac does not significantly increase the incidence of postoperative nausea and vomiting compared to other analgesics or placebos. Although it contributes to a reduction in length of stay, the clinical significance of this reduction appears modest. The considerable variability in study designs, dosages, and combination therapies results in significant heterogeneity in outcomes. Future research should aim to standardize protocols and determine optimal dosing strategies. Additionally, long-term safety and efficacy studies are needed to fully elucidate Ketorolac's role in postoperative pain management.

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Authors' contributions
JBG and KTY designed the systematic review. JBG and NNF drafted the protocol and KTY revised the manuscript. GJB and NNF will independently screen the potential studies, extract data, assess the risk of bias and finish data synthesis. GJB and KTY will arbitrate any disagreements during the review. Abudouaini H and Peng Liu correct spelling mistakes, grammatical errors, and inconsistent sentences. All authors approved the publication of the protocol. JBG is the first author, and Peng Liu and Abudouaini H are corresponding authors.

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Data availability
All data generated or analyzed during this study are included in this published article or are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
Not applicable.

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