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REVIEW

Ketorolac use in the emergency department in children: a systematic review and meta-analysis

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Abstract

Acute pain is a frequent reason for pediatric patients visiting the emergency department (ED). Non-steroidal anti-inflammatory drugs (NSAIDs) and opioids are often used to manage pain in this setting. This systematic review and meta-analysis evaluates the effectiveness of ketorolac, a NSAIDs, in managing acute pain in children in the ED, comparing its efficacy and potential advantages over other pain management options. The search was conducted in PubMed and Web of Science, for English-language articles published from 1991 to February 2023. Only randomized controlled trials (RCTs) evaluating the analgesic effect of ketorolac in commonly painful conditions such as migraine, traumatic and non-traumatic musculoskeletal pain, abdominal pain, and renal colic treated in the ED were included. Pediatric studies were specifically selected. A meta-analysis was subsequently conducted to compare efficacy of ketorolac with other analgesic medications. Eight RCTs have investigated the efficacy of ketorolac for acute pain in children in the ED, reflecting limited pediatric evidence. Ketorolac showed variable effectiveness for conditions such as migraine, musculoskeletal trauma, acute abdominal pain, renal colic, and vaso-occlusive crisis in sickle cell disease. The meta-analysis revealed no significant differences in analgesic performance between ketorolac and other drugs, including opioids and other NSAIDs. The risk of bias across the studies was evaluated. However, the evidence remains insufficient to confidently recommend a specific intervention, highlighting the need for further research to guide clinical decision-making.

Conclusion: Despite its limitations, the systematic review highlights that ketorolac seems effective for managing acute pain in pediatric ED patients, but not superior to other analgesic drugs. It emphasizes the necessity for further research to define optimal dosing, administration methods, and its comparative effectiveness with other analgesics across various clinical scenarios.

Keywords Ketorolac · Emergency department · Children

Introduction

Acute pain is a common complaint among pediatric and adult patients in the emergency department (ED) [1, 2]. Adequate analgesia is a crucial treatment goal, however pain management in the ED often remains insufficient [3, 4]. Non-steroidal anti-inflammatory drugs (NSAIDs) and opioids are the class of analgesics most frequently used in this clinical setting. Ketorolac is a potent NSAID employed for the short-term management of severe acute pain in adults. Its analgesic and anti-inflammatory effects stem from its inhibition of cyclo-oxygenase, reducing prostaglandins, prostacyclin, and thromboxane synthesis.

To date, ketorolac is still not labelled for pediatric use, with the exception of short term postoperative pain [5]. Evidence highlights ketorolac's strong efficacy in managing post-operative pain in pediatric patients. However, its role in treating acute pediatric pain in the ED remains largely unexplored [6], warranting further investigation. The side effects of ketorolac include gastritis and increased risk of bleeding, particularly with repeated administrations. Additionally,

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renal adverse effects should be considered. However, unlike opioids, ketorolac, is not associated with respiratory depression, nausea, vomiting, constipation, or, most importantly, tolerance and physical dependence, making it a potentially safer alternative in certain clinical scenarios [6].

The aim of this study is to systematically review the evidence on the use of ketorolac for acute pain in children in ED setting, and conduct a meta-analysis to evaluate its efficacy compared to other analgesic drugs.

Methods

This systematic review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards. Ethical approval was not necessary for this work, due to its literature examination nature.

A literature structured search was conducted in PubMed and Web of Science by using the terms "ketorolac" and "emergency department," and all the research items from 1991 to February 2023 were considered.

Inclusion criteria of the articles were pediatric patients (0–17 years), access to and treatment at the ED, conditions characterized by acute pain, pharmacologic treatment, English language, peer-reviewed papers, and randomized controlled trials (RCTs). Exclusion criteria were adult patients, administration or evaluation of the therapy at home, non-pharmacological treatment, and type of study different from RCT (including case series, cohort, cross-sectional, uncontrolled studies, and reviews).

Two authors (A.T. and L.Z.) independently assessed the research for potentially eligible studies and those that met the inclusion criteria were included. Discrepancies were resolved by consensus or by a third author (F.C.).

Two hundred twenty-eight articles were retrieved. Records not relevant for this review were 152, additionally 27 articles were excluded because they were not RCTs, and 40 were excluded because they referred to adult patients. After this assessment, eight articles were included in this review.

Figure 1 shows the study search flow.

Selected studies were analyzed. From each study, the following information were collected: study design, sample size, age of participants, type of painful condition, type of intervention, study outcomes, and key results. All the data were reported in an electronic sheet specifically developed for this study.

Meta-analysis

The risk of bias was assessed following the 14 questions of the NHLBI (National Heart, Lung and Blood Institute)'s Study Quality Assessment of Controlled Intervention Studies (available at (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools, Table supplementary 1) and visualized by using the "robvis" online tool (available at https://mcguinlu.shinyapps.io/robvis/).

Two authors (A.T., L.Z.) judged the articles categorizing each item of the 14 NHLBI questions (Supplementary Fig. 1) as low (numeric value = 0), moderate (numeric value = 1), high (numeric value = 2), critical (numeric value = 3), or not informative (numeric value = 3). The mean evaluation between the two authors was calculated. To display a numeric "overall classification" the sum of all items was classified as follow: low = 0–10 (0–25%), moderate = 11–21 (25–50%), high = 21–31 (50–75%), and critical = 32–42 (75–100%).

The articles fulfilling the inclusion criteria and with low risk of bias were eligible for the meta-analysis.

Meta-analysis was performed in Rstudio (available at https://posit.co/download/rstudio-desktop/) using the "metafor" package (available at https://www.metafor-project.org/doku.php/metafor).

Due the high heterogeneity of the studies, the random-effects (RE) model was selected to conduct the analysis within "metacont" function considering mean difference "MD" measure. The I^2 (total heterogeneity/total variability) and τ^2 (estimated amount of total heterogeneity) metrics were employed to evaluate heterogenicity.

To identify the influence of individual studies on the overall results of a meta-analysis, the "influence.analysis" tool was employed ("dmetar" package) (available at URL http://dmetar.protectlab.org/).

The efficacy of ketorolac in reducing pain level was assessed by comparing its administration to all the other drugs used in the included study. Additionally, a subgroup analysis was conducted categorizing the studies based on the condition treated, such as musculoskeletal trauma, migraine, abdominal pain, and sickle cell vaso-occlusive crises, as well as the comparison drugs including, other NSAIDs, or opioids.

The grade of evidence was assessed following the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework (detailed information can be found at guidelinedevelopment.org/handbook).

Results

Eight RCTs explored ketorolac's efficacy for acute pain in children in the ED and are summarized in Table 1.

The analyzed studies included a total of 941 children and adolescents, with a number of enrolled patients in each trial ranging from 29 to 212. The minimum age of enrolled children was 4 years, and the maximum age was 18 years.

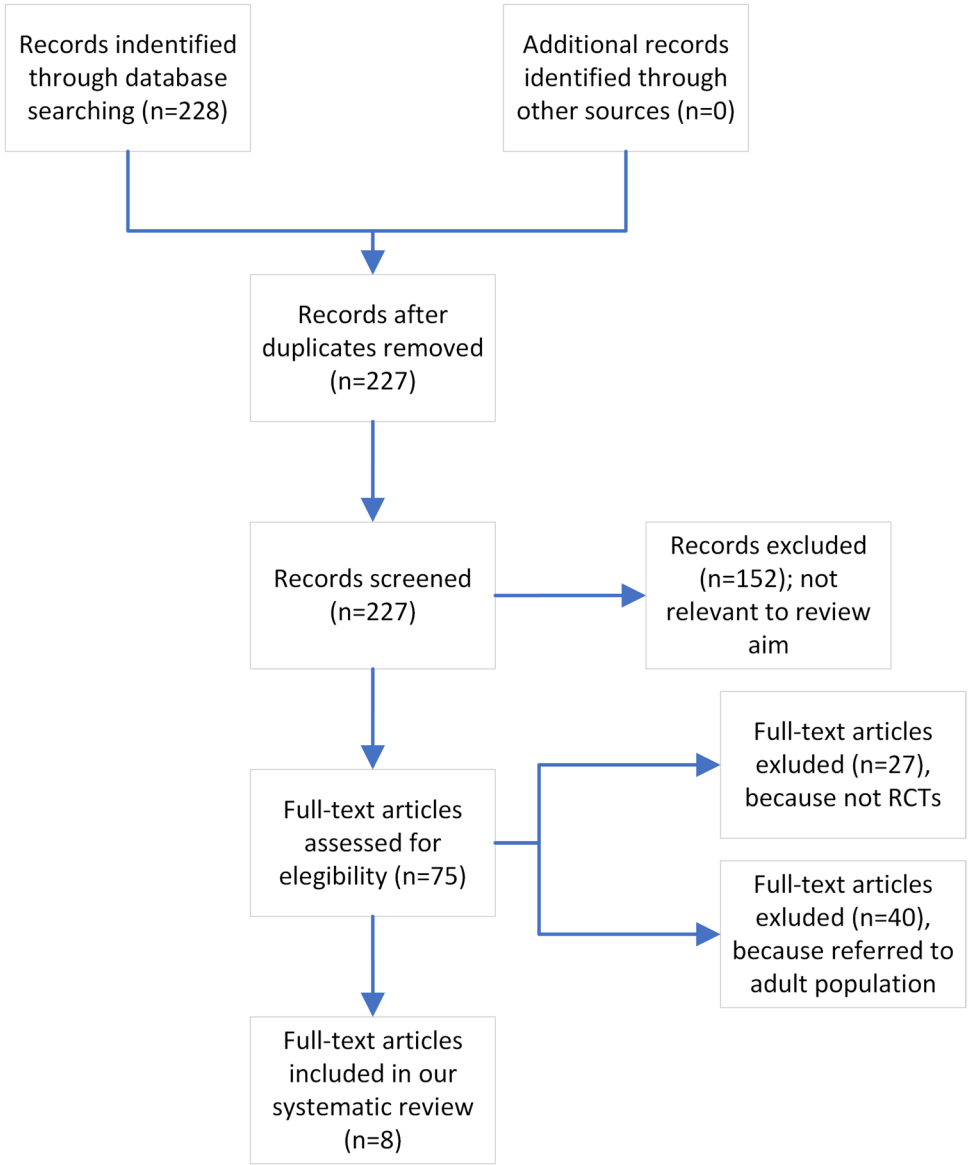

Fig. 1 Flow diagram of the selection process. RCT, randomized controlled trial

Three RCTs were focused on migraine [7–9], two on musculoskeletal trauma [10, 11], one on renal colic [12], one on acute abdominal pain [13], and one on acute vaso-occlusive crisis in sickle cell disease [14].

The route of administration of ketorolac was intravenous in five RCTs [7–9, 12, 14], sublingually in two RCTs [11, 13], orally in one RCT [10], and intranasally in another one [7].

Among trials, the dosage of ketorolac ranged between 0.5 and 1 mg/kg.

Ketorolac was compared to sublingual tramadol in two RCTs [11, 13], to oral ibuprofen [10], nebulized fentanyl [12], sublingual paracetamol [13], and intravenous prochlorperazine [9] in one. A single trial compared the combination of intravenous ketorolac and metoclopramide to metoclopramide alone [8]. Another one compared the combination of intravenous ketorolac and morphine to intravenous morphine alone [14]. One trial compared intranasal to intravenous ketorolac [7].

When looking at the potential risk of bias, all the studies were classified in the "low" range (Supplementary Fig. 1). No critical information was missing. Overall, all the RCT described accurately the randomization procedure, the statistical power calculation; moreover, the blinding of the participants and medical staff was asserted. Drop-out was negligible in all studies. Therefore, all the studies are eligible for the following meta-analysis.

In the three RCTs focused on the treatment of migraine, ketorolac was employed intravenously at a dose of 0.5 mg/kg, alone or in combination with metoclopramide [8] and compared to 1 mg/kg intranasal ketorolac [7], 0.2 mg/kg intravenous metoclopramide alone [8], or 0.15 mg/kg

Table 1 Pediatric

Citation	Study type	Study group	Clinical condition	Intervention	Outcomes	Key results	Comment
Ghirardo et al. (2023) [10]	Double-blind RCT	212 children aged 8–17 years	Limb trauma	Ibuprofen (10 mg/kg) vs ketorolac (0.5 mg/kg), orally	Primary: NRS-11 score reduction at 60 min Secondaries: NRS-11 score reduction at 30–60-120 min; NRS-11 score < 4; NRS-11 reduction > 3 points at each time point; rescue analgesics	No difference	Oral ketorolac was not superior to oral ibuprofen in children with severe acute traumatic pain
Tsze et al. (2022) [7]	Double-blind RCT	58 children aged 8–17 years	Migraine with self-reported pain score of ≥ 4/10	Ketorolac 1 mg/kg intranasal vs. ketorolac 0.5 mg/kg intravenous	Primary: difference in pain intensity reduction 60 min after administration, measured using the Faces Pain Scale-Revised (FPS-R) Secondaries: difference in pain intensity reduction 10, 30, and 120 min after administration; time to onset of clinically meaningful reduction in pain	Intranasal ketorolac was non-inferior to intravenous ketorolac at 30, 60, and 120 min No difference in the other outcomes	Intranasal ketorolac was non-inferior to intravenous ketorolac in children with migraine

Table 1 (continued)

Citation	Study type	Study group	Clinical condition	Intervention	Outcomes	Key results	Comment
Richer et al. (2022) [8]	Double-blind RCT	53 children aged 6–17 years	Migraine, meeting the International Classification of Headache Disorders, 2nd edition	0.2 mg/kg intravenous metoclopramide vs. 0.2 mg/kg intravenous metoclopramide with 0.5 mg/kg intravenous ketorolac	Primary: mean change in pain intensity from baseline to 120 min after study drug administration, using the VAS or FPS-R according with patients' age Pain freedom; headache relief; nausea; emesis; rescue medication	The mean pain difference at 120 min was − 44 mm (SD: 24, 95% CI: 32–57) for the metoclopramide group and − 36 mm (SD 24, 95% CI 23–49) for the metoclopramide + ketorolac group The difference between groups was not statistically significant No evidence of a statistically significant difference between groups for any of the secondary outcomes	Children treated with metoclopramide for migraine did not have any advantage adding ketorolac
Rezaei et al. (2021) [12]	Double-blind RCT	186 children aged over 12 years	Acute renal colic	3 µg/kg nebulized fentanyl vs. 0.9 mg/kg intravenous ketorolac	Primary: comparison of pain reduction between the two groups, using numeric pain rating scale (NPRS) before the commencement of the treatment, at the time of drug administration, and at 15, 30, 45, 60, 75, 90, 105, and 120 min after the administration	Ketorolac: pain decreased by 57% at 60 min and by 91.26% at 120 min Fentanyl: pain decreased by 70.33% at 60 min and by 91.60% at 120 min Patients with complete pain relief were significantly higher in the ketorolac group (p-value < 0.001)	Both intravenous ketorolac and nebulized fentanyl were able to significantly reduce the severity of pain in children with renal colic
Cozzi et al. (2019) [13]	Single-blind RCT	210 children aged 4–17 years	Moderate-to-severe acute abdominal pain	0.5 mg/kg sublingual ketorolac vs. 2 mg/kg sublingual tramadol vs. 20 mg/kg melt in the mouth powder paracetamol	Primary: Self-reported pain after 120 min Pain scores at 30 and 60 min; number of complicated cases of appendicitis; adverse events	No statistically significant differences of pain scores between the three groups	Sublingual analgesia with ketorolac and tramadol was similarly effective in children with acute abdominal pain, and similar to analgesia provided by a melt in the mouth power of paracetamol

Table 1 (continued)

Citation	Study type	Study group	Clinical condition	Intervention	Outcomes	Key results	Comment
Neri et al. (2013) [11]	Double-blind RCT	131 children aged 4–17 years	Limb trauma, with moderate-to-severe pain	0.5 mg/kg sublingual ketorolac *vs* 2 mg/kg sublingual tramadol	Primary: Comparison of pain reduction between the two groups, using VAS pain scale or analogue McGrath-type scale every 20 min Secondaries: Need for rescue therapy after 120 min Adverse effects	No statistically significant difference in pain scores between groups	Both ketorolac and tramadol were effective for the treatment of acute traumatic pain
Brousseau et al. (2004) [9]	Double-blind RCT	62 children aged 5 to 18 years	Migraine according to Prensky and Sommer criteria	0.5 mg/kg intravenous ketorolac *vs* 0.15 mg/kg intravenous prochlorperazine	Primary: reduction of 50% or greater in the child's Nine Faces Pain Scale score at 30 or 60 min Secondaries: Need for rescue therapy Adverse effects	Treatment success at 60 min was significantly higher in prochlorperazine group (84.8% vs 55.2%). In addition, greater number of children reported the lowest possible pain score at 60 min with prochlorperazine	There was a significantly greater treatment success rate and a greater reduction in pain score with IV prochlorperazine compared to ketorolac
Hardwick Jr et al. (1999) [14]	Double-blind RCT	29 children aged 5 to 18 years with 41 episodes	Acute vaso-occlusive pain crisis	0.9 mg/kg intravenous ketorolac *vs* placebo All patients received IV fluids and an initial 0.1 mg/kg of intravenous morphine. More doses of morphine were given every 2 ho over a 6-h observation	Primary: 50% reduction in the total morphine requirement over 6-h observation	Ketorolac group received 0.28 ± 0.08 mg/kg of morphine, while placebo group received 0.32 ± 0.08 mg/kg ($p = 0.118$)	Children with vaso-occlusive crisis treated also with ketorolac did not have any advantage compared to children treated with morphine alone

intravenous prochlorperazine [9]. These trials showed that the intranasal administration of ketorolac was non-inferior to intravenous ketorolac considering pain scores at 30, 60, and 120 min after the administration [7–9]. On the other hand, the administration of ketorolac in combination with metoclopramide did not provide statistically significant changes in pain scores 120 min after the administration [8]. Finally, intravenous prochlorperazine was significantly more effective than intravenous ketorolac in decreasing headache 60 min after administration [9].

Considering musculoskeletal trauma, ketorolac was tested through the oral and sublingual route [10, 11]. One trial compared 0.5 mg/kg oral ketorolac and 10 mg/kg oral ibuprofen in children with severe pain and showed that pain scores were similar 30, 60, and 120 min after administration [10]. Another trial comparing 0.5 mg/kg sublingual ketorolac and 2 mg/kg sublingual tramadol showed a similar reduction in pain scores after 30, 60, and 120 min [11].

A single trial investigated the efficacy of ketorolac for acute abdominal pain in children [13]. In this trial, 0.5 mg/kg sublingual ketorolac was compared to 2 mg/kg sublingual tramadol or to 20 mg/kg of a melt in mouth powder of paracetamol. This trial showed that the three regimens were similarly effective.

The trial focused on children with acute renal colic compared intravenously administered ketorolac (0.9 mg/kg) with 3 mcg/kg nebulized fentanyl and showed that both regimens were able to decrease the intensity of pain at 60 and 120 min [12]. The number of patients with complete pain relief were significantly more in the ketorolac group.

Finally, the trial performed in children with an acute vaso-occlusive crisis in sickle cell disease showed that the combination of intravenously 0.5 mg/kg of ketorolac with 0.1 mg/kg morphine did not provide a superior analgesia compared to the administration of morphine alone [14].

Regarding the meta-analysis, due to the low number of RCT studies available on pediatric patients, the efficacy of ketorolac was evaluated using the random-effects (RE) model. Three studies were excluded from the meta-analysis, Richer et al., since it used a combination of ketorolac and metoclopramide, and Razaei et al., since it included adult patients and did not divide the pediatric results separately, and Tsze et al. because they compared different routes of ketorolac administration.

No major analgesic effect was observed for ketorolac with respect to the other drugs, opioid (RE model, MD = 0.24, 95% CI − 0.37; 0.84) and other NSAID (RE model, MD = 0.48; 95% CI − 0.14; 1.10). Overall, there was also not a different effect between ketorolac and other drugs (RE model, MD = 0.27, 95% CI − 0.57; 1.11). The heterogenicity was low between the studies employing opioid ($I^2 = 0\%$, $\tau^2 = 0$), medium between the studies using NSAID ($I^2 = 41\%$, $\tau^2 = 0.13$), and medium–high across all the studies ($I^2 = 73\%$, $\tau^2 = 1.00$) (Fig. 2).

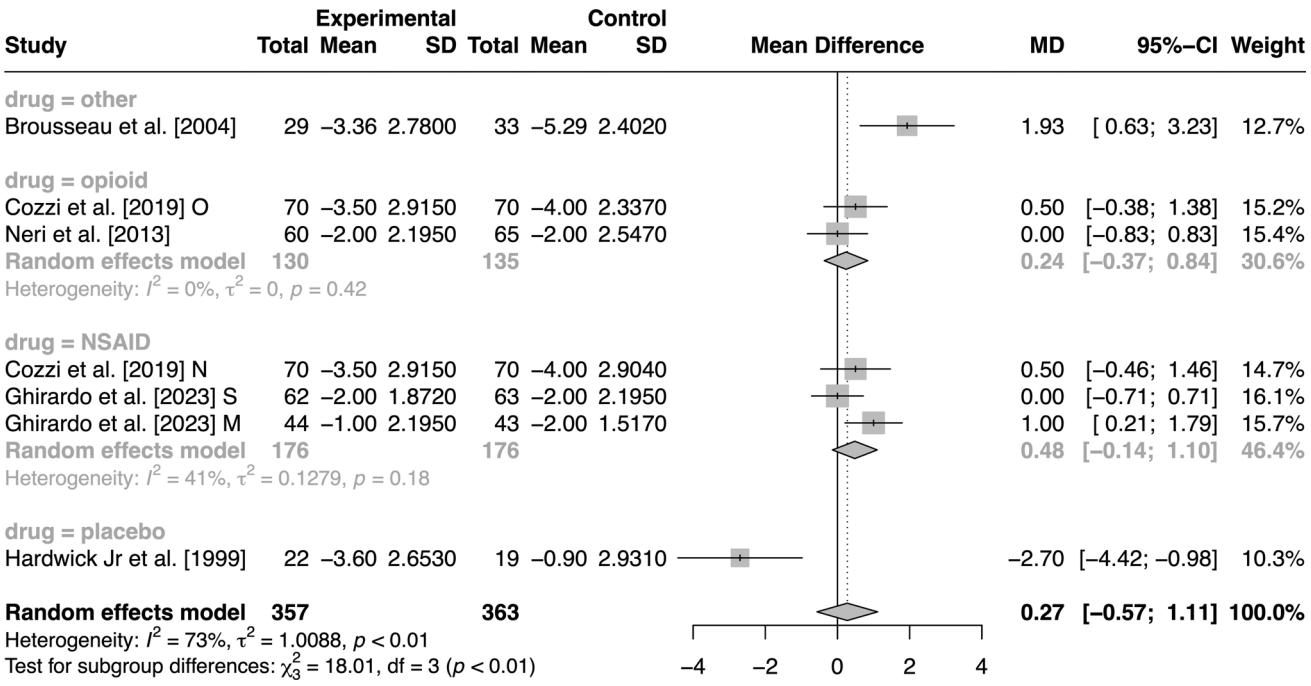

Fig. 2 Forest plot of the analysis for ketorolac effect versus other NSAIDs and opioid. The results from RE (random-effects model), using mean differences (MD), and 95% confidence interval (CI) were reported. Heterogenicity I^2 and τ^2 were shown. Abbreviations: O, opioids; N, NSAIDs; S, severe pain; M, moderate pain

Then, the studies were categorized based on the main condition treated. Ketorolac was not different to other drugs for abdominal pain (RE, MD = 0.5; CI − 0.15, 1.15), and musculoskeletal trauma (RE, MD = 0.33; CI − 0.32, 0.98). The overall efficacy of ketorolac was not different from the other drugs (RE, MD = 0.27; CI − 0.57, 1.11) (Fig. 3). The heterogenicity was medium among musculoskeletal trauma studies ($I^2 = 52\%$, $\tau^2 = 0.17$), low in abdominal pain studies ($I^2 = 0\%$, $\tau^2 = 0$), and medium–high across all studies ($I^2 = 73\%$, $\tau^2 = 1.01$).

Influence analysis showed that the studies by Broasseus et al., Ghirardo et al., and Hardwick et al. may impact on the meta-analysis results; however, we cannot exclude them from the analysis due to the very limited number of the eligible studies (Figure supplementary 2).

Accordingly, to the GRADE system, due to the lack of significant differences in efficacy between ketorolac and other drugs for pain managing in the ED, and the presence of medium–high heterogenicity among the studies, a conditional recommendation was formulated for either the intervention or the comparison (Table 2 and Table supplementary 2).

Discussion

This review indicates that evidence regarding the use of ketorolac for acute pain in pediatric patients in the ED is still limited with only eight pediatric RCTs available. This finding could be attributed to the fact that the use of ketorolac is still considered off-label for children according to several national pharmacological agencies.

Available evidence shows conflicting results about ketorolac's efficacy in children, but it is essential to note that most comparisons between individual drug regimens were based on single studies.

Ketorolac does not appear to provide greater pain relief than dopaminergic agents for migraine in children, a finding consistent with adult studies focused on headaches [15–18]. Notably, there are no pediatric or adult trials that compared ketorolac to other NSAID drugs for headaches. Considering migraine or headaches in general, the pediatric results are primarily derived from single studies, so it is not possible to identify a pharmacological approach of choice, involving the use of ketorolac. This observation was confirmed by the meta-analysis.

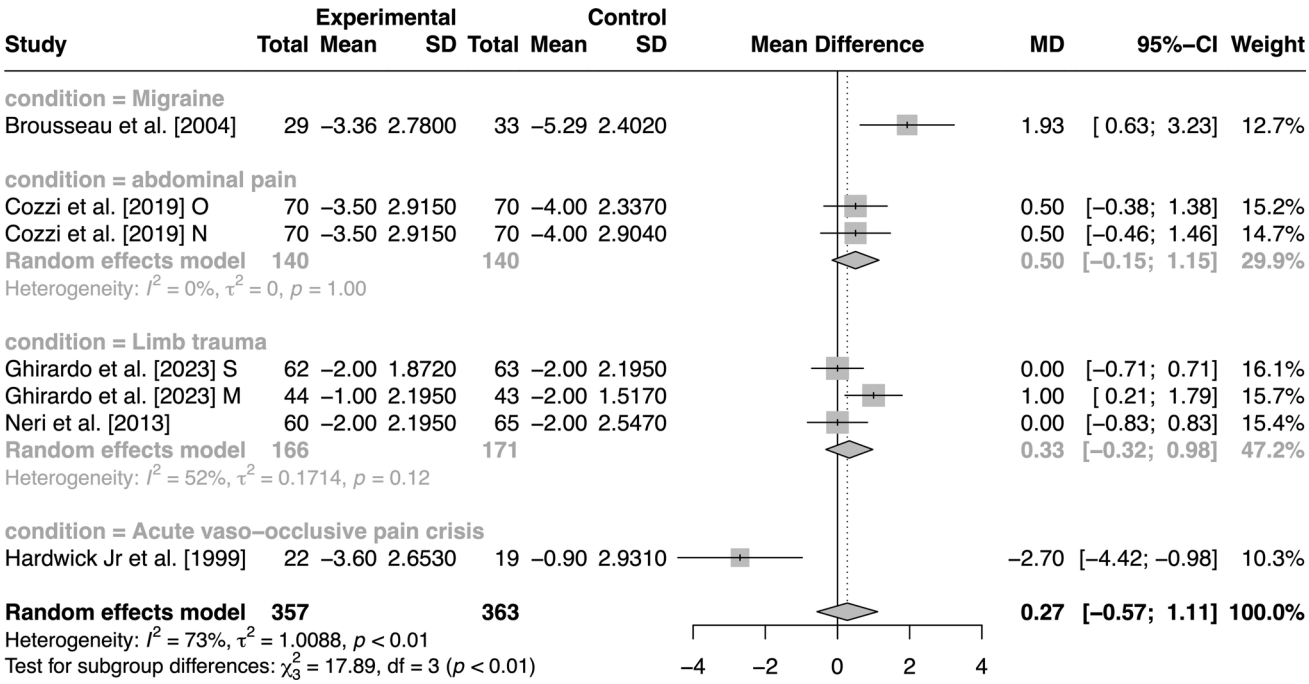

Fig. 3 Forest plot of the analysis for ketorolac effect versus other drugs in musculoskeletal trauma (limb trauma), migraine, abdominal pain, and sickle cell vaso-occlusive crises. The results from RE (random-effects model), using mean differences (MD), and 95% confidence interval (CI) were reported. Heterogenicity I^2 and τ^2 were shown. Abbreviations: O, opioids; N, NSAIDs; S, severe pain; M, moderate pain

Table 2 Summary of findings accordingly to GRADE

Certainty assessment							№. of patients		Effect	Certainty	Importance	Impact
№. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ketorolac	Other drugs	Mean Difference (95% CI confidence interval)			
Outcome: effectiveness of ketorolac versus other drugs in pediatric patients												
6	Randomized trials	Not serious	Serious	Not serious	Not serious	Medium–high heterogenicity	357	363	0.27 (−0.57; 1.11)	⨁⨁⨁◯ Moderate due to inconsistency	CRITICAL	Lack of significant differences in efficacy between ketorolac and other drugs for pain managing in the ED A conditional recommendation was formulated for either the intervention or the comparison

Moreover, no evidence suggests that ketorolac works better than other NSAID drugs for musculoskeletal trauma, but these results are limited to one pediatric study in which ketorolac was not more effective than ibuprofen. More broadly, among the studies included in this review, any trials compared ketorolac to other NSAIDs in a way that demonstrated its superior efficacy.

Considering traumatic musculoskeletal pain, when compared to opioids, ketorolac demonstrated similar analgesic efficacy in the single pediatric study available. These data confirm that opioids present similar effects than NSAIDs for musculoskeletal trauma [19]. Furthermore, it should be underlined that ketorolac was studied only through the oral and sublingual route for trauma in children, and no data are available about intravenous ketorolac in this clinical setting.

In general, the efficacy of ketorolac was not inferior to opioids in all the painful conditions explored in this review, and this data was confirmed by the meta-analysis that did not highlight a different pain level when the patients were treated with ketorolac. On the other hand, ketorolac seems not to provide any analgesic advantage to patients with sickle cell disease treated with opioids.

Evidence about the treatment of acute abdominal pain in children is limited to a single trial in which ketorolac was given sublingually, and its effect was similar to tramadol and paracetamol. Also, in this case, it should be underlined that no evidence is available about oral or intravenous ketorolac in this setting.

Nevertheless, it is important to consider that the lack of superiority of ketorolac applies only to its analgesic efficacy, which is comparable to other analgesic drugs. However, its lower risk of side effects compared to opioids, such as respiratory depression, nausea, vomiting, constipation, tolerance, and physical dependence, may be considered an advantage in clinical practice, favoring its use in the pediatric setting [6].

This review had some limitations. Only articles written in the English language were considered, so it is possible that some relevant studies were not included. The number of pediatric studies was very limited so no clear indications can be drawn. In general, the studies were very heterogeneous, with comparisons between different drug regimens limited to few studies. Moreover, the heterogeneity evaluation conducted in the meta-analysis showed medium–high heterogeneity across the studies.

In conclusion, this systematic review suggests that ketorolac appears to be effective in managing acute pain in the ED in pediatric patients, but not superior to other analgesic drugs. Therefore, these findings supported a conditional recommendation for either the intervention or the comparison. Despite variations in efficacy across diverse pain conditions, ketorolac consistently emerges as a potentially valuable analgesic option. Further research is warranted to establish optimal dosages, administration routes, and comparative efficacy against other analgesics in specific clinical scenarios.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00431-025-06128-2.

Author contributions GC conceived and designed the work. AT, GC, and AA analysed the data and drafted the first version of the text. LZ, FC, and VC performed the computations and verified the analytical methods. EB reviewed and edited the work. All authors approved the final version of the manuscript.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate Ethical approval was not necessary for this work, due to its literature examination nature.

Competing interests The authors declare no competing interests.

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