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Systematic Review

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Ketorolac analgesia in the emergency department in adults: a systematic review and meta-analysis

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Objective Acute painful conditions are a common reason for emergency department (ED) referral, and a broad variety of analgesic drugs can be used. Among them, ketorolac is a nonsteroidal anti-inflammatory drug (NSAID) that has been increasingly used in the past two decades. To clarify the evidence for using ketorolac in EDs, a systematic review and meta-analysis was performed.

Methods A search was performed in PubMed for English-language articles published on or before February 2023. Only randomized controlled trials in adult patients with acute painful conditions treated in an ED were selected. A meta-analysis was performed to evaluate the effectiveness of ketorolac in different pain conditions.

Results Forty randomized controlled trials were selected, including studies focused on acute renal colic, headache, traumatic and nontraumatic musculoskeletal pain, and biliary colic. In these studies, ketorolac was mainly compared to opioids and showed a similar analgesic efficacy. On the other hand, ketorolac does not seem to have a stronger analgesic effect than other NSAIDs.

Conclusion This systematic review indicates that ketorolac may be a valuable alternative to opioids for inducing analgesia in adult ED patients. This meta-analysis showed no significant difference in efficacy between ketorolac and other drugs. Nevertheless, the evidence comparing its efficacy with other common NSAIDs is sparse and should be further explored in future studies.

Keywords Ketorolac; Emergency departments; Pain

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Capsule Summary

What is already known

Ketorolac is a nonsteroidal anti-inflammatory drug (NSAID) that is increasingly used in emergency departments (EDs) to treat acute painful conditions.

What is new in the current study

A meta-analysis was performed to evaluate the effectiveness of ketorolac in different pain conditions: acute renal colic, headache, traumatic and nontraumatic musculoskeletal pain, and biliary colic. In the 40 studies selected, ketorolac showed analgesic efficacy similar to opioids and other NSAIDs. This systematic review indicates that ketorolac could be a valuable alternative to opioids for inducing analgesia in adult ED patients.

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INTRODUCTION

Adequate management of acute pain is one of the main goals of emergency department (ED) care. Various analgesic drugs are currently available in this clinical setting, with nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids the most frequently used. Among NSAIDs, ketorolac has emerged as a potent analgesic that inhibits cyclo-oxygenase I and II and reduces prostaglandins, prostacyclin, and thromboxane synthesis, producing analgesic and anti-inflammatory effects. It is commonly used for short-term management of severe acute pain in adults [1]. Although its use in patients younger than 16 years is still off-label, several studies have demonstrated its efficacy and safety in children in EDs [2–4]. A recent systematic review addressed this topic, but clear evidence supporting the effectiveness of ketorolac remains limited due to the small number of available studies. Ketorolac generally performed at a level comparable to other drugs [5].

Previous systematic reviews have focused on ketorolac use for specific acute painful conditions, such as migraine or renal colic [6–8]. Although ketorolac appears comparable to other pharmacological agents for migraine treatment [6,9], it showed greater efficacy for renal colic in a 2021 meta-analysis and performance similar to ibuprofen in a 2023 meta-analysis [8,10]. However, conditions that are frequently managed in the ED, such as musculoskeletal pain (traumatic and nontraumatic) and biliary colic, remain unexplored.

Consequently, clear recommendations have yet to be established to support or discourage ketorolac use in those broader contexts. Moreover, to the best of our knowledge, no systematic review has comprehensively examined the use of ketorolac in the ED setting across a range of conditions.

Therefore, we systematically reviewed the literature to find evidence for the effectiveness of ketorolac in adult patients presenting to an ED for various pain-related conditions. By including a broad spectrum of clinical scenarios that might potentially be managed with ketorolac, we seek to provide a comprehensive overview. Additionally, we performed a meta-analysis to evaluate the efficacy of ketorolac in different conditions.

METHODS

This systematic review was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A literature search up to February 2023 was performed in the PubMed electronic database using the terms "ketorolac" and "emergency department." All returned papers that were written in English and available in full-text form were screened, but only randomized controlled trials (RCTs) comparing the efficacy of ketorolac with that of other drugs for managing pain, whatever the cause, in adult ED populations (>16 years) were included. Case series, cohort studies, cross-sectional studies, uncontrolled studies, and reviews were excluded.

Two authors independently assessed the potential eligible studies and selected those that met the inclusion criteria. Any discrepancies were resolved by consensus or by involving a third author.

The original search returned 228 items with 1 duplicate. After manual screening, 187 were excluded: 152 for being irrelevant to the scope of the review, 27 for not being RCTs, and 8 for involving pediatric subjects. Ultimately, 40 research articles met the inclusion criteria and are reviewed here (Fig. 1).

The following information was collected from each selected study: study design, sample size, age of participants, type of pain, type of intervention, study outcomes, and key results (mainly median with interquartile range and mean±standard deviation of pain assessment). All the information was collected in an electronic sheet specifically developed for this study.

The comparison drugs used in the studies were morphine, ibuprofen, ketamine, metoclopramide, valproate, diphenhydramine, prochlorperazine, chlorpromazine hydrochloride, meperidine plus

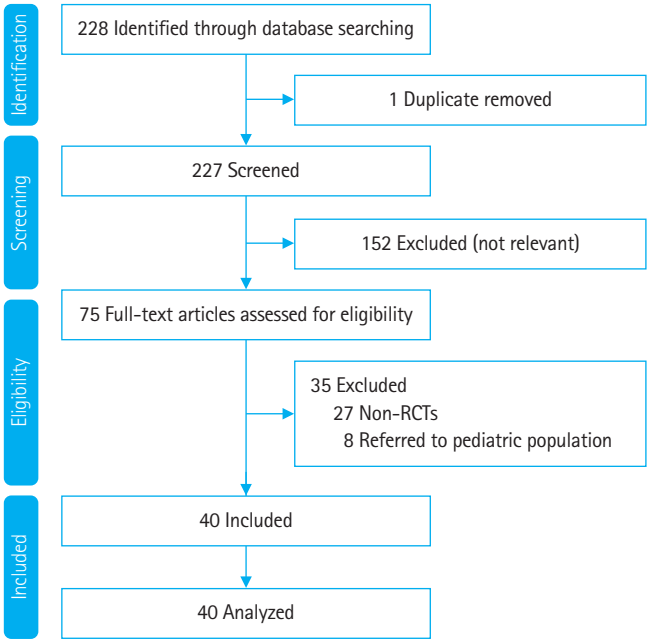

Fig. 1. PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) flow diagram of the selection process. RCT, randomized controlled trial.

promethazine, meperidine plus hydroxyzine, lidocaine, desmopressin, diclofenac, acetaminophen, codeine, butorphanol, and meperidine.

Meta-analysis

The metafor and dmetar packages in RStudio (Posit) were used to perform the meta-analysis. Effect sizes were estimated using the "escalc" function and expressed as standardized mean differences (SMDs), calculated from changes in pain scores from baseline (pain score reductions). Random-effects models were fitted using the rma function with restricted maximum likelihood estimation. The influence analysis was conducted using the "influence" function, and outliers were identified with the "find.outliers" function. The studies were divided based on the types of drugs analyzed within each group and then by route of ketorolac administration.

The US National Heart, Lung, and Blood Institute (NHLBI) Study Quality Assessment of Controlled Intervention Studies was used to grade the risk of bias [11], which was visualized using the "robvis" online tool. Two authors examined the articles and categorized each item on the risk-of-bias scale as low (numeric value, 0), moderate (numeric value, 1), high (numeric value, 2), critical (numeric value, 3), or not informative. The sum of all items for each article was categorized as low (range, 0–10), moderate (range, 11–21), high (range, 22–31), or critical (range, 32–42).

The judgments used to inform the recommendation were structured using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) evidence-to-decision framework [12].

RESULTS

Acute renal colic

We included 14 trials focused on analgesia in adult patients with acute renal colic (Table 1) [13–26]. These trials included 1,776 patients aged 18 to 80 years. Ketorolac was administered intravenously in 11 trials [13–15,19–26] and intramuscularly in the remaining 3 trials [16–18].

Four trials compared intravenous ketorolac with intravenous morphine alone or in combination with other drugs (ibuprofen, butylscopolammonium bromide, or ketorolac itself) [13,24–26]. In one trial, the combination of 800 mg of intravenous ibuprofen and 5 mg of intravenous morphine and the combination of 30 mg of intravenous ketorolac and 5 mg of intravenous morphine were similarly effective and more effective than 5 mg of morphine alone [13]. Moreover, the combination of 0.1 mg/kg of intravenous morphine and 30 mg of ketorolac was superior to both single drugs alone [24]. In the same way, the combination of 5 mg of intravenous morphine and 15 mg of intravenous ketorolac was more effective than either drug alone [26]. On the contrary, 5 mg of intravenous morphine alone was as effective as an intravenous combination of 5 mg of morphine, 30 mg of ketorolac, and 20 mg of butylscopolammonium bromide [25].

One trial compared 0.6 mg/kg of intravenous ketamine and 30 mg of intravenous ketorolac and reported that the analgesic effects of the two regimens were similar at 5, 15, 30, 60, and 120 minutes after administration [19]. However, patients in the ketamine group experienced significantly more frequent side effects.

One trial reported that 800 mg of intravenous ibuprofen was more effective than 30 mg of intravenous ketorolac in reducing renal colic pain [20].

The combination of 30 mg of intravenous ketorolac and 50 mg/kg of intravenous magnesium sulphate was not more effective than ketorolac alone [22]. In the same way, the combination of 30 mg of intravenous ketorolac and 0.125 mg of hyoscyamine did not produce any additive effect over ketorolac alone [15].

A dose of 40 μg of intranasal desmopressin was less effective than 30 mg of intravenous ketorolac [23].

One trial compared doses of intravenous ketorolac and reported that 10, 20, and 30 mg were equally effective in decreasing pain related to renal colic [14].

In three trials that administered ketorolac through the intramuscular route, 60 mg was more effective than 100 and 150 mg of intramuscular meperidine [16] and as effective as 75 mg of intramuscular diclofenac [18]. In the third study, 30 mg of intramuscular ketorolac had the same efficacy as 75 mg of intramuscular diclofenac [17].

Collectively, the available results are inconclusive in establishing the intensity of ketorolac effects compared to those of other therapeutic agents. Consequently, we conducted a meta-analysis to statistically aggregate and compare the findings systematically. Only the studies by Sotoodehnia et al. [19], Forouzanfar et al. [20], Motov et al. [21], Maleki Verki et al. [22], Arhami Dolatabadi et al. and Cohen et al. [17] were included in the meta-analysis.

The results indicate no different effectiveness of ketorolac over that of the other drugs (estimated coefficient, −0.09; 95% confidence interval [CI], −1.11 to 0.93; $P > 0.05$; $I^2 = 84.73\%$; $H^2 = 6.55$) (Fig. 2A, Suppl. 1) [17,19–21,23]. No outlier was identified (Suppl. 2).

Headache

Ten RCTs focused on treatment of headache in adult patients comprised of 942 subjects from 18 to 65 years old (Table 2) [27–36].

Table 1. Acute renal colic

Study	Study design	No. of patients	Age (yr)	Clinical condition	Intervention	Outcome	Key results	Comment
Safaie et al. [13] (2022)	Double-blind RCT	195	18–65	Acute renal colic with moderate to severe pain	5 mg IV morphine with 800 mg IV ibuprofen vs. 5 mg IV morphine with 30 mg IV ketorolac vs. 5 mg IV morphine	Primary: pain score reduction at 30 min Secondary: pain score reduction at 60 and 120 min; adverse events; rescue analgesia; duration of hospitalization	Pain score reduction in ibuprofen and ketorolac group was significantly greater than morphine alone group ($P<0.001$), but the difference between pain scores reduction among ibuprofen and ketorolac group was not statistically significant ($P=1.0$) No difference in adverse events	The efficacy of ketorolac+morphine and ibuprofen+morphine in the reduction of pain was similar in patients with acute renal colic
Eidinejad et al. [14] (2021)	Double-blind RCT	165	18–65	Acute severe flank or abdominal pain considered related to renal colic	10 mg vs. 20 mg vs. 30 mg IV ketorolac	Primary: pain scores 30 min after ketorolac administration Secondary: pain scores at 15, 45, and 60 min; adverse events; need for rescue treatment	Pain scores were not statistically different among the groups Headache was more frequently observed in the 30 mg group	Administration of 10 mg IV ketorolac was comparable to higher doses in patients with renal colic
Sotoodehnia et al. [19] (2019)	Double-blind RCT	126	>18	Suspected acute renal colic	0.6 mg/kg IV ketamine vs. 30 mg IV ketorolac	Primary: comparison of pain reduction between the two groups, using the NRS at 5, 15, 30, 60, and 120 min after administration Secondary: adverse reactions	No significant difference in the mean pain scores at any different time points between the two groups ($P>0.05$). The pain severity decreased significantly in both groups over time ($P<0.001$) The rate of side effects was significantly higher in the ketamine group for dizziness and blood pressure rising ($P=0.001$)	Low-dose IV ketamine was as effective as IV ketorolac in pain management, but its use was associated with a higher rate of side effects
Forouzanfar et al. [20] (2019)	Double-blind RCT	240	18–65	Acute renal colic	30 mg IV ketorolac or 800 mg IV ibuprofen	Primary: comparison of pain reduction, success defined as relief of 3 points based on VAS score at 15, 30, and 60 min after administration Secondary: treatment failure and need for rescue medication	Pain severity in the ketorolac group was significantly higher than the group receiving ibuprofen (all $P<0.0001$) Rate of success in reducing pain severity by at least 3 points was significantly higher in the group receiving IV ibuprofen compared with IV ketorolac group ($P<0.0001$)	Ibuprofen was superior to ketorolac in controlling renal colic pain
Motov et al. [21] (2020)	Double-blind RCT	150	18–64	Suspected renal colic	1.5 mg/kg IV lidocaine vs. 30 mg IV ketorolac vs. 1.5 mg IV lidocaine + 30 mg IV ketorolac	Primary: difference in pain scores between the three groups at 30 min with recorded difference up to 60 min Secondary: comparative reduction in pain scores in each group from baseline to 30 and 60 min; rates of adverse events; need for rescue analgesia at 30 and 60 min	The difference in mean pain scores at 30 min between lidocaine and lidocaine/ketorolac groups was −2.89 (95% CI, −4.39 to −1.39) favoring the combination group; between ketorolac and lidocaine/ketorolac groups was −0.92 (95% CI, −2.44 to 0.61); and between ketorolac and lidocaine groups was −1.98 (95% CI, −3.69 to −0.27) favoring ketorolac group	The administration of a combination of IV lidocaine and ketorolac was equally effective compared to ketorolac alone and more effective compared to lidocaine alone
Maleki Verki et al. [22] (2019)	Double-blind RCT	88	18–65	Acute renal colic	30 mg IV ketorolac vs. 30 mg IV ketorolac + 50 mg/kg IV magnesium sulphate 50%	Primary: pain scores after 15 and 30 min	Pain scores were statistically similar between the groups	Adding magnesium sulphate to ketorolac did not cause a significant increased analgesic effect in patients with renal colic

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Table 1. (Continued)

Study	Study design	No. of patients	Age (yr)	Clinical condition	Intervention	Outcome	Key results	Comment
Arhami Dolatabadi et al. [23] (2017)	Double-blind RCT	40	16–50	Acute renal colic	40 μg intranasal desmopressin vs. 30 mg IV ketorolac	Primary: severity of pain according to VAS score 10, 30, and 60 min after drug administration (significant if decreasing of 3 or more scores) Secondary: need for rescue therapy	The mean pain scores at 10, 30, and 60 min in the ketorolac group were significantly lower than in the desmopressin group	Ketorolac was more effective than desmopressin in decreasing pain in patients with renal colic
Hosseininejad et al. [24] (2017)	Triple-blind RCT	300	18–55	Acute renal colic with moderate or severe pain	30 mg IV ketorolac + 0.1 mg/kg IV morphine vs. 0.1 mg/kg IV morphine vs. 30 mg IV ketorolac	Primary: pain scores at 20 and 40 min after intervention; adverse events	Pain intensity was significantly lower in combined analgesia group when compared to morphine or ketorolac alone after 40 min No difference in adverse events	Ketorolac+morphine was more effective compared to single drug therapy in patients with renal colic
Song et al. [25] (2012)	Double-blind RCT	115	>18	Acute renal colic with moderate to severe pain	30 mg IV ketorolac + 5 mg IV morphine vs. 30 mg IV ketorolac + 5 mg IV morphine + 20 mg IV butylscopolammonium bromide	Primary: pain reduction changes between the two groups at 40 min Secondary: rate of change in analgesic response; need for rescue morphine; occurrence of adverse effects	Mean pain reduction difference between groups was −1.2 (95% CI, −2.2 to −0.2; P=0.024) at 40 min The difference was not considered clinically significant since it did not reach the threshold of a 1.8 reduction.	Adding IV butylscopolammonium bromide in patients with renal colic receiving ketorolac+morphine was not useful
Safdar et al. [26] (2006)	Double-blind RCT	130	18–55	Acute renal colic with moderate to severe pain	5 mg IV morphine vs. 15 mg IV ketorolac vs. 5 mg IV morphine + 15 mg IV ketorolac	Primary: pain reduction at 40 min; rescue analgesia of 5 mg morphine; adverse events	No difference in reduction in mean pain scores between the morphine and ketorolac groups Mean difference in pain was conversely significant between the combination and morphine and ketorolac groups alone (P<0.003) Combination therapy was significantly less likely to require rescue morphine Adverse events were more frequent in the morphine group	Combining ketorolac and morphine provided more effective pain relief, reducing the need for rescue analgesia, in patients with renal colic
Jones et al. [15] (2001)	Double-blind RCT	43	≥18	Acute renal colic	30 mg IV ketorolac vs. 30 mg IV ketorolac + 0.125 mg sublingual hyoscyamine sulfate	Primary: change in pain scores from baseline to 30 min; adverse events; rescue medicine	No clinically important difference between the two groups No difference in adverse events No clinically important difference in the percentage of patients requiring rescue analgesia	The use of an anticholinergic compound together with ketorolac did not produce any additive effects in patients with renal colic
Larkin et al. [16] (1999)	Double-blind RCT	70	>18	Acute renal colic	60 mg IM ketorolac vs. 100 mg IM meperidine (if weight <90 kg) or 150 mg IM meperidine (if weight >90 kg)	Primary: comparison of pain reduction, using VAS at 20, 40, 60, and 90 min after administration Secondary: need for rescue medication. time to discharge from the ED	Significantly greater improvement in the pain scores with ketorolac across time at 40, 60, and 90 min (P=0.0002). No difference for rescue medication	IM ketorolac is more effective than IM meperidine in the treatment of renal colic

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Table 1. (Continued)

Study	Study design	No. of patients	Age (yr)	Clinical condition	Intervention	Outcome	Key results	Comment
Cohen et al. [17] (1998)	Double-blind RCT	57	> 18	Suspected renal colic	30 mg IM ketorolac vs. 75 mg IM diclofenac	Primary: pain scores at 1, 2 and 6 hr Secondary: adverse events; rescue therapy	No significant differences between ketorolac and diclofenac in pain scores, need for rescue therapy, or adverse events were found	Ketorolac and diclofenac were equally effective treating pain in patients with renal colic
Stein et al. [18] (1996)	Double-blind RCT	57	18–80	Acute renal colic with moderate to severe pain	60 mg IM ketorolac vs. 75 mg IM diclofenac	Primary: comparison of pain reduction, using 4-point verbal rating scale at baseline, 1 and 2 hr after administration, and at discharge Secondary: adverse events	Significant pain relief achieved in 77.7% with ketorolac and 86.6% with diclofenac at 1 hr (P = 0.4) and 81.4% and 96.6% at 2 hr (P = 0.15); pain relief at discharge was identical (91%) No difference in adverse events	Ketorolac was as effective as diclofenac for pain management in patients with renal colic

RCT, randomized controlled trial; IV, intravenous; NRS, numerical rating scale; VAS, visual analog scale; CI, confidence interval; IM, intramuscular.

Ketorolac was administered intravenously at a dose of 30 mg in five trials [27–31], intramuscularly at a dose of 30 mg in one trial [32], and intramuscularly at a dose of 60 mg in four trials [33–36].

Intravenous ketorolac was compared with 10 mg of intravenous metoclopramide in two trials [28,29], to 0.75 mg/kg of intranasal ketamine in one trial [27], to 1 g of intravenous valproate in one trial [29], to a combination of 20 mg of metoclopramide and 25 mg of diphenhydramine in one trial [30], and to 10 mg of intravenous prochlorperazine in one trial [31].

Intramuscular ketorolac was compared with 25 mg of intravenous chlorpromazine in one trial [33], to a combination of 50 mg of intramuscular meperidine and 25 mg of intramuscular promethazine in one trial [34], to a combination of 75 mg of intramuscular meperidine and 25 mg of intramuscular promethazine in one trial [35], to a combination of 100 mg of meperidine and 50 mg of hydroxyzine in one trial [36], and to 75 mg of meperidine in one trial [32].

The two trials that compared 30 mg of intravenous ketorolac with 10 mg of intravenous metoclopramide reported similar effectiveness after 60 minutes [28,29]. The trial that compared 30 mg of intravenous ketorolac with a combination of 20 mg of intravenous metoclopramide and 25 mg of diphenhydramine reported that the combination was more effective than ketorolac after 60 minutes [30]. The trial that compared 0.75 mg/kg of intranasal ketamine with 30 mg of intravenous ketorolac found that ketorolac was less effective after 30 minutes and more effective after 60 and 120 minutes [27]. The trial that compared 1 g of intravenous valproate and 30 mg of intravenous ketorolac showed that valproate was less effective than ketorolac after 60 minutes [29]. The study that compared 30 mg of intravenous ketorolac with 10 mg of intravenous prochlorperazine reported that prochlorperazine was more effective than ketorolac after 60 minutes [31].

The trial that compared 60 mg of intramuscular ketorolac with 25 mg of intravenous chlorpromazine showed that the two regimens were similarly effective after 120 minutes [32].

Among the four trials that compared intramuscular ketorolac with intramuscular meperidine, alone or in combination with promethazine or hydroxyzine, three showed that ketorolac and meperidine were similarly effective [34–36], and one reported that ketorolac was less effective after 60 minutes [32]. Unlike the other trials, in which the dose of intramuscular ketorolac was 60 mg, Larkin [32] administered it at a dose of 30 mg.

When the meta-analysis was performed to statistically compare the studies, the work by Larkin [32] was excluded due to the

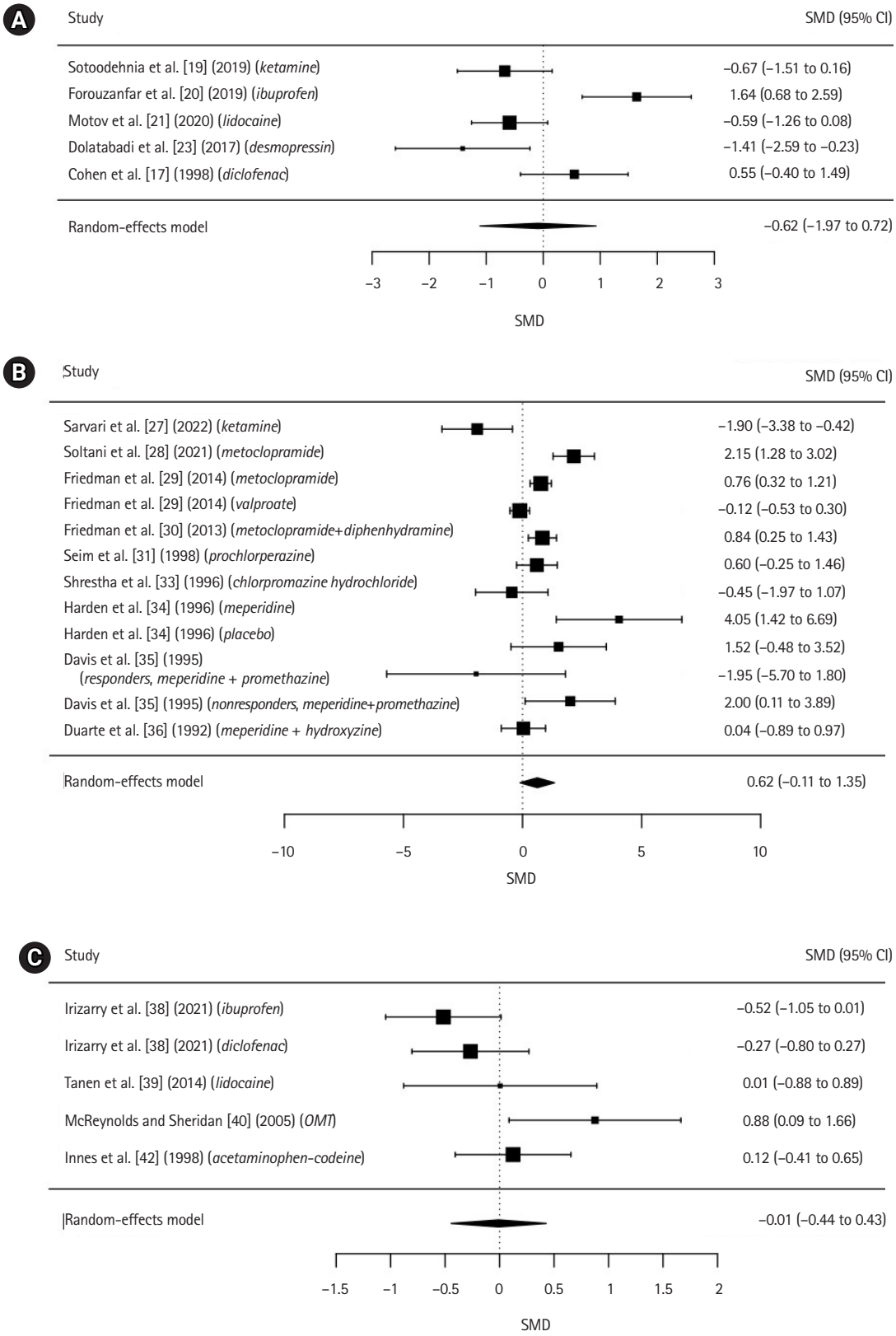

Fig. 2. Forest plot of the meta-analysis for effectiveness of ketorolac versus other drugs in treating painful conditions. Values left of 0 (negative standardized mean difference [SMD]) favor ketorolac. (A) Renal colic. (B) Headache. (C) Nontraumatic musculoskeletal pain. (D) Traumatic musculoskeletal pain. (E) Biliary colic. CI, confidence interval; OMT, osteopathic manipulative treatment.

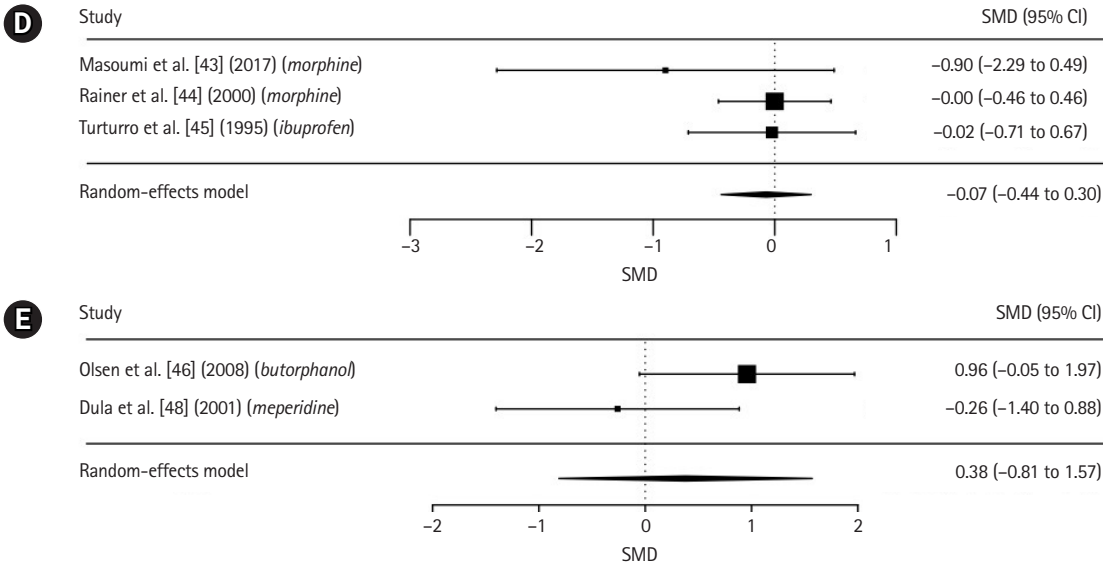

Fig. 2. (Continued).

use of a different pain assessment method than the other studies. The results of the meta-analysis did not demonstrate a clear advantage or inferiority of ketorolac compared with the other therapeutic agents (estimated coefficient, 0.62; 95% CI, −0.11 to 1.35; P > 0.05). Although a trend of minor efficacy for ketorolac was observed, the heterogeneity was medium-high (I^2 = 86.14%, H^2 = 7.21) (Fig. 2B, Suppl. 1, 2) [27–31,33–36].

When assessing outliers, the studies by Sarvari et al. [27] and Harden et al. [34] (only ketorolac vs. meperidine promethazine) were identified and removed. The new results showed that ketorolac was slightly less effective than the other drugs used to treat headaches (estimated coefficient, 0.67; CI, 0.02 to 1.21; P = 0.02; I^2 = 74.13%; H^2 = 3.87).

Nontraumatic musculoskeletal pain

Six RCTs focused on the treatment of nontraumatic musculoskeletal pain, mainly low back pain, in adults, including 683 patients aged 18 to 65 years (Table 3) [37–42]. Ketorolac was administered intramuscularly in three trials [37,40,41], orally in two [38,42], and intravenously in one [39].

One trial investigated the analgesic effect of doses of 15 and 60 mg of ketorolac and showed that they were similarly effective 60 minutes after administration [37]. Another study compared the effect of 30 mg of intramuscular ketorolac with an osteopathic manipulative treatment and showed that the two approaches were similarly effective in pain reduction after 1 hour [40]. When compared with 1 mg/kg of intramuscular meperidine, 60 mg of intramuscular ketorolac had a similar analgesic effect 60 minutes after administration [41].

One trial compared oral administrations of 600 mg of ibuprofen, 50 mg of diclofenac, and 10 mg of ketorolac every 8 hours, as needed, for 5 days [38]. At the scheduled follow-up, no significant difference was found among the three regimens.

Ten milligrams of oral ketorolac every 4–6 hours was about as effective as oral acetaminophen (600 mg) + codeine (60 mg) every 4–6 hours [42].

A trial that compared 100 mg of intravenous lidocaine with 30 mg of intravenous ketorolac showed similar effectiveness after 60 minutes in addressing acute radicular low back pain [39].

Overall, the included studies did not demonstrate a significant difference between ketorolac and other drugs.

The study by Turner et al. [37] was excluded from the meta-analysis because it compared different doses of ketorolac, and the study by Veenema et al. [41] was excluded because it lacked sufficient data for analysis.

The meta-analysis indicated comparable effectiveness between ketorolac and other drugs (estimated coefficient, −0.01; 95% CI, −0.44 to 0.43; P > 0.05), although a high degree of heterogeneity was observed (I^2 = 58.40%, H^2 = 2.40) (Fig. 2C, Suppl. 1) [38–40,42]. No outliers were identified in this analysis (Suppl. 2).

Musculoskeletal trauma

Three RCTs including 318 subjects aged 16 to 70 years focused on pain related to musculoskeletal trauma (Table 4) [43–45]. Two of them administered ketorolac intravenously [43,44], and one used the intramuscular route [45]. Intravenously, ketorolac was admin-

Table 2. Headaches

Study	Study design	No. of patients	Age (yr)	Clinical condition	Intervention	Outcome	Key results	Comment
Sarvari et al. [27] (2022)	Double-blind RCT	140	18–65	Nontraumatic headaches (migraine, tension, and cluster) with moderate to severe pain	30 mg IV ketorolac vs. 0.75 mg/kg intranasal ketamine	Primary: pain scores at 30, 60, and 120 min after intervention Secondary: side effects (fatigue, dizziness, general discomfort, and nausea)	Reduction of pain in the first 30 min was higher in the ketamine group (P = 0.003) At 60 min pain decrease was greater in the ketorolac group (P = 0.005), and also at 120 min (P < 0.001) Side effects were more frequent in the ketamine group	Both drugs effectively and almost similarly reduced patients' headaches, while ketamine in the short term and ketorolac in the long term further reduced the severity of pain
Soltani et al. [28] (2021)	Double-blind RCT	108	18–65	Acute primary (migraine or tension type) headaches with moderate to severe pain	10 mg IV metoclopramide vs. 30 mg IV ketorolac	Primary: improvement of pain scores at 60 min Secondary: adverse effects; rescue therapy	Mean pain scores did not statistically differ between the two groups	Either metoclopramide and ketorolac was an effective therapy in patients with headaches
Friedman et al. [29] (2014)	Double-blind RCT	330	> 18	Acute migraine or acute probable migraine headache as defined by ICHD	1 g IV valproate vs. 10 mg IV metoclopramide vs. 30 mg IV ketorolac	Primary: improvement of headache 1 hr after baseline Secondary: adverse effects; rescue therapy	Patients randomly allocated to valproate improved by 2.8 points (95% CI, 2.3–3.3); those receiving metoclopramide improved by 4.7 points (95% CI, 4.2–5.2); and those receiving ketorolac improved by 3.9 points (95% CI, 3.3–4.5)	Metoclopramide and ketorolac were more effective than valproate in patients with migraine No significant difference was noted between metoclopramide and ketorolac
Friedman et al. [30] (2013)	Double-blind RCT	120	18–65	Headaches not meeting migraine or cluster headache criteria as defined by ICHD	20 mg IV metoclopramide + 25 mg IV diphenhydramine vs. 30 mg IV ketorolac	Primary: difference in the 1-hr change using an 11-point NRS Secondary: medication fulfilment; headache freedom; rescue medication; percentage improvement in pain score	Metoclopramide combination had greater pain relief (improved by a median of 71%; IQR, 35%–100%), compared to ketorolac (improved by a median of 44%; IQR, 23%–83%) Metoclopramidecombination were also more likely to achieve headache freedom, reported wanting the same medication if treated again, and were less likely to ask rescue medication	Tension-type headache or non-migraine, noncluster recurrent headache had more pain relief with metoclopramide+diphenhydramine compared to ketorolac
Seim et al. [31] (1998)	Double-blind RCT	64	18–65	Migraine headaches	10 mg IV prochlorperazine vs. 30 mg IV ketorolac	Primary: changes in pain scores 1 hr after receiving medication	Decrease in pain score was significant for both groups (P = 0.0001) Change in pain score in the prochlorperazine group was significantly greater than ketorolac group (P = 0.04)	Patients with migraine who received prochlorperazine had more advantage than patients receiving ketorolac
Shrestha et al. [33] (1996)	Double-blind RCT	30	18–65	Migraine without aura	60 mg IM ketorolac vs. 25 mg IV chlorpromazine hydrochloride	Primary: pain scores at 30, 60, 90, and 120 min	Comparing the two groups at 2 hr, neither the pain score magnitude (P = 0.36) nor percentage decrease (P = 0.85) were significantly different	IM ketorolac was as effective as IV chlorpromazine hydrochloride in patients with migraine

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Table 2. (Continued)

Study	Study design	No. of patients	Age (yr)	Clinical condition	Intervention	Outcome	Key results	Comment
Harden et al. [34] (1996)	Double-blind RCT	30	18–55	Headache crisis	60 mg IM ketorolac vs. 50 mg IM meperidine + 25 mg IM promethazine vs. IM normal saline	Primary: pain scores after 60 min	Significant pain reduction for each treatment group and no significantly greater reduction in comparison to placebo for either the meperidine group (P=0.49) or ketorolac group (P=0.49)	Ketorolac and meperidine were not more useful than placebo
Davis et al. [35] (1995)	Double-blind RCT	42	18–65	Acute migraine attack	75 mg IM meperidine + 25 mg IM promethazine vs. 60 mg IM ketorolac	Primary: perceived reduction in headache pain and nausea calculated at 30, 60, and 360 min after a single injection	No differences among pain scores were found at any time points	IM ketorolac was as effective as meperidine/promethazine in patients with migraine
Duarte et al. [36] (1992)	Double-blind RCT	47	>18	Acute migraine attack with or without aura	60 mg IM ketorolac vs. 100 mg IM meperidine + 50 mg IM hydroxyzine	Primary: pain scores at 30 and 60 min	Pain scores revealed no significant differences at 30 or 60 min	Ketorolac was as effective as meperidine/hydroxyzine in patients with migraine
Larkin et al. [32] (1992)	Double-blind RCT	31	18–60	Acute attack of classic migraine (with aura) or common migraine (without aura)	75 mg IM meperidine vs. 30 mg IM ketorolac	Primary: pain scores every 15 min to measure pain relief Secondary: adverse events; rescue therapy	Ketorolac was significantly less effective than meperidine in reducing headache pain at 60 min (P=0.02) It was less effective in reducing nausea, photophobia, and the need for rescue medication No difference in side effects	IM ketorolac was less effective than meperidine in the ED treatment of severe migraine

RCT, randomized controlled trial; IV, intravenous; ICHD, International Classification of Headache Disorders; CI, confidence interval; NRS, numeric rating scale; IQR, interquartile range; IM, intramuscular.

Table 3. Nontraumatic musculoskeletal pain

Study	Study design	No. of patients	Age (yr)	Clinical condition	Intervention	Outcome	Key results	Comment
Turner et al. [37] (2021)	Single-blind RCT	110	18–55	Acute musculoskeletal pain and VAS score ≥20/100	15 mg vs. 60 mg IM ketorolac	Change in VAS score after 60 min administration Change in VAS score after 30 min administration; adverse effects	15 mg dose patients had a decrease in pain of 29.7±22.5, while those receiving 60 mg had a decrease of 29.9±23.1 No statistically difference at 30 min Minor adverse effects were more frequent in the 60 mg group (burning at the injection site)	For the primary outcome of pain relief at 60 min, 15 mg of IM ketorolac was noninferior to 60 mg for adults presenting with acute musculoskeletal pain
Irizarry et al. [38] (2021)	Double-blind RCT	198	18–65	Functionally impairing musculoskeletal low back pain, defined as RMDQ score >5	600 mg ibuprofen vs. 10 mg ketorolac vs. 50 mg diclofenac every 8 hr as needed for 5 days, orally	Change in RMDQ score between baseline and the 5-day follow-up Improvement in RMDQ between baseline and 2 days; side effects	Improvement in the median RMDQ score: ibuprofen 11 (IQR, 2–18), ketorolac 14 (IQR, 5–18), and diclofenac 11 (IQR, 4–19) (ANOVA, P=0.34) At 2 days, the RMDQ score favored ketorolac over ibuprofen by 4.3 (95% CI, 1.1–7.5) No stomachache reported by 74% in the ibuprofen arm, 95% in the ketorolac arm, and 91% in the diclofenac arm (P<0.01)	No statistically significant difference between the groups was found The data do not rule out that ketorolac could result in better pain relief and less stomach irritation than ibuprofen

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Table 3. (Continued)

Study	Study design	No. of patients	Age (yr)	Clinical condition	Intervention	Outcome	Key results	Comment
Tanen et al. [39] (2014)	Double-blind RCT	41	18–55	Acute radicular low back pain	100 mg IV lidocaine vs. 30 mg IV ketorolac	VAS score to assess pain at baseline and 20, 40, and 60 min adverse events; rescue therapy	Median VAS scores from baseline to 60 min were significantly reduced within each group, but no difference was found between the degree of reduction between groups (P = 0.835) Rescue medication 67% in lidocaine group vs. 50% in the ketorolac group (not statistically significant, P = 0.350)	IV lidocaine was found to be statistically effective in reducing radicular pain; however, it did not reach the threshold of a 13-mm reduction In addition, 67% of the patients receiving the IV lidocaine required rescue therapy
McReynolds and Sheridan [40] (2005)	RCT	58	18–50	Acute musculoskeletal neck pain < 3 wk duration	30 mg IM ketorolac vs. OMT	Change in NRS-11 pain intensity at 1 hr after treatment	OMT group showed a statistically significant decrease in self-reported pain intensity (P = 0.02; 95% CI, 0.2–1.9) When comparing perceived pain relief at 1 hr, no significant difference	For patients who have contraindications to NSAIDs, OMT is a reasonable treatment alternative
Veenema et al. [41] (2000)	Prospective, double-blind RCT	153	> 18	Low back pain judged to be musculoskeletal in origin	1 mg/kg IM meperidine vs. 60 mg IM ketorolac	Outcomes at 60 min were pain intensity decrease, patient satisfaction, rescue analgesia, sedation level, and adverse effects	Pain reduction of at least 30% occurred in 63% ketorolac group vs. 67% meperidine group (95% CI, 0.43–1.61) Rescue analgesia was required in 35% ketorolac group vs. 37% of meperidine group (95% CI, 0.47–1.74) Patient satisfaction was less in the ketorolac group (95% CI, 0.66– 2.72) Sedation level and adverse effects were significantly greater in the meperidine group	Ketorolac shows comparable single dose analgesic efficacy to a single moderate dose of meperidine with less sedation and adverse effects
Innes et al. [42] (1998)	Multicenter double-blind RCT	123	18–60	Acute musculoskeletal low back pain	10 mg ketorolac orally every 4–6 hr as needed, up to four daily doses vs. 600 mg acetaminophen + 60 mg codeine orally, every 4–6 hr as needed, up to six daily doses	VAS score for the 0–6 hr treatment phase; adverse events; analgesic efficacy, functional capacity, or overall pain relief	Both drugs provided pain relief, with maximal effect 2.2 hr after No significant differences in analgesic efficacy, functional capacity, or overall pain relief Two of 62 (3%) ketorolac patients and 10 of 59 (17%) acetaminophen-codeine patients reported severe adverse events (P = 0.03), especially involving digestive system or nervous system	Both drugs offer substantial and comparable analgesia Ketorolac has the advantage of causing fewer adverse effects

RCT, randomized controlled trial; VAS, visual analog scale; IM, intramuscular; RMDQ, Roland-Morris Disability Questionnaire; IQR, interquartile range; ANOVA, analysis of variance; CI, confidence interval; IV, intravenous; OMT, osteopathic manipulative treatment; NSAID, nonsteroidal anti-inflammatory drug.

Table 4. Traumatic musculoskeletal pain

Study	Study design	No. of patients	Age (yr)	Clinical condition	Intervention	Outcome	Key results	Comment
Masoumi et al. [43] (2017)	Double-blind RCT	88	> 18	Pain secondary to long bones fractures	10 mg IV ketorolac followed by 5 mg every 5 min to 20 min, if VAS ≥ 4 vs. 5 mg IV morphine followed by 2.5 mg every 5 min to 20 min, if VAS ≥ 4	Primary: pain scores at 5, 30, and 60 min	Pain scores were similar between groups	Morphine and ketorolac were equally effective in patients with long bone fractures
Rainer et al. [44] (2000)	Double-blind RCT	148	≥ 16	Limb trauma	10 mg IV loading dose followed by 5 mg every 5 min up to 20 min vs. 5 mg IV morphine loading dose followed by 2.5 mg every 5 min up to 20 min	Primary: pain relief presented as ORs of reaching 50%, 75%, and 100% reduction in pain scores Secondary: adverse events	No statistically significant differences were found Participants were 16 times more likely to develop adverse effects with morphine than with ketorolac	IV ketorolac and IV morphine were equally effective in the management of isolated limb trauma
Turturro et al. [45] (1995)	Double-blind RCT	82	18–70	Acute musculoskeletal pain due to trauma	60 mg IM ketorolac vs. 800 mg oral ibuprofen	Primary: pain scores at 15, 30, 45, 60, 75, 90, and 120 min after dosing; side effects	Mean pain scores did not differ significantly between groups at any time points	IM ketorolac and oral ibuprofen provide similar analgesia in patients with musculoskeletal trauma

RCT, randomized controlled trial; IV, intravenous; VAS, visual analog scale; OR, odds ratio; IM, intramuscular.

istered at an initial dose of 10 mg, followed by 5 mg doses for a total of up to 30 mg, as needed [43,44]. In the trial in which ketorolac was used intramuscularly, it was administered at a dose of 60 mg [45].

Intravenous ketorolac was compared with intravenous morphine in two RCTs [43,44], and intramuscular ketorolac was compared with oral ibuprofen in one RCT [45]. These trials showed that 10 mg of intravenous ketorolac (titrated up to 30 mg, as needed) was as effective as 5 mg of intravenous morphine (titrated up to 15 mg, as needed) in providing pain relief 5 and 30 minutes and 1 hour after administration [43,44]. Moreover, 60 mg of intramuscular ketorolac was as effective as 800 mg of oral ibuprofen 15, 30, 45, 60, 75, 90, and 120 minutes after administration [45].

The meta-analysis confirmed that the effectiveness of ketorolac was comparable to that of morphine and ibuprofen alone (estimated coefficient, −0.07; 95% CI, −0.44 to 0.30; $P > 0.05$). These studies showed low heterogeneity ($I^2 = 0\%$, $H^2 = 1.00$) (Fig. 2D, Suppl. 1) [43–45]. No outlier was identified (Suppl. 2).

Biliary colic

The three RCTs focused on biliary colic in adults included 400 patients aged 18 to 71 years (Table 5) [46–48]. In these trials, ketorolac was administered intravenously in two [46,47] and intramuscularly in one [48].

One trial compared 30 mg of intravenous ketorolac and 1 mg of intravenous butorphanol and showed that the regimens were similarly effective 30 minutes after administration [46]. Another trial compared 30 mg of intravenous ketorolac and 50 mg of intravenous meperidine and showed similar efficacy between the two regimens 30, 60, and 120 minutes after administration [47]. The third trial compared 60 mg of intramuscular ketorolac with 1.5 mg/kg of intramuscular meperidine (maximum, 100 mg), and they were also similarly effective 30 minutes after administration [48].

Overall, the available studies did not demonstrate clear superior effectiveness of ketorolac over other drugs for management of biliary colic; however, only two studies were included in the analysis [46,48].

The results of the meta-analysis similarly indicate no significant difference in potency between ketorolac and the other treatments used for pain associated with biliary colic (estimated coefficient, 0.38; 95% CI, −0.81 to 1.57; $P > 0.05$), with moderate heterogeneity observed ($I^2 = 59.00\%$, $H^2 = 2.44$) (Fig. 2E, Suppl. 1) [46,48]. No outliers were identified (Suppl. 2).

Other conditions

Trials of other conditions are summarized in Table 6 [49–52]. One randomized trial of 101 adult patients (aged 34.8 ± 9.0 years in the ketorolac group and 35.1 ± 10.3 years in the ibuprofen group) with moderate to severe pain of various origins compared 60 mg of intramuscular ketorolac to 800 mg of oral ibuprofen [49]. After 15, 30, 45, 60, 90, and 120 minutes, the decrease in pain scores was similar in the two regimens. In the same way, another trial that enrolled 93 patients aged 18 to 75 years with acute pain of various etiologies compared the analgesic effects of 60 mg of intramuscular ketorolac and 100 mg of intramuscular meperidine [50]. No differences were found in pain scores after 60, 120, and 180 minutes. One trial enrolled 240 patients (18–65 years old) with pain from different origins to investigate the effects of three intravenous doses of ketorolac: 10, 15, and 30 mg [51]. Thirty minutes after administration, the reduction in pain scores was similar for all three doses.

Finally, a trial considering adult subjects with sickle cell–related pain crises investigated whether adding 60 mg of intramuscular ketorolac to a combination of 50 mg of intravenous meperidine and 12.5 mg of intravenous promethazine would improve pain outcomes. Those results showed that adding ketorolac did not provide an advantage in pain scores compared with the control [52].

Due to the heterogeneous conditions analyzed across these studies, no meta-analysis was conducted for this group of RCTs.

Other comparisons

To provide a more comprehensive overview of ketorolac use, two additional sets of comparisons were conducted. The studies were stratified based on type of comparator drug or subclassified according to route of ketorolac administration. Ketorolac demonstrated efficacy superior to that of anesthetic drugs but lower efficacy than antiemetic agents. When comparing the different routes of administration (intramuscular, intravenous, or oral), no significant differences in efficacy were observed among the subgroups. The detailed results of these analyses are presented in Suppl. 3 and Suppl. 4.

Risk of bias and grade of evidence assessments

The risk of bias was low in all the studies included in the meta-analysis (Fig. 3) [17,19–23,27–31,33–36,38–40,42–46,48]. The main issue was limited information regarding power analysis because some studies did not report their sample size calculation.

Funnel plot analysis was performed to assess potential publication bias related to small studies and did not reveal any highly divergent studies (Suppl. 5). The judgments used to inform the recommendation are summarized in the GRADE evidence-to-decision framework in Suppl. 6. The final assessment produced a conditional recommendation for either the intervention or the comparison.

DISCUSSION

This review shows that the effectiveness of ketorolac has been studied in a broad variety of acute painful conditions in the ED setting, with several studies specifically focused on acute renal colic, headache, nontraumatic musculoskeletal pain, traumatic pain, or biliary colic.

In general, ketorolac was compared more frequently with opioids than with other NSAIDs. Among the studies analyzed, only seven (four focused on acute renal colic, one on musculoskeletal pain, one on traumatic pain, and one on pain from various conditions) compared ketorolac with other NSAIDs, namely, ibuprofen and diclofenac. Notably, no RCTs compared ketorolac with other NSAIDs for headaches. Interestingly, none of the reviewed studies showed that ketorolac had better efficacy than other NSAIDs, and that result was confirmed by our meta-analysis.

On the other hand, according to the studies included in this review, ketorolac showed comparable analgesic efficacy to opioids in treating the acute painful conditions analyzed, and the meta-analysis produced the same result. These data confirm that opioids do not seem to be superior to NSAIDs for treatment of headache, acute renal colic, traumatic and nontraumatic musculoskeletal pain, and biliary colic. These results are extremely relevant during the so-called "opioid crisis" that is killing thousands of people every year in the United States [53]. Even though opioids are an evidence-based cornerstone of treatment for patients with postoperative pain or cancer, nonopioid analgesics seem to be just as effective for numerous acute painful conditions treated in EDs [54]. In this sense, the available knowledge should lead to more thoughtful and evidence-based management of prescriptions in clinical ED practice [55].

In the studies analyzed, ketorolac was administered intramuscularly or intravenously. It was not administered intranasally, and only two studies reported oral administration. This finding contrasts with pediatric studies, in which ketorolac is mainly used intranasally and orally [2–4]. Stratifying the studies by route of ketorolac administration revealed no significant differences in its effectiveness compared with other drugs.

In specific painful conditions, ketorolac did not show superior efficacy to a dopamine antagonist for headache, and no studies

Table 5. Biliary colic

Study	Study design	No. of patients	Age (yr)	Clinical condition	Intervention	Outcome	Key results	Comment
Olsen et al. [46] (2008)	Double-blind RCT	46	18–65	Acute upper abdominal pain consistent with biliary colic	30 mg IV ketorolac vs. 1 mg IV butorphanol	Primary: pain scores at 15 and 30 min Secondary: rescue analgesia; side effects	Pain scores improved significantly in both groups; comparing pain relief between ketorolac vs. butorphanol revealed a significant difference (P=0.047) in the 15-min pain scores, but not at 30 min No differences in rescue analgesia request were noted	Both ketorolac and butorphanol provide effective pain relief in patients with biliary colic
Henderson et al. [47] (2002)	Double-blind RCT	324	18–65	Suspected biliary colic	30 mg IV ketorolac vs. 50 mg IV meperidine	Primary: change in 4-point pain scores at 60 min and 120 min Secondary: adverse reaction	No significant difference in pain scores was found between the two groups at 60 and 120 min Meperidine had a significantly higher incidence of both nausea and dizziness	Ketorolac and meperidine were similarly effective in patients with biliary colic
Dula et al. [48] (2001)	Double-blind RCT	30	18–71	Pain consistent with biliary colic	1.5 mg/kg IM meperidine (maximum, 100 mg) vs. 60 mg IM ketorolac	Primary: pain scores at 30 min Secondary: rescue therapy	Pain relief at time 30 min was 3.8±2.6 (95% CI, 2.4–5.2) in the ketorolac group and 3.9±2.5 (95% CI, 2.4–5.3) in the meperidine group (P=0.962) Rescue medication was needed in 28.6% in the meperidine group vs. 12.5% in the ketorolac group (P=0.378)	Ketorolac and meperidine were similarly effective in patients with biliary colic

RCT, randomized controlled trial; IV, intravenous; IM, intramuscular; CI, confidence interval.

Table 6. Other conditions

Study	Study design	No. of patients	Age (yr)	Clinical condition	Intervention	Outcome	Key results	Comment
Motov et al. [51] (2017)	Double-blind RCT	240	18–65	Acute flank pain, abdominal pain, musculoskeletal pain, or headache with moderate to severe pain	10 mg vs. 15 mg vs. 30 mg IV ketorolac	Primary: pain scores at 30 min Secondary: adverse events; rescue analgesia	Reductions in pain scores were statistically significant for all subjects No differences in pain scores were noted between the three groups	10 mg IV ketorolac had equal analgesic power compared to higher doses
Neighbor and Puntillo [49] (1998)	Double-blind RCT	101	>18	Moderate to severe acute pain of various etiologies	60 mg IM ketorolac vs. 800 mg oral ibuprofen	Primary: pain scores at 15, 30, 45, 60, 90, and 120 min	Significant decrease in pain over time in both groups (no differences between groups)	Oral ibuprofen was as effective as parenteral ketorolac
Koenig et al. [50] (1994)	Double-blind RCT	93	18–75	Acute pain of various etiologies	60 mg IM ketorolac vs. 100 mg IM meperidine	Primary: pain scores at 60, 120, 180 min Secondary: levels of sedation	No significant difference was observed between ketorolac and meperidine at any evaluation Ketorolac caused significantly less sedation than meperidine at 60 min (P<0.005), and there was a tendency for less sedation with ketorolac at 120 and 180 min	Ketorolac produced analgesia similar to meperidine with a fewer level of sedation
Wright et al. [52] (1992)	Double-blind RCT	18[a]	>18	Sickle cell crisis pain	60 mg IM ketorolac vs. IM placebo (normal saline) All patients simultaneously received 50 mg IV meperidine and 12.5 mg IV promethazine	Primary: pain scores every 30 min for 4 hr Secondary: rescue therapy with meperidine A 40% reduction in the total narcotic requirement was considered clinically significant	The ketorolac group received an average of 231±92 mg meperidine, whereas the placebo group received an average meperidine dose of 250±85 mg (P=0.61)	The use of intramuscular ketorolac did not lead to a clinically significant reduction in the requirement for narcotics in patients with sickle cell pain crisis

RCT, randomized controlled trial; IV, intravenous; IM, intramuscular.

[a]Patients who presented with sickle cell crisis pain 24 times.

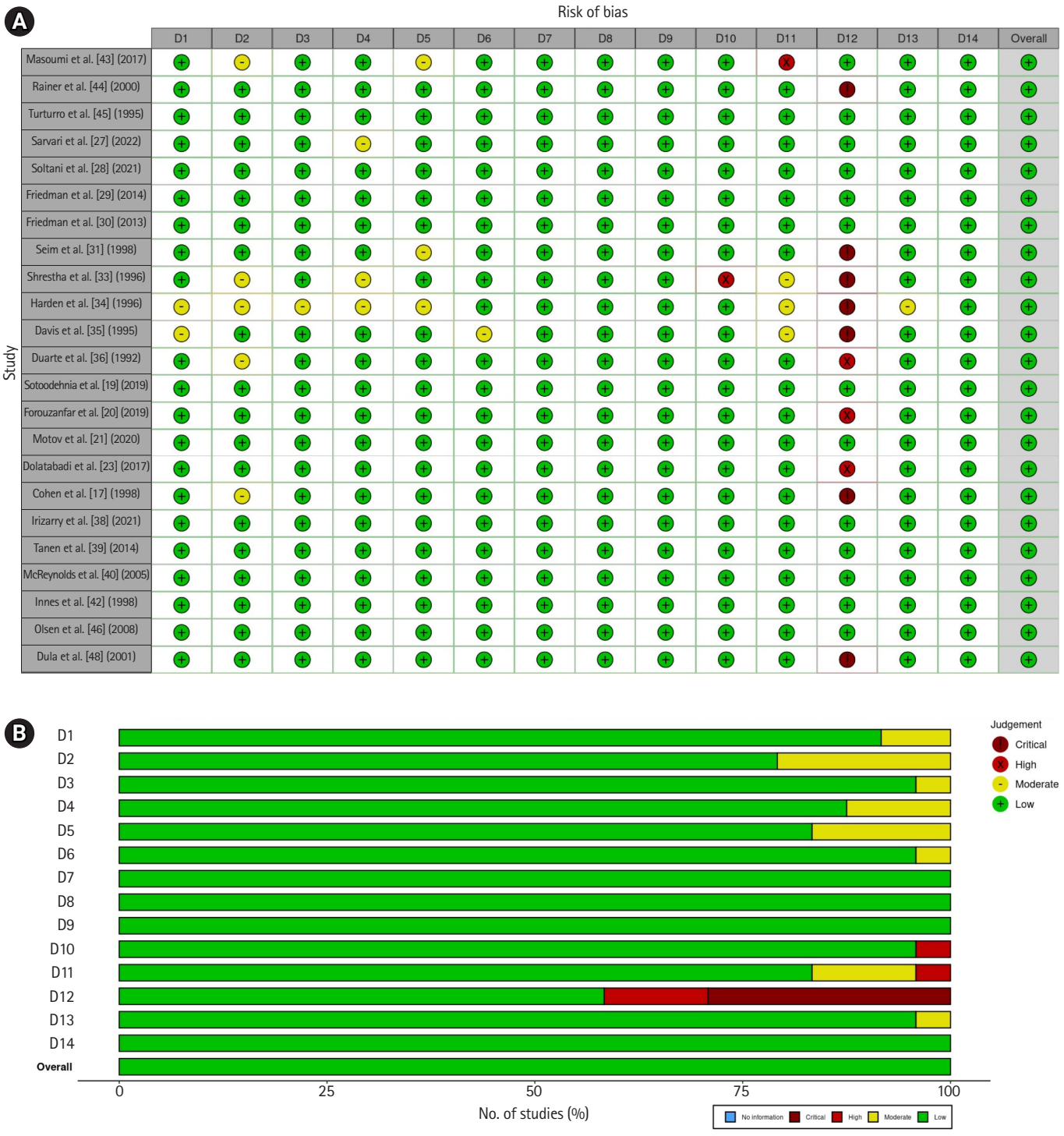

Fig. 3. Risk of bias visualization according to the 14 domains of the US National Heart, Lung, and Blood Institute (NHLBI) Study Quality Assessment Tool for Controlled Intervention Studies. (A) A traffic plot depicting the risk of bias in each study across all questions. (B) The weighted bar plot illustrating the distribution of risk of bias. D1, randomized study design; D2, adequate randomization method; D3, allocation concealment; D4, blinding of participants and providers; D5, blinding of outcome assessors; D6, baseline group similarity; D7, overall dropout rate ≤20%; D8, differential dropout rate ≤15%; D9, adherence to intervention protocols; D10, avoidance of cointerventions; D11, valid and reliable outcome measures; D12, adequate statistical power/sample size; D13, prespecified outcomes or subgroup analyses; D14, intention-to-treat analysis.

comparing ketorolac with other NSAIDs are available for headache. Several studies focused on the painful abdominal conditions of renal and biliary colic. For acute renal colic, which was more extensively studied, ketorolac was as effective as opioids and ketamine but not more effective than other NSAIDs.

The studies of traumatic and nontraumatic musculoskeletal pain report no evidence of ketorolac superiority to ibuprofen, but the number of studies comparing the two drugs was small. In agreement with those observations, our meta-analysis did not reveal superiority of ketorolac over the other drugs tested, indicating that the performance of ketorolac is comparable across various conditions. The risk of bias was evaluated to be low in all the studies included in the meta-analysis.

Limitations

This review has some limitations. First, the search was conducted only in PubMed, and only articles written in English were considered, so we cannot exclude the possibility that some relevant studies might not have been included. Additionally, the included studies displayed considerable heterogeneity, with variability in drug dosing, study conditions, and other factors. Comparisons between regimens were often based on single studies, potentially reducing the strength of the conclusions. This variability is reflected in the heterogeneity metrics of the meta-analysis and might partly account for the lack of significant findings. Given that newer studies often introduce methodological variations, a certain degree of heterogeneity was anticipated. To address this, we reported the heterogeneity metrics, conducted outlier and influence analyses, and repeated our meta-analysis after excluding highly divergent studies. Nevertheless, the risk of bias assessment indicated no studies at high risk, and the funnel plot analysis for small-study effects did not reveal substantial publication bias.

Conclusions

This review highlights ketorolac as a good option for analgesia in the ED setting in several acute painful conditions: renal colic, headache, traumatic and nontraumatic musculoskeletal pain, and biliary colic. The results of the meta-analysis confirm that ketorolac has efficacy comparable to other drugs for management of acute pain in adult ED patients. Future studies are needed to further compare the efficacy of ketorolac with other common NSAIDs frequently prescribed in the ED setting.

ARTICLE INFORMATION

Author contributions

Conceptualization: GC; Data curation: AT, LZ, GC, AA; Formal analysis: AT, LZ, GC, AA; Funding acquisition: LZ; Methodology: GC; Validation: FC, VC, EB; Writing–original draft: AT, LZ, GC, AA; Writing–review & editing: FC, VC, EB. All authors read and approved the final manuscript.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Data availability

Data analyzed in this study are available from the corresponding author upon reasonable request.

Supplementary materials

Suppl. 1. Heterogeneity analysis.
Suppl. 2. Influence analysis.
Suppl. 3. Forest plot of meta-analysis of ketorolac effect versus opioids, NSAIDs, or another drug.
Suppl. 4. Forest plot of meta-analysis of ketorolac effect versus other drugs, classified according to the route of ketorolac administration, intravenous, intramuscular or oral.
Suppl. 5. Funnel plot of the studies included in the meta-analysis.
Suppl. 6. GRADE evidence-to-decision framework.
Supplementary materials are available from https://doi.org/10.15441/ceem.25.002.

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