Received: 27 September 2021 | Revised: 10 January 2022 | Accepted: 22 January 2022

DOI: 10.1111/bcp.15241

META-ANALYSIS

Postoperative administration of ketorolac compared to other drugs for pain control after third molar surgery: A meta-analysis of double-blind, randomized, clinical trials

Mario Alberto Isiordia-Espinoza[1] | Ángel Josabad Alonso-Castro[2] | Nicolás Serafín-Higuera[3] | Demian Ismael Castañeda-Santana[4] | Maximiliano de la Rosa Coronado[5] | Ronell Eduardo Bologna-Molina[6]

[1]Instituto de Investigación en Ciencias Médicas, Departamento de Clínicas, División de Ciencias Biomédicas, Centro Universitario de los Altos, Universidad de Guadalajara, Tepatitlán de Morelos, Jalisco, Mexico

[2]Departamento de Farmacia, División de Ciencias Naturales y Exactas, Universidad de Guanajuato, Guanajuato, Mexico

[3]Facultad de Odontología, Universidad Autónoma de Baja California, Mexicali, Baja California, Mexico

[4]Consultorio Privado, Xalisco, Nayarit, Mexico

[5]Especialidad de Ortodoncia, Universidad Cuauhtémoc, San Luis Potosí, SLP, Mexico

[6]Patología Molecular, Facultad de Odontología, Universidad de la República (UDELAR), Montevideo, Uruguay

Correspondence
Mario Alberto Isiordia-Espinoza, Instituto de Investigación en Ciencias Médicas, Departamento de Clínicas, División de Ciencias Biomédicas, Centro Universitario de los Altos, Universidad de Guadalajara, Av. Rafael Casillas Aceves No. 1200, Tepatitlán de Morelos, Jalisco, México.
Email: mario.isiordia162@yahoo.com

Aims: The aim of this study was to evaluate the analgesic effectiveness and adverse reactions of ketorolac in comparison with other drugs when administered postoperatively after third molar surgery.

Methods: PubMed and Google Scholar were utilized to search for articles comparing the efficacy and safety of ketorolac and other analgesic agents after third molar surgery. Data from papers with a lower risk of bias were recorded. The overall evaluation of analgesia onset, general and subgroup evaluation of the number of patients requiring rescue analgesic medication, general and subgroup assessment of the study medication (satisfaction on the study drugs), and the overall estimation of adverse effects were performed using the Review Manager Software 5.3 to analyse the data and obtain the meta-analysis plot.

Results: The subgroup evaluation of the study medication showed that patients who received ketorolac 30 mg were more satisfied than those who were given parecoxib 1 mg (odds ratio [OR] = 8.57, 95% confidence interval [CI] = 3.66–20.08, $P = .00001$), parecoxib 2 mg (OR = 7.17, 95% CI = 2.88–17.86, $P = .0001$), parecoxib 5 mg (OR = 3.03, 95% CI = 1.69–5.41, $P = .0002$), and parecoxib 10 mg (OR = 2.42, 95% CI = 1.36–4.32, $P = .003$). Moreover, patients who received ketorolac reported fewer adverse reactions compared with those who had received opioid analgesics (OR = 0.14, 95% CI = 0.32–1.76, $P = .0001$).

Conclusions: The data from this study demonstrates that the postoperative administration of ketorolac 30 mg presents better results on patient satisfaction when compared to parecoxib 1 mg to 10 mg, and presents a similar satisfaction to parecoxib 20 mg following third molar removal.

KEYWORDS
diclofenac, opioid analgesics, ketorolac, parecoxib, third molar surgery

1 | INTRODUCTION

Postoperative use of nonsteroidal anti-inflammatory drugs (NSAIDs) following third molar surgery is common.[1,2] These agents are employed to control the most habitual post-surgical complications (i.e., postoperative pain, facial inflammation and trismus).[1,3,4] Most NSAIDs are used to control low to moderate pain and when this symptom is severe, ketorolac can be used.[1,2]

Ketorolac is a member of the pyrrolo-pyrrole group of NSAIDs and is chemically related to tolmetin and indomethacin.[5] This drug has analgesic, anti-inflammatory and antipyretic properties, including inhibition of platelet aggregation activities.[6] These effects are the result of the traditional mechanism of action of NSAIDs—the inhibition of the enzyme cyclooxygenase which blocks the production of prostaglandins.[7]

It is important to highlight the great analgesic activity of ketorolac in comparison with other NSAID-type drugs.[5,7] Animal models have shown that ketorolac has a greater analgesic effect compared to acetylsalicylic acid (aspirin), indomethacin, naproxen and phenylbutazone.[5] In the same way, it has been demonstrated in animal tests that ketorolac and morphine induce comparable analgesia.[5,6]

Recently, a systematic review showed that the preventive administration of ketorolac has some advantages in postoperative pain control when compared with other drugs following surgical removal of third molars.[8] However, there is a lack of systematic reviews employing a meta-analytic evaluation on the analgesic efficacy of postoperative administration of ketorolac after third molar removal. Thus, the aim of this study was to assess the analgesic efficacy and systemic adverse effects of ketorolac in comparison to other analgesics following removal of third molars.

2 | METHODS

2.1 | Study design

This study was carried out following PRISMA guidelines[9,10] and the *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* (2011),[11] and it was registered in the PROSPERO database (ID: CRD42021227135).

2.2 | Selection criteria

Inclusion criteria (PICO)[12]:

Population: Randomized, double-blind, parallel-groups, or split-mouth (crossover) studies comparing the efficacy and adverse reactions of ketorolac and other drugs following third molar removal.
Interventions: Postoperative administration of ketorolac.
Control: Postoperative administration of other analgesics.
Outcome: Total pain relief (TOTPAR) at 2, 4, 6, 8 and 24 hours, evaluation of pain intensity using the visual analog scale (VAS), number of

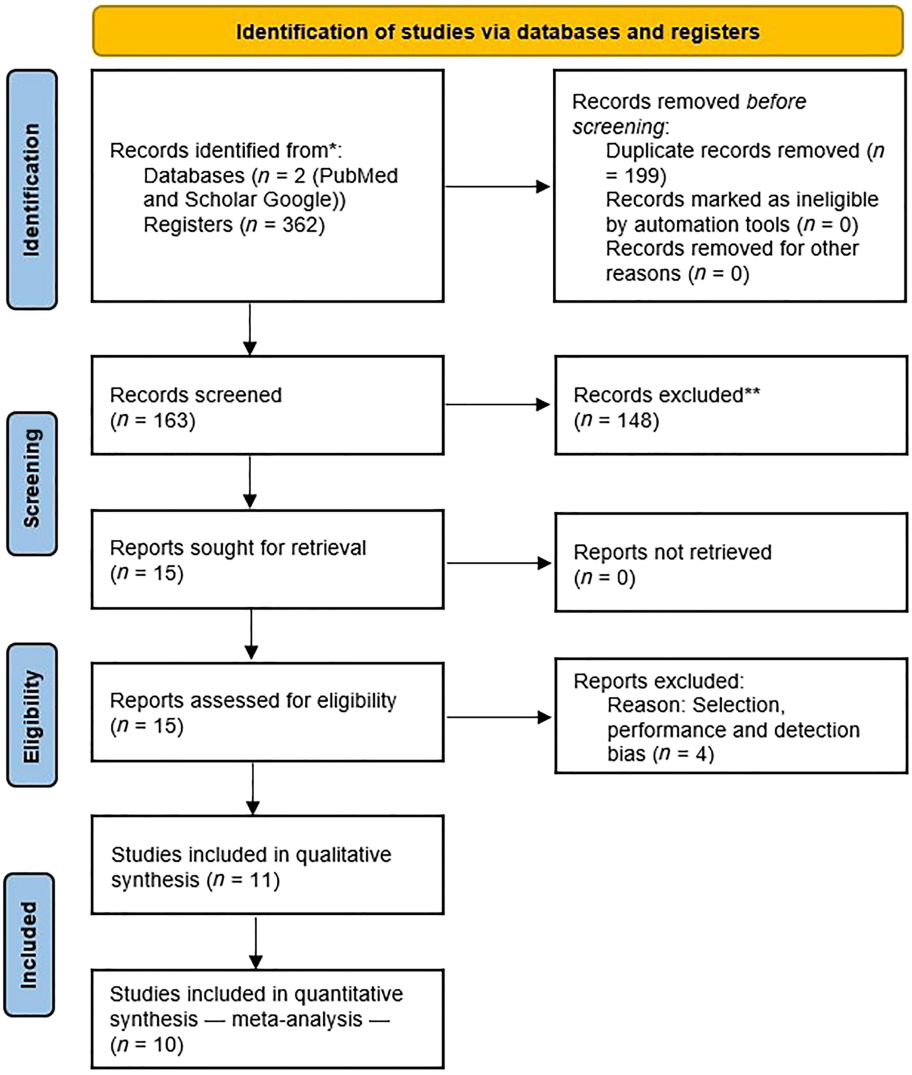

FIGURE 1 Study flow chart

patients reporting onset of analgesia, number of patients needing rescue analgesic medication, overall assessment of study medication (patient satisfaction) and adverse effects.

Exclusion criteria:

Trials with more than a 20% loss of follow-up.

2.3 | Electronic search

PubMed and Google Scholar were used to identify clinical assays comparing ketorolac and other drugs after surgical removal of wisdom teeth. "Diclofenac", "ibuprofen", "naproxen", "sodium", "metamizole", "meloxicam", "piroxicam", "lornoxicam", "celecoxib", "etoricoxib", "parecoxib", "morphine", "codeine", "tramadol", "oxycodone", "meperidine" or "tapentadol" were the words used to perform the search in the databases. Each of these words was used in combination with "ketorolac" and "third molar surgery", or "third molar removal", "wisdom teeth surgery", "wisdom tooth removal" or "wisdom teeth removal". The article types were as follows: "Clinical trial", "Controlled clinical trial", "Clinical study". "English" and "Spanish" were selected in the language option. Two independent evaluators agreed on the selection of eligible studies and achieved consensus of which studies to include during the full assessment of papers.[13–15]

2.4 | Assessment of bias

The Cochrane Collaboration's risk of bias tool was used.[1,2] The clinical trials with a high risk of bias (a red ball) were excluded from the qualitative and quantitative assessments.[1,2] This stage included the participation of two blinded independent evaluators and the differences were resolved with the participation of a third researcher.[13–15]

2.5 | Data extraction and statistical analysis

Author, design study, treatment groups, size sample (*n*), dose, total pain relief (TOTPAR), evaluation of pain intensity using the VAS, number of patients needing rescue medication, overall assessment of study medication and adverse effects were extracted. Data were

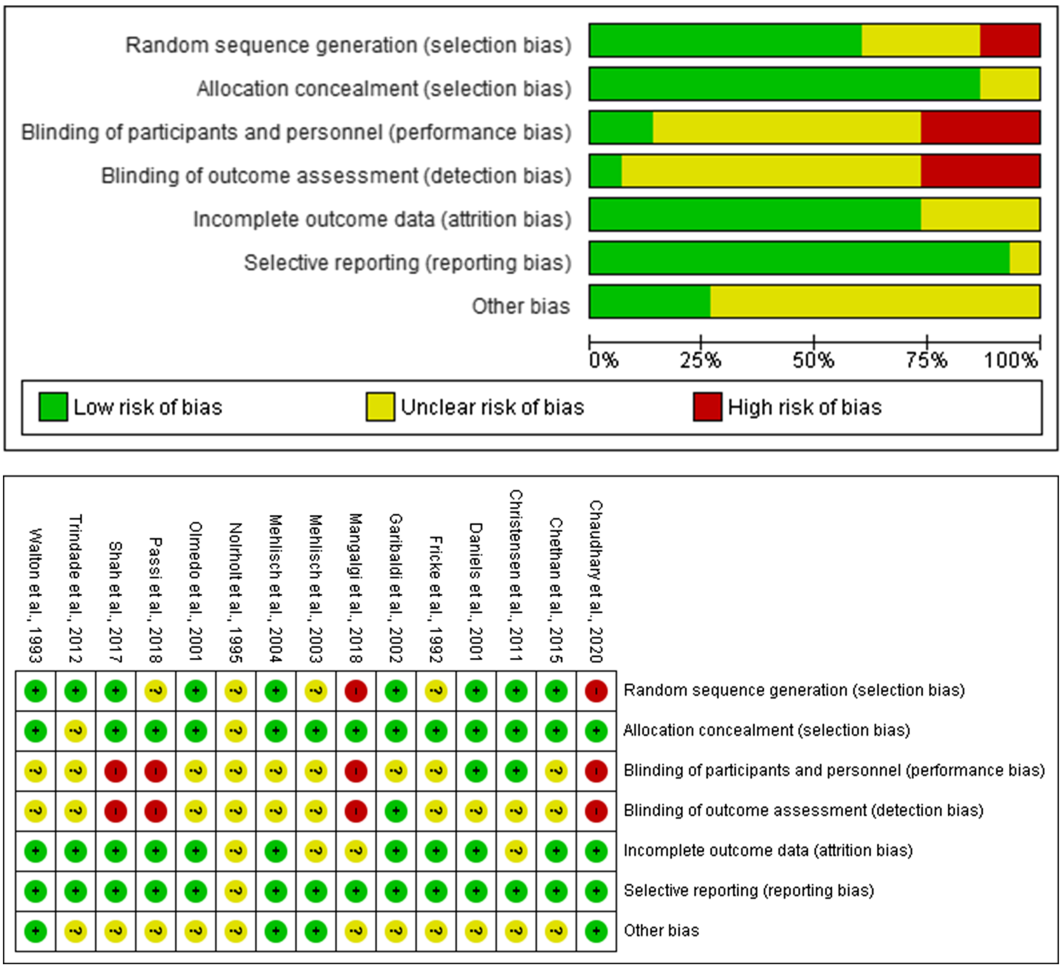

FIGURE 2 Evaluation of bias risk and quality of the clinical studies

TABLE 1 Details of the included studies

First author, and study design	Treatments (*n*)	Details of patients, surgical procedure and evaluation	Conclusion
Chethan et al., 2015.[24] Randomized, double-blind, parallel, clinical study. Multiple-dose approach. Post-operative analgesia.	Group A: Tramadol 50 mg orally following surgery with a dose repetition after 6 h ($n = 20$). Group B: Ketorolac 10 mg orally following surgery with a dose repetition after 6 h ($n = 20$).	Patients aged 18–25 years old, either gender, free systemic disease. A third molar surgical removal under local anaesthesia was carried out by the same surgeon. Rescue analgesic was not used. The evaluation period was 24 h. The efficacy was assessed using the VAS and vital signs. Adverse effects were not evaluated.	Tramadol had better analgesia and safety profile than ketorolac.
Christensen et al., 2011.[25] Randomized, double-blind, parallel, clinical study. Single-dose approach. Post-operative analgesia.	Group A: Ketorolac 30 mg ($n = 47$). Group B: Diclofenac 3.75 mg ($n = 51$). Group C: Diclofenac 9.4 mg ($n = 51$). Group D: Diclofenac 18.75 mg ($n = 51$). Group E: Diclofenac 37.5 mg ($n = 51$). Group F: Diclofenac 75 mg ($n = 51$). Group G: Placebo ($n = 51$). All treatments were IV administered.	Subjects had to be in good health. Surgical removal of one or more third molar (at least one fully or partially impacted tooth). All subjects received lidocaine 20 mg/mL with epinephrine 12.5 mg/mL. The rescue analgesics were oral ibuprofen 400–600 mg and a hydrocodone 5 mg and acetaminophen 500 mg combination. Patients were assessed for 24 hours post-operative hours and 5–9 days after surgery. Dental pain using a categorical scale and VAS, TOTPAR, SPID, SPRID and adverse effects were assessed.	Diclofenac produced a more rapid analgesic effect than ketorolac.
Daniels et al., 2001.[26] Randomized, double-blind, parallel, clinical investigation. Single-dose study. Post-operative analgesia.	Group A: Parecoxib sodium 20 mg IM and placebo IV ($n = 51$). Group B: Parecoxib sodium 20 mg IV and placebo IM ($n = 50$) Group C: Parecoxib sodium 40 mg IM and placebo IV ($n = 50$). Group D: Parecoxib sodium 40 mg IV and placebo IM ($n = 51$). Group E: Ketorolac 60 mg IM and placebo IV ($n = 51$). Group F: Placebo IM and IV ($n = 51$).	Healthy patients, aged 18–64 years old, and undergoing ≥2 third molar surgery. Patients were evaluated across 24 h. The drug used as a rescue analgesic was not specified. The number of patients taking rescue analgesics, pain intensity by VAS, pain relief, overall evaluation and adverse effects were assessed. The number of patients reporting adverse effects was recorded.	Parecoxib sodium 20 mg had comparable analgesia to that of ketorolac 60 mg.
Fricke et al., 1992.[27] Randomized, double-blind, parallel, clinical trial. Single-dose approach. Post-operative analgesia.	Group A: Ketorolac 10 mg ($n = 29$). Group B: Ketorolac 30 mg ($n = 28$). Group C: Ketorolac 90 mg ($n = 30$). Group D: Meperidine 50 mg ($n = 28$). Group E: Meperidine 100 mg ($n = 30$).	Patients of at least 15 years of age. Three or four third molar surgery using a uniform IV sedation regimen using four drugs and local anaesthesia. A standard analgesic (not specified) was used for patients needing re-medication. The assessment was through 8 hours.	Ketorolac induced a superior analgesia when compared with meperidine.

TABLE 1 (Continued)

First author, and study design	Treatments (*n*)	Details of patients, surgical procedure and evaluation	Conclusion
	All treatments were IV administered.	Evaluated variables were: Pain using a verbal categorical pain intensity scale, VAS, global pain relief scale, % of patients by inadequate pain relief, and overall rating of study medication. Ketorolac presented lower adverse effects than meperidine.	
Garibaldi et al., 2002.[28] Randomized, double-blind, parallel, clinical assay. Multiple-dose trial. Post-operative analgesia.	Group A: Ketorolac 10 mg and placebo ($n = 20$). Group B: Ketorolac 10 mg and codeine 7.5 mg ($n = 20$). Group C: Ketorolac 10 mg and codeine 15 mg ($n = 20$). All treatments were given orally. Group D: Ketorolac 10 mg and codeine 30 mg ($n = 20$). Group E: Placebo and codeine 30 mg ($n = 20$).	Patients aged 18–32 years old. Four third molar extractions using IV sedation and local anaesthesia. Patients were assessed for 5 days. Pain intensity, pain relief and global evaluation and side effects were evaluated.	Ketorolac-codeine combination provided good analgesia and side effects were observed.
Mehlisch et al., 2003.[29] Randomized, double-blind, parallel, clinical study. Single-dose approach. Post-operative analgesia.	Group A: Ketorolac 30 mg ($n = 50$). Group B: Parecoxib sodium 1 mg ($n = 51$). Group C: Parecoxib sodium 2 mg ($n = 51$). Group D: Parecoxib sodium 5 mg ($n = 51$). Group E: Parecoxib sodiem 10 mg ($n = 51$). Group F: Parecoxib sodium 20 mg ($n = 51$). Group G: Parecoxib sodium 50 mg ($n = 51$). Group H: Parecoxib sodium 100 mg ($n = 51$). Group I: Placebo ($n = 50$). Treatments were given by IV route.	Patients of good health and aged 18 years. Removal of more than two third molars. Acetaminophen 1000 mg and hydrocodone 7.5 mg plus acetaminophen 500 mg. Patients were evaluated across 24 h. The onset of analgesia, pain intensity, global evaluation of the study medication and adverse effects were recorded.	Similar analgesic effect was observed between ketorolac and parecoxib sodium.
Mehlisch et al., 2004.[30] Randomized, double-blind, parallel, clinical trial. Single-dose approach. Post-operative analgesia.	Group A: Ketorolac 30 mg ($n = 51$). Group B: Parecoxib sodium 1 mg ($n = 51$). Group C: Parecoxib sodium 2 mg ($n = 50$). Group D: Parecoxib sodium 5 mg ($n = 51$). Group E: Parecoxib sodium 10 mg ($n = 50$). Group F: Parecoxib sodium 20 mg ($n = 50$). Group G: Placebo ($n = 50$). All treatments were given using the IM route.	The participants were adults, aged 18 and 45. At least two surgical removals of impacted third molars. Acetaminophen 1 g, hydrocodone 5 mg with acetaminophen 500 mg, hydrocodone 7.5 mg with acetaminophen 500 mg or meperidine 50 mg with promethazine 25 mg were used as rescue analgesics by oral route. The full evaluation period was 1 day. The recorded variables were the onset of analgesia, pain intensity using a categorical scale, the VAS, TOTPAR and SPID, adverse	Parecoxib 20 mg showed an analgesic effect approximate to ketorolac 30 mg.

(Continues)

TABLE 1 (Continued)

First author, and study design	Treatments (*n*)	Details of patients, surgical procedure and evaluation	Conclusion
		effects and overall assessment of the study medication.	
Nørholt et al., 1995.[31] Randomized, double-blind, parallel, clinical investigation. Single-dose study. Post-operative analgesia.	Group A: Ketorolac 10 mg ($n = 46$). Group B: Lornoxicam 4 mg ($n = 43$). Group C: Lornoxicam 8 mg ($n = 45$). Group D: Lornoxicam 16 mg ($n = 48$). Group E: Lornoxicam 32 mg ($n = 48$). Group F: Placebo ($n = 48$). Drugs were orally administered.	Patients aged 17–40 years. A third molar under local anaesthesia was removed. Acetaminophen 500 mg rescue analgesia was used. Patients were assessed through 24 h. Total pain relief, pain relief, peak pain relief, time with effect, pain intensity, time to re-medication, and adverse effects were evaluated.	Similar analgesic effect between ketorolac 10 mg, lornoxicam 8 and 16 mg.
Olmedo et al., 2001.[32] Randomized, double-blind, parallel, clinical study. Multiple-dose trial. Post-operative analgesia.	Group A: Ketorolac 10 mg ($n = 33$). Group B: Ketorolac 20 mg ($n = 36$). Group C: Ketoprofen 50 mg ($n = 39$). Group D: Placebo ($n = 42$). All treatments were given every 6 hours.	Surgical extraction of a third molar under local anaesthesia (articaine/epinephrine). Acetaminophen 650 mg rescue medication was used. Patients were evaluated across two post-operative days. Pain intensity with VAS and verbal scale, rescue analgesic consumption, and adverse effects were evaluated.	Ketorolac was more effective than ketoprofen.
Trindade et al., 2012.[33] Randomized, double-blind, crossover, clinical investigation. Multiple-dose study. Post-operative analgesia.	Group A: Sublingual ketorolac 10 mg for every 6 h (four times daily) for 4 days ($n = 47$). Group B: Sublingual piroxicam 20 mg once a day for 4 days ($n = 47$).	Volunteers aged ≥18 years who had two lower third molars in similar positions. Surgeries were performed using local anaesthesia (articaine/epinephrine). Acetaminophen 750 mg rescue analgesic medication was used. Patients were evaluated for 7 days. The variables assessed were time to first rescue analgesic medication, number of patients who took rescue analgesics, mouth opening, facial swelling, pain with VAS, adverse effects and global evaluation of the studied drugs.	Similar control of post-operative pain, facial swelling and trismus using either ketorolac or piroxicam.
Walton et al., 1993.[34] Randomized, double-blind, parallel, clinical study. Multiple-dose trial. Post-operative analgesia.	Group A: Ketorolac 30 mg ($n = 100$). Group B: Diclofenac 75 mg ($n = 50$). Group C: Placebo ($n = 50$). All drugs were given first by oral route and after that by IM.	Patients between the ages of 16 and 65 years. At least two mandibular wisdom molars for surgery under general anaesthesia. Acetaminophen was used like rescue analgesic medication. The evaluation period was 3 days. The analgesic indicators evaluated were time for rescue medication, pain using the AUC from VAS, patients needing rescue analgesics and adverse reactions.	Patients administered with ketorolac needing less rescue analgesic medication than those who received diclofenac. However, patients who received ketorolac had more adverse effects when compared with those who were given diclofenac.

analysed using the Mantel–Haenszel test, odds ratio (OR) and a random effects model using the Review Manager Software 5.3 for Windows. The I^2 test was utilized to determine the inconsistency value as follows: insignificant = 0–30%; reasonable or moderate = 31–70%; and significant or considerable = 71–100%. An overall test with a *P*-value of <.05 and an OR of >1 (within the 95% confidence interval [CI]) was considered a statistical difference.[11,16–19]

3 | RESULTS

3.1 | Electronic search and evaluation of bias

The search for investigation reports was performed in PubMed and Google Scholar. A total of 362 scientific papers were found. After records were screened, a total of 15 clinical trials were evaluated for eligibility,[20–34] of which four were rejected for problems related to selection, performance and detection of bias.[20–23] Finally, 11 and 10 clinical studies were included in the qualitative[24–34] and quantitative[25–34] analyses, respectively (Figures 1 and 2).

3.2 | Qualitative analysis

Qualitative assessment was performed using 11 clinical reports,[24–34] of which, three produced results in favour of ketorolac,[27,32,34] five clinical assays presented a similar effect comparing ketorolac and active controls,[26,29–31,33] in two studies the conclusion was not in favour of ketorolac,[24,25] and one trial drew no conclusions about this drug[28] (Table 1).

3.3 | Quantitative analysis

The number of patients reporting onset of analgesia was evaluated with data from three clinical investigations ($n = 960$).[26,29,30] The data trend was in favour of ketorolac without a statistical difference ($I^2 = 78\%$, $Z = 1.55$, OR = 2.07, 95% CI = 0.82–5.20, $P = .12$, Figure 3A).

The overall assessment of the number of patients who took rescue analgesic medication included five clinical assays ($n = 1217$).[26,29,30,32,34] The meta-analytical evaluation showed no statistical differences between ketorolac and other analgesics ($I^2 = 80\%$,

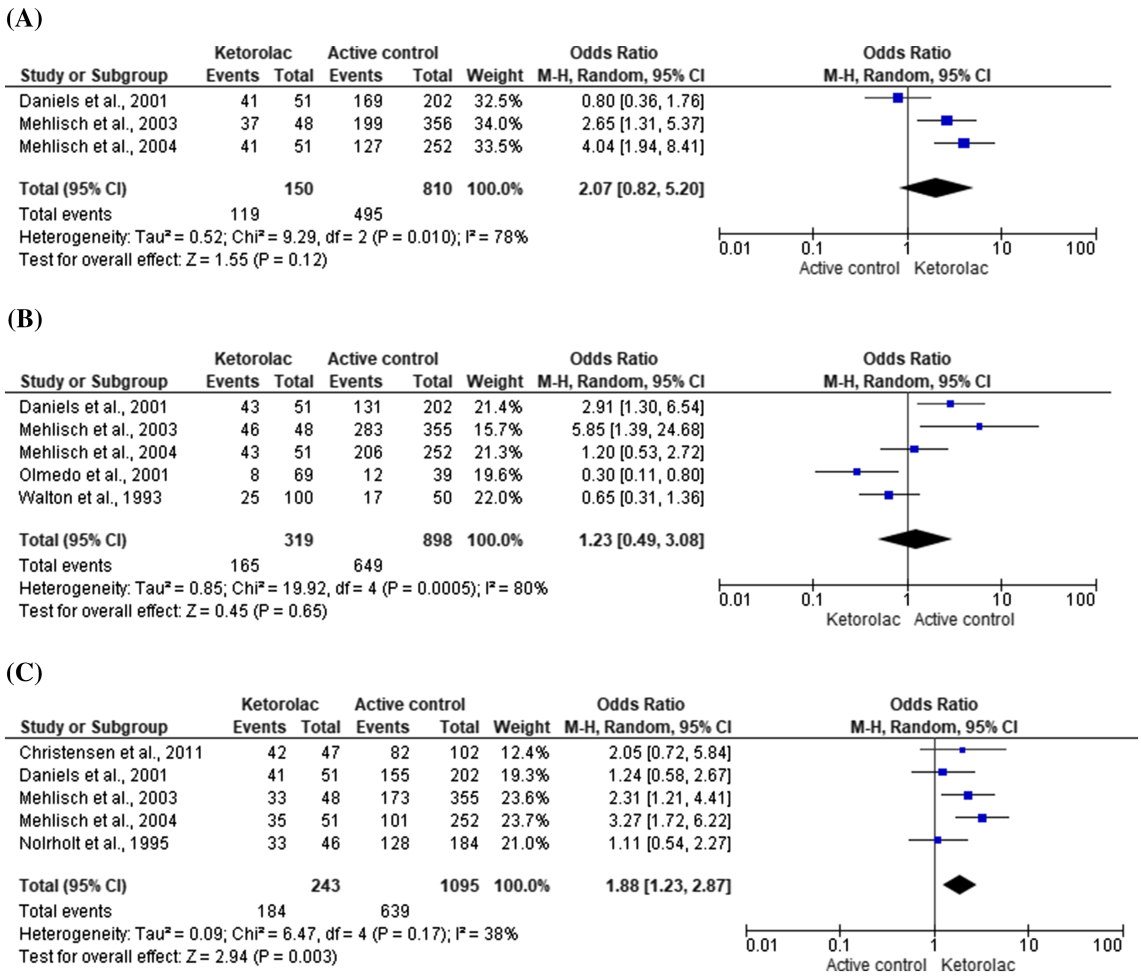

FIGURE 3 Meta-analytical assessment of the number of patients reporting onset of analgesia (A), overall evaluation of rescue analgesic medication (B), and general analysis of the patient satisfaction (C)

$Z = 0.45$, OR = 1.23, 95% CI = 0.49–3.08, $P = .65$, Figure 3B). Conversely, the subgroup analysis showed that patients who were given ketorolac 30 mg required more rescue analgesics than those who received parecoxib 20 mg (Figure 4).

The global evaluation of the study drugs or patient satisfaction was performed with five studies ($n = 1338$).[25,26,29–31] The general meta-analysis showed that patients who received ketorolac had a better opinion—on the analgesic efficacy and adverse effects—than those who were given other analgesics ($I^2 = 38\%$, $Z = 2.94$, OR = 1.88, 95% CI = 1.23–2.87, $P = .003$, Figure 3C). Moreover, the subgroup comparison showed that ketorolac 30 mg was superior to parecoxib 1 mg–10 mg (Figure 5).

3.4 | Adverse effects

The global analysis of the number of patients reporting adverse reactions was carried out using data from seven clinical trials ($n = 1446$).[26–30,33,34] The statistical analysis showed no differences between ketorolac and active controls ($I^2 = 85\%$, $Z = 0.65$, OR = 0.75, 95% CI = 0.32–1.76, $P = .51$, Figure 6A).[26–30,33,34] The number of subjects recording adverse events for ketorolac and traditional NSAIDs or COX-2 inhibitors was similar ($n = 244$, $I^2 = 63\%$, $Z = 1.01$, OR = 3.54, 95% CI = 0.30–41.50, $P = .31$, Figure 6A, and $n = 963$, $I^2 = 0\%$, $Z = 1.01$, OR = 1.20, 95% CI = 0.84–1.71, $P = .31$, Figure 6A; respectively). However, the number of patients receiving opioid agents reported a higher number of adverse reactions when compared to those who received ketorolac ($n = 239$, $I^2 = 27\%$, $Z = 4.30$, OR = 0.14, 95% CI = 0.32–1.76, $P = .0001$, Figure 6A). The evaluation of adverse effects according to the administration route showed no statistical difference (Figure 6B).

The frequencies of local bleeding ($n = 432$, $I^2 = 0\%$, $Z = 0.24$, OR = 0.84, 95% CI = 0.21–3.32, $P = .81$), alveolar osteitis ($n = 1195$, $I^2 = 0\%$, $Z = 0.62$, OR = 0.85, 95% CI = 0.50–1.44, $P = .54$), nausea ($n = 1650$, $I^2 = 65\%$, $Z = 0.60$, OR = 0.78, 95% CI = 0.35–1.74, $P = .55$), vomiting ($n = 1650$, $I^2 = 22\%$, $Z = 0.36$, OR = 0.87, 95% CI = 0.41–1.83, $P = .72$), dizziness ($n = 1650$, $I^2 = 0\%$, $Z = 1.95$,

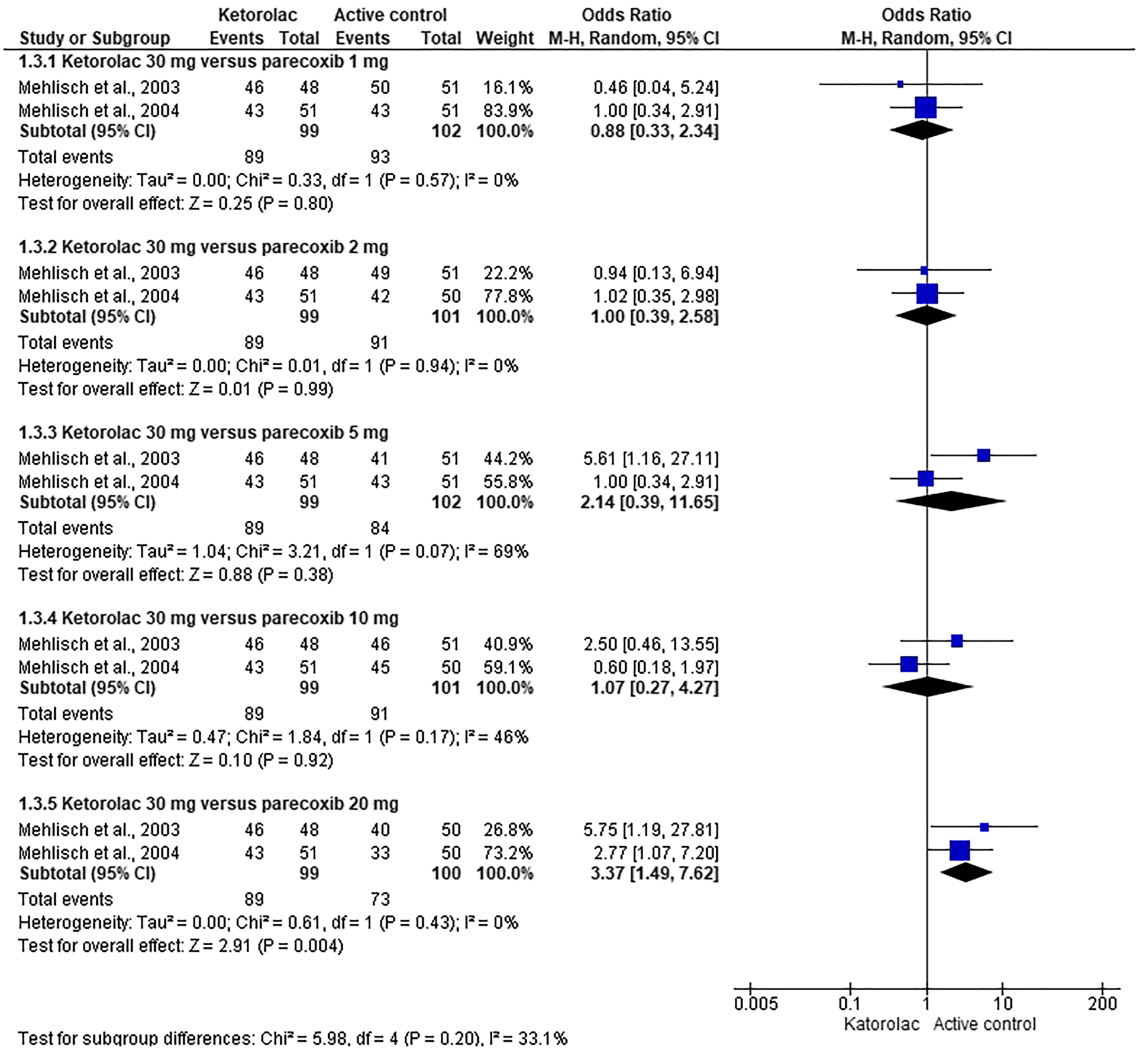

FIGURE 4 Subgroup analysis of rescue analgesic medication

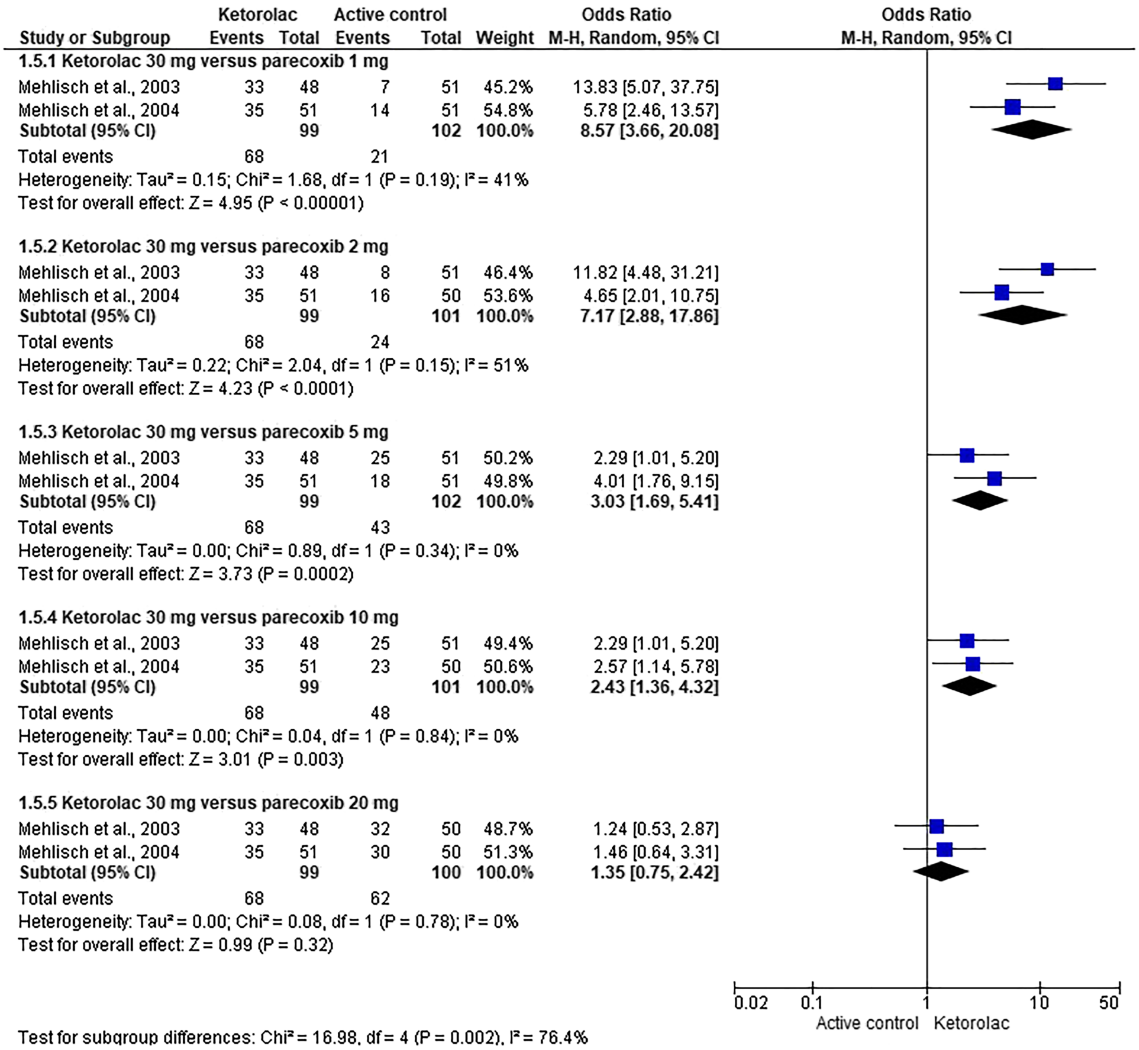

FIGURE 5 Subgroup evaluation of the study treatments (patient satisfaction)

OR = 0.58, 95% CI = 0.34–1, $P = .05$), and headache ($n = 1193$, $I^2 = 0\%$, $Z = 1.81$, OR = 1.65, 95% CI = 0.96–2.83, $P = .07$) for ketorolac and active controls showed no statistical difference (Figure 7).

4 | DISCUSSION

This is the first systematic review and meta-analytical assessment of the analgesic effectiveness of ketorolac for postoperative administration after surgical removal of third molars in comparison with other analgesic agents. The most important qualitative findings include three clinical trials that were in favour of ketorolac and five studies showed similar analgesic efficacy between ketorolac and active controls. The most important quantitative results showed that patients who received ketorolac 30 mg needed more rescue analgesics when compared with parecoxib 20 mg. The overall evaluation of the drug study indicated that patients who took ketorolac 30 mg were more satisfied than those who received parecoxib 1 mg–10 mg. A similar level of satisfaction of the studied drugs between patients receiving ketorolac 30 mg and parecoxib 20 mg was observed. However, the evaluation of the patient satisfaction could have been influenced by the high amount of rescue analgesics taken by the patients who received ketorolac in comparison to those who were given an active control.

Recently, the main results regarding the benefits and risks of using single-dose intravenous ketorolac in comparison with other NSAIDs—four studies comparing parecoxib and two trials versus diclofenac—for pain relief in adults undergoing pelvic/abdominal, dental and orthopaedic surgeries showed no statistical differences for TOTPAR at 4 and 6 hours for first rescue analgesic medication, and the number of volunteers who took rescue analgesic medication.[35] On the other hand, McNicol et al. assessed the analgesic effectiveness of ketorolac for postoperative pain control in children; however, the authors concluded a lack of sufficiently high-quality clinical evidence to carry out the statistical analysis on the efficacy and safety of this drug. Based on the above, the authors do not support but do not reject the use of ketorolac in children.[36] Furthermore, De Oliveira

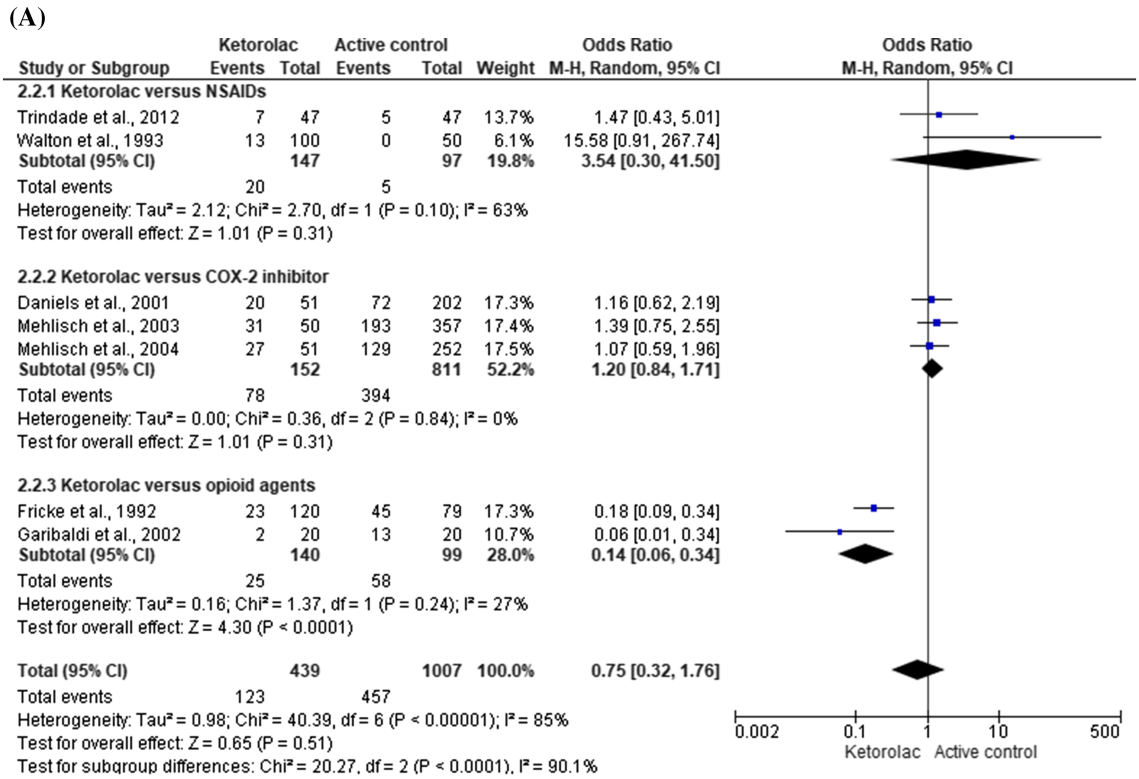

FIGURE 6 Global assessment of adverse effects (A) and adverse effects according to the administration route (B)

et al. carried out a systematic review and meta-analytical estimation on the efficacy and safety of a single dose of systemic ketorolac administered preoperatively. The authors concluded that the preoperative administration of ketorolac reduces postoperative pain and it was recommended as an adjunct in multimodal analgesia.[37] Wan et al. demonstrated—across a meta-analytical evaluation—the

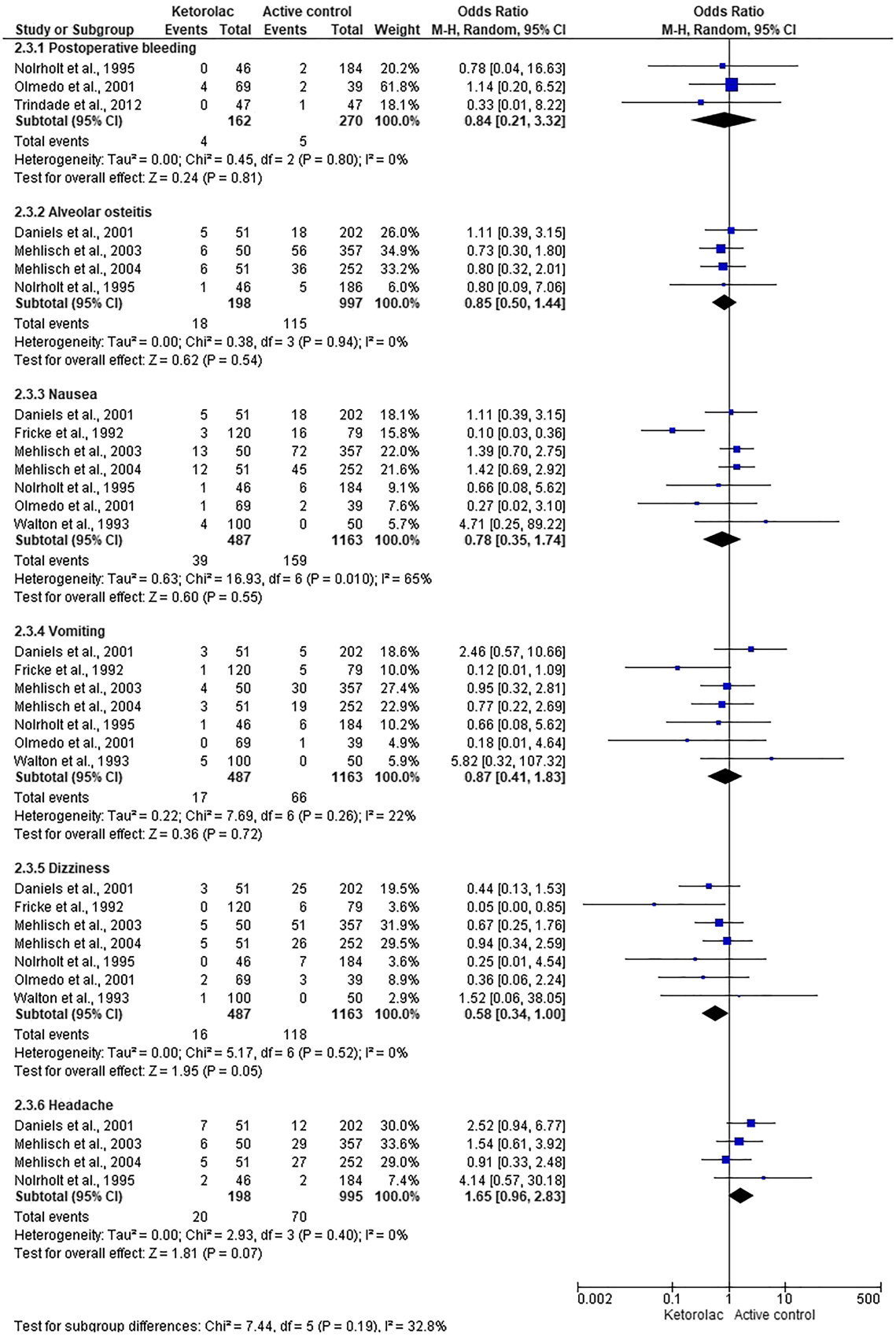

FIGURE 7 Subgroup evaluation of adverse effects

efficacy of ketorolac supplementation on the management of postoperative pain after knee arthroscopy.[38] Finally, referring to the analgesic efficacy of ketorolac, doses of intramuscular ketorolac 10 mg and 30 mg have been pointed out as having similar analgesic effectiveness for postoperative pain control.[39,40] Moreover, Nagendrababu et al. performed a meta-analysis to evaluate the influence of ketorolac on the inferior alveolar nerve block (IANB) in patients with symptomatic pulpitis and they concluded that ketorolac 10 mg increased the IANB success index when compared to placebo.[41]

Adverse reactions of ketorolac have previously been measured using meta-analytical statistical methods.[35–37,42–45] McNicol et al. showed that ketorolac increased the rate of adverse reactions when compared to another NSAID after surgery.[35] However, the number to treat (NNT) was 12.5 patients with 95% CI = 6.7–∞.[35] McNicol et al. also reported that there was not enough information to assess the adverse effects of ketorolac after surgery in children.[36] De Oliveira et al. found no statistical difference between ketorolac 30 mg and placebo on nausea and vomiting risk, but they reported that ketorolac 60 mg presented a reduction in nausea and vomiting in comparison to placebo.[37] Moreover, Gobble et al.[42] and Davidson and Turner[43] reported that perioperative ketorolac did not increase the risk of bleeding after surgery. Furthermore, Chan et al. reported contradictory results to Gobble et al.[42] and Davidson and Turner[43] on the risk of bleeding after tonsillectomy in adults.[44] Massó-González et al reported that ketorolac presented a high risk of upper gastrointestinal bleeding and/or perforation.[45] In our meta-analytical estimation, the results showed a similar risk of adverse effects using ketorolac and other NSAIDs or COX-2 agents. In addition, ketorolac had a lower adverse events risk when compared to opioid analgesics ($P < .05$). The subgroup evaluation of adverse effects (alveolar osteitis, nausea, vomiting, etc.) showed no statistical differences between ketorolac and active controls following third molar surgery.

Some important limitations of this meta-analytical evaluation were as follows: (1) according to the studies with a lower risk of bias, the analgesic efficacy and safety profile of ketorolac has been compared with a limited number of active controls: traditional NSAIDs (ketoprofen and diclofenac), oxicams (lornoxicam and piroxicam), COX-2 agents (parecoxib only), and opioid analgesics (codeine and meperidine); (2) the pooled assessment of TOTPAR and pain intensity was not possible because the articles did not present the data; (3) some clinical studies included a small sample size; and (4) it was only possible to perform a subgroup analysis of doses comparing ketorolac and parecoxib.

In conclusion, the data from this meta-analytical estimation demonstrated that the postoperative administration of ketorolac 30 mg presented better results on the overall assessment of the studied drugs when compared to parecoxib 1 mg, 2 mg, 5 mg and 10 mg, and it showed a similar satisfaction level to parecoxib 20 mg after third molar surgery. Moreover, ketorolac had a similar safety profile to traditional NSAIDs and COX-2 agents, but it presented significantly fewer adverse effects when compared to opioid analgesics.

COMPETING INTERESTS

The authors have no conflicts of interest to declare.

CONTRIBUTORS

M.A.I.-E.: Conception and design of the study (review), analysis and interpretation of data collected, drafting of the article and critical revision, and final approval and guarantor of the manuscript. A.J.A.-C., N.A.S.-H. and R.E.B.-M.: Acquisition of data, literature search, data extraction, and interpretation of data collected, and final approval, and guarantor of the manuscript. D.I.C.-S. and M.R.-C.: Interpretation of data collected, critical revision, and final approval of the manuscript.

ORCID

Mario Alberto Isiordia-Espinoza https://orcid.org/0000-0001-8389-6866

REFERENCES

1. Franco-de la Torre L, Figueroa-Fernández NP, Franco-González DL, Alonso-Castro ÁJ, Rivera-Luna F, Isiordia-Espinoza MA. A meta-analysis of the analgesic efficacy of single-doses of ibuprofen compared to traditional non-opioid analgesics following third molar surgery. *Pharmaceuticals (Basel)*. 2021;14(4):360. doi:10.3390/ph14040360
2. Isiordia-Espinoza MA, Franco-González MA, Alonso-Castro ÁJ, Franco-de la Torre L. Analgesic effectiveness and safety of celecoxib versus non-opioid active controls after third molar surgery: a meta-analytical evaluation. *J Stomatol Oral Maxillofac Surg*. 2021; S2468-7855(21)00141-5. doi:10.1016/j.jormas.2021.06.015
3. Carrasco-Labra A, Brignardello-Petersen R, Yanine N, Araya I, Guyatt G Secondary versus primary closure techniques for the prevention of postoperative complications following removal of impacted mandibular third molars: a systematic review and meta-analysis of randomized controlled trials. *J Oral Maxillofac Surg*. 2012;70(8): e441-e457. doi:10.1016/j.joms.2012.03.017
4. Al-Delayme RMA. Randomized clinical study comparing piezoelectric surgery with conventional rotatory osteotomy in mandibular third molars surgeries. *Saudi Dent J*. 2021;33(1):11-21. doi:10.1016/j.sdentj.2019.11.010
5. Litvak KM, McEvoy GK. Ketorolac, an injectable nonnarcotic analgesic. *Clin Pharm*. 1990;9(12):921-935.
6. Buckley MM, Brogden RN. Ketorolac. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential. *Drugs*. 1990;39(1):86-109. doi:10.2165/00003495-199039010-00008
7. Redden RJ. Ketorolac tromethamine: an oral/injectable nonsteroidal anti-inflammatory for postoperative pain control. *J Oral Maxillofac Surg*. 1992;50(12):1310-1313. doi:10.1016/0278-2391(92)90233-P
8. Tirupathi S, Rajasekhar S, Maloth SS, Arya A, Tummalakomma P, Lanke RB Pre-emptive analgesic efficacy of injected ketorolac in comparison to other agents for third molar surgical removal: a systematic review. *J Dent Anesth Pain Med*. 2021;21(1):1-14. doi:10.17245/jdapm.2021.21.1.1
9. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *J Clin Epidemiol*. 2021;134:178-189. doi:10.1016/j.jclinepi.2021.03.001
10. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern*

Med. 2009;151(4):W65-W94. doi:10.7326/0003-4819-151-4-200908180-00136

11. Higgins JP, Green S (Eds). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*. Oxford: The Cochrane Collaboration; 2011. https://training.cochrane.org/handbook
12. Leonardo R. PICO: model for clinical questions. *Evid Based Med Pract*. 2018;3:2. https://www.researchgate.net/publication/326922937_PICO_Model_for_Clinical_Questions
13. Jones A, Steel D. Evaluating the quality of medical evidence in real-world contexts. *J Eval Clin Pract*. 2018;24(5):950-956. doi:10.1111/jep.12983
14. Atkins D, Eccles M, Flottorp S, et al. Systems for grading the quality of evidence and the strength of recommendations I: critical appraisal of existing approaches The GRADE Working Group. *BMC Health Serv Res*. 2004;4(1):38. https://pubmed.ncbi.nlm.nih.gov/15615589/
15. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926. doi:10.1136/bmj.39489.470347.AD
16. Isiordia-Espinoza MA, Aragon-Martinez OH, Bollogna-Molina RE, Alonso-Castro ÁJ. Infection, alveolar osteitis, and adverse effects using metronidazole in healthy patients undergoing third molar surgery: a meta-analysis. *J Maxillofac Oral Surg*. 2018;17(2):142-149. doi:10.1007/s12663-017-1031-x
17. Huynh TM, Marret E, Bonnet F. Combination of dexamethasone and local anaesthetic solution in peripheral nerve blocks: a meta-analysis of randomised controlled trials. *Eur J Anaesthesiol*. 2015;32(11):751-758. doi:10.1097/EJA.0000000000000248
18. Whitley E, Ball J. Statistics review 3: hypothesis testing and P values. *Crit Care*. 2002;6(3):222-225. doi:10.1186/cc1493
19. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560. doi:10.1136/bmj.327.7414.557
20. Chaudhary B, Gurung D, Dahal S, Twyana R, Khanal P, Adhikari P. Comparison of nimesulide and ketorolac in control of pain, swelling, and trismus following extraction of impacted third molar. *J Nepal Dent Assoc*. 2020;20:79-87. https://www.researchgate.net/publication/346262446_Comparison_of_Nimesulide_and_Ketorolac_in_Control_of_Pain_Swelling_and_Trismus_following_Extraction_of_Impacted_Third_Molar
21. Mangalgi A, Mallasure D, Shah K, Sajjanshetty S, Patil S, Halkai S. Intramuscular administration of ketorolac versus tramadol post operatively in minor oral surgery. *Int J Sci Res*. 2018;7:68-71.
22. Passi D, Singh M, Kishore M, et al. Comparative evaluation of analgesic efficacy of oral ketorolac and tramadol after impacted mandibular third molar surgery: short clinical study with literature review. *Ann Med Health Sci Res*. 2018;8:157-162. https://www.researchgate.net/publication/346262446_Comparison_of_Nimesulide_and_Ketorolac_in_Control_of_Pain_Swelling_and_Trismus_following_Extraction_of_Impacted_Third_Molar
23. Shah D, Shah S, Mahajan A, Shah N, Sanghvi D, Shah R. A comparative clinical evaluation of analgesic efficacy of Tapentadol and ketorolac in mandibular third molar surgery. *Natl J Maxillofac Surg*. 2017;8(1):12-18. doi:10.4103/njms.NJMS_4_17
24. Chethan R, Ramamuthy TK, Patil S, Reddy S. Comparative study of analgesic effectiveness of tramadol and ketorolac in the pain management of surgical removal of third molar: a randomized double blinded study. *J Res Dent*. 2015;3(4):775-780. doi:10.19177/jrd.v3e42015775-780
25. Christensen K, Daniels S, Bandy D, et al. A double-blind placebo-controlled comparison of a novel formulation of intravenous diclofenac and ketorolac for postoperative third molar extraction pain. *Anesth Prog*. 2011;58(2):73-81. doi:10.2344/0003-3006-58.2.73
26. Daniels SE, Grossman EH, Kuss ME, Talwalker S, Hubbard RC. A double-blind, randomized comparison of intramuscularly and intravenously administered parecoxib sodium versus ketorolac and placebo in a post-oral surgery pain model. *Clin Ther*. 2001;23(7):1018-1031. doi:10.1016/S0149-2918(01)80088-6
27. Fricke JR Jr, Angelocci D, Fox K, McHugh D, Bynum L, Yee JP. Comparison of the efficacy and safety of ketorolac and meperidine in the relief of dental pain. *J Clin Pharmacol*. 1992;32(4):376-384. doi:10.1002/j.1552-4604.1992.tb03850.x
28. Garibaldi JA, Elder MF. Evaluation of ketorolac (Toradol) with varying amounts of codeine for postoperative extraction pain control. *Int J Oral Maxillofac Surg*. 2002;31(3):276-280. doi:10.1054/ijom.2002.0216
29. Mehlisch DR, Desjardins PJ, Daniels S, Hubbard RC. Single doses of parecoxib sodium intravenously are as effective as ketorolac in reducing pain after oral surgery. *J Oral Maxillofac Surg*. 2003;61(9):1030-1037. doi:10.1016/S0278-2391(03)00315-X
30. Mehlisch DR, Desjardins PJ, Daniels S, Hubbard RC. The analgesic efficacy of intramuscular parecoxib sodium in postoperative dental pain. *J Am Dent Assoc*. 2004;135(11):1578-1590. doi:10.14219/jada.archive.2004.0085
31. Nørholt SE, Sindet-Pedersen S, Bugge C, Branebjerg PE, Ersbøll BK, Bastian HL. A randomized, double-blind, placebo-controlled, dose-response study of the analgesic effect of lornoxicam after surgical removal of mandibular third molars. *J Clin Pharmacol*. 1995;35(6):606-614. doi:10.1002/j.1552-4604.1995.tb05018.x
32. Olmedo MV, Gálvez R, Vallecillo M. Double-blind parallel comparison of multiple doses of ketorolac, ketoprofen and placebo administered orally to patients with postoperative dental pain. *Pain*. 2001;90(1):135-141. doi:10.1016/S0304-3959(00)00396-1
33. Trindade PA, Giglio FP, Colombini-Ishikiriama BL, et al. Sublingual ketorolac and sublingual piroxicam are equally effective for postoperative pain, trismus, and swelling management in lower third molar removal. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2012;114(1):27-34. doi:10.1016/j.tripleo.2011.05.027
34. Walton GM, Rood JP, Snowdon AT, Rickwood D. Ketorolac and diclofenac for postoperative pain relief following oral surgery. *Br J Oral Maxillofac Surg*. 1993;31(3):158-160. doi:10.1016/0266-4356(93)90115-D
35. McNicol ED, Ferguson MKC, Schumann R. Single-dose intravenous ketorolac for acute postoperative pain in adults. *Cochrane Database Syst Rev*. 2021;2021(5):CD013263. doi:10.1002/14651858.CD013263.pub2
36. McNicol ED, Rowe E, Cooper TE. Ketorolac for postoperative pain in children. *Cochrane Database Syst Rev*. 2018;7(7):CD012294. doi:10.1002/14651858.CD012294.pub2
37. De Oliveira GS Jr, Agarwal D, Benzon HT. Perioperative single dose ketorolac to prevent postoperative pain: a meta-analysis of randomized trials. *Anesth Analg*. 2012;114(2):424-433. doi:10.1213/ANE.0b013e3182334d68
38. Wan RJ, Liu SF, Kuang ZP, Ran Q, Zhao C, Huang W. Influence of ketorolac supplementation on pain control for knee arthroscopy: a meta-analysis of randomized controlled trials. *Orthop Surg*. 2020;12(1):31-37. doi:10.1111/os.12608
39. Lloyd R, Derry S, Moore RA, McQuay HJ. Intravenous or intramuscular parecoxib for acute postoperative pain in adults. *Cochrane Database Syst Rev*. 2009;(2):CD004771. doi:10.1002/14651858.CD004771.pub4
40. Smith LA, Carroll D, Edwards JE, Moore RA, McQuay HJ. Single-dose ketorolac and pethidine in acute postoperative pain: systematic review with meta-analysis. *Br J Anaesth*. 2000;84(1):48-58. doi:10.1093/oxfordjournals.bja.a013381
41. Nagendrababu V, Pulikkotil SJ, Veettil SK, Teerawattanapong N, Setzer FC. Effect of nonsteroidal anti-inflammatory drug as an oral premedication on the anesthetic success of inferior alveolar nerve block in treatment of irreversible pulpitis: a systematic review with meta-analysis and trial sequential analysis. *J Endod*. 2018;44(6):914-922.e2. doi:10.1016/j.joen.2018.02.017

42. Gobble RM, Hoang HLT, Kachniarz B, Orgill DP. Ketorolac does not increase perioperative bleeding: a meta-analysis of randomized controlled trials. *Plast Reconstr Surg*. 2014;133(3):741-755. doi: 10.1097/01.prs.0000438459.60474.b5
43. Davidson JSD, Turner K. Ketorolac does not increase perioperative bleeding: a meta-analysis of randomized controlled trials. *Plast Reconstr Surg*. 2015;135(3):648e-649e. doi:10.1097/PRS.0000000000001046
44. Chan DK, Parikh SR. Perioperative ketorolac increases post-tonsillectomy hemorrhage in adults but not children. *Laryngoscope*. 2014;124(8):1789-1793. doi:10.1002/lary.24555
45. Massó González EL, Patrignani P, Tacconelli S, García Rodríguez LA. Variability among nonsteroidal antiinflammatory drugs in risk of upper gastrointestinal bleeding. *Arthritis Rheum*. 2010;62(6):1592-1601. doi: 10.1002/art.27412

How to cite this article: Isiordia-Espinoza MA, Alonso-Castro ÁJ, Serafín-Higuera N, Castañeda-Santana DI, de la Rosa Coronado M, Bologna-Molina RE. Postoperative administration of ketorolac compared to other drugs for pain control after third molar surgery: A meta-analysis of double-blind, randomized, clinical trials. *Br J Clin Pharmacol*. 2022; 88(6):2591-2604. doi:10.1111/bcp.15241