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REVIEW PAPER

UROLITHIASIS

Methodology and findings of randomized clinical trials on pharmacologic and non-pharmacologic interventions to treat renal colic pain – a review

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Introduction Renal colic pain is considered one of the most excruciating pains ever experienced and ranks as one of the most common urological emergencies. Despite existing established recommendations, new therapies and their combinations are continuously being tested. The aim of this systematic review is to analyze and compare studies involving pharmacologic and non-pharmacologic interventions used in the treatment of renal colic pain.

Material and methods This systematic review was conducted following the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. Medline, Scopus, Cochrane Library, and Google Scholar were searched for relevant randomized controlled trials (RCTs) involving adult patients. The quality and results of the included studies were assessed and discussed.

Results This review provides an extensive analysis of 71 identified RCTs. Opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and dipyrone/metamizole have demonstrated effectiveness as single medications. Some evidence points to opioids having a potential disadvantage compared to others when used as a first-line single medication. Among the 63 studies exploring pharmacological therapy, 51 reported opioids utilization for rescue therapy in significant proportion of patients. Promising combination therapies involve the administration of an NSAID alongside opioids, ketamine, desmopressin, steroids, or nitric oxide. Conversely, spasmolytics, magnesium, and lidocaine exhibited limited or no additional effect. Noteworthy methodological shortcomings encompass a low pain threshold during participant recruitment and the reliance on pain reduction rather than complete pain elimination as an endpoint.

Conclusions Frequent use of opioids as rescue medications in RCTs undermine their conclusions on effectiveness of other therapeutics. Combination therapies should be considered as first choice in renal colic pain management. RCTs should define success of therapy as achieving complete or near-complete pain relief rather than pain reduction.

Key Words: renal colic ‹› ureteric stone ‹› urolithiasis ‹› pain ‹› review ‹› morphine ‹› acetaminophen

INTRODUCTION

Urolithiasis is a very common condition that affects roughly 10% of the population [1] and can lead to episodes of excruciating pain, often resulting in visits to emergency departments [2]. Renal colic pain is regarded as one of the most severe forms of pain. Numerous individuals who have encountered both childbirth and renal colic assert that the pain associated with the latter is more intense [3]. Given the urgency and severity of the condition, swift and efficient management is paramount. Thus, it is vital to discover the most potent analgesic approach, considering the continually rising incidence of kidney stones. The foremost goal in addressing acute renal colic in patients is the successful management

of pain. The 2023 Guidelines from the European Urological Association (EAU) advocate for the initial utilization of non-steroidal anti-inflammatory drugs (NSAIDs), metamizole, or paracetamol as the preferred primary medications [4]. Opioids like hydromorphone, pentazocine, and tramadol are proposed as a secondary choice with limited supporting evidence. Interestingly, when examining retrospective evaluations of real-world medication usage, opioids are still observed to be more frequently utilized than NSAIDs [5]. Even initiatives aimed at curbing opioid usage show only a modest 12% reduction [6]. However, it's important to note that recommendations and existing systematic reviews do not definitively resolve certain controversies regarding the management of pain in renal colic. These uncertainties encompass the most effective combinations of therapies involving anxiolytics and spasmolytics, the impact of integrating non-pharmacological interventions, the selection between different NSAIDs or opioids while considering the balance between efficacy and safety, and the choice of second-line treatments.

In light of these knowledge gaps, the objectives of this review were as follows: to systematically identify all pertinent randomized clinical trials investigating diverse approaches to treating renal colic, to evaluate the quality of these trials, and to thoroughly discuss the outcomes they have documented.

MATERIAL AND METHODS

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. The literature search was not restricted by date of publication, but it was restricted to English. We searched Medline, Scopus, and the Cochrane Library with the following search strategy: ('renal colic' [Ti] AND randomized). We searched Google Scholar with the following string: ('renal colic' OR 'ureteral pain') (randomized OR comparison] [treatment OR management). We also searched relevant individual urologic journals and citation lists from reviews and other identified relevant papers. We scrutinized references and citations of each relevant study to extend the search range. The search was completed on July 1st, 2023.

The titles and abstracts of the considered studies were independently reviewed by two researchers using the inclusion and exclusion criteria mentioned below. Ineligible studies were rejected, and any disagreements were discussed and resolved during a consensus meeting.

The inclusion criteria for this study were as follows: patients aged 18 years and older presenting to the emergency department with a sudden onset of renal colic pain, clinical or radiographic or urine sampling based confirmation of diagnosis, and assessment of pain severity using the Visual Analog Scale (VAS), Numeric Rating Scale (NRS), Verbal Rating Scale [VRS], Pain Intensity Difference (PID), or Pain Analogue Scale (PAS). The following criteria were applied for exclusion: pregnancy or breastfeeding, allergy to the tested medication, patients with multiorgan failure or active bleeding, studies with fewer than 40 participants, and the use of solely placebo in a control group.

RESULTS

After careful consideration, 71 studies were included in this analysis out of a total of 85 randomized controlled trials [RCTs] that were identified. 14 studies were excluded from the analysis due to the following reasons: participants younger than 18 years old [n = 2], study described in language other than English [n = 2], undesirable topic and/or study design [n = 10]. These selected studies were conducted in various countries worldwide, with participant numbers ranging from 40 to 1645 per study. Pain assessment methods used included the NRS, VRS, and VAS, which were measured before and after treatment at different time intervals. The most commonly used criterion for success was a decrease in pain of at least 2 points on a 0–10 scale, although it should be noted that only 29 studies followed this principle or a similar one.

Each identified study was allocated into one of three tables summarizing the findings divided according to the type:

1. Comparison of single medications: 37 studies analyzed (Table 1) [7–43];
2. Evaluation of combination therapy of two or more medications against single medication or another combination: 26 studies analyzed (Table 2) [11, 16, 44–67];
3. Evaluation of non-pharmacological treatments – both as standalone methods and as adjunctive measures: 8 studies analyzed (Table 3) [68–75].

In summary, selected studies evaluated 36 medications and 3 non-pharmacological methods [Table 4].

Single medications

Thirty-seven RCTs were identified directly comparing two or three pharmaceutics administered individually in each investigating group (Table 1). The sample sizes ranged from 40 to 1645 subjects per study.

Morphine has been used as a reference substance in 12 of those trials. The typical dosing scheme

Table 1. *Studies comparing single substances arranged according to the pharmacological groups and dates. Only most important outcomes and adverse events are presented. VAS scores within 30 minutes from administration are presented if available. Intravenous administration if not otherwise specified*

Article	Year	Study size	Groups	Rescue treatment	Side effects	Outcomes
				Opioid vs Opioid		
Payandemehr P et al. [7]	2014	69	Morphine 0.1 mg/kg Buprenorphine 2 mg sl	Fentanyl 0.75 µg/kg 6% 13%	Dizziness 37% 62%	VAS @20 min: 4.2 5.2, P = 0.3
Eray O et al. [8]	2002	47	Tramadol 50 mg Meperidine 50 mg	Meperidine 50 mg 16 (67%) 11 (48%), P <0.05	No difference	Pain relief better in meperidine group @15 and 30 min. P <0.05
O'Connor A at al. [9]	2000	94	Dose titrated to max: Morphine 10 mg Pethidine 100 mg	Not specified 'standard analgesia'	No difference	VAS @30 min: 3.8 vs 3.2, P = 0.3
Jasani NB et al. [10]	1994	73	Meperidine 50 mg Hydromorphone 1 mg	Second dose of the same 68% 31%, P <0.01	Nausea and vomiting 40% vs 28% Dizziness 11% vs 22%	Pain relief better after hydromorphone @15, 30, 60 and 120 min. P <0.05
				NSAID vs Opioid		
Hosseininejad SM et al. [11]	2017	200	Ketorolac 30 mg Morphine 0.1 mg/kg	Morphine 0.05 mg/kg	Vomiting 2% vs 4% Dizziness 1% vs 6%	Pain score @20 min: 5.3 4.6, P = NS
Mozafari J et al. [12]	2017	63	Buprenorphine 2 mg sl Ketorolac 30 mg	Fentanyl 1 µg/kg 23 (74%) 19 (59%)	Buprenorphine: Vomiting 19% Dizziness 22% Ketorolac: no AE	VAS @20 min: 5.9 5.5
Pathan SA et al. [13]	2016	1645	Diclofenac 75 mg im Morphine 0.1 mg/kg	Morphine 63 (12%) 126 (23%), P <0.0001	Acute AEs: Diclofenac: 1% Morphine 3%	≥50% pain reduction @30 min: 371 (68%) 335 (61%), P = 0.04
Zamanian F et al. [14]	2016	158	Indomethacin 100 mg supp. Morphine 10 mg supp.	Morphine 5 mg	No difference	Pain score decrease 0–20 min: 5.46 4.36, P <0.001
Ay MO et al. [15]	2014	52	Dexketoprofen 50 mg Meperidine 100 mg	Meperidine 50 mg 3 (5.8%) patients in both groups	No difference	Pain score @30 min: 1.7 2.6, P = NS
Safdar B et al. [16]	2006	130	Ketorolac 15 + 15 mg Morphine 5 + 5 mg			P = NS
Wood VM et al. [17]	2000	142	Ketorolac 30 mg Meperidine 50 mg	Second dose of the same	Drowsiness 7% vs 50% Dry mouth: 10% vs 52% Dizziness: 1% vs 19%	VAS @15 min. and @30 min 4.5 2.8 5 4.2 P = NS
al-Sahlawi KS et al. [18]	1996	150	Acetylasalicylic acid 2 g Indomethacin 100 mg Pethidine 100 mg	Pethidine 13 (26%) 2 (4%) 0 (0%)	No significant AEs	Complete pain relief @15, 30 and 60 min: 20%, 40%, 74% (inferior) 54%, 70%, 96% 70%, 90%, 100%
Sandhu DP et al. [19]	1994	154	Ketorolac 30 mg im Pethidine 100 mg im	Not specified 56% 74%	Side effects: 21 (14%) 40 (26%)	Improvement of VRS at 1 h: 87% 89%, P = NS
				NSAID vs NSAID		
Eidinejad L et al. [20]	2021	165	Ketorolac 10 mg Ketorolac 20 mg Ketorolac 30 mg	Morphine 0.1 mg/kg 16 (29.1%) 19 (34.6%) 16 (29.1%), P = NS	Headache: 9.1% vs 14.5% vs 18.2% Dizziness: 3.6% vs 7.3% vs 14.5%	VAS change from 0 to 60 min: 9 to 5 8 to 5 9 to 5, P=NS
Forouzanfar MM et al. [21]	2019	240	Ketorolac 30 mg Ibuprofen 800 mg	Morphine 0.1 mg/kg	Nausea and vomiting 19% 24%	VAS @15 min. @30 min. 5.9 3.4, P <0.0001 4.7 2.3, P <0.0001
Soylu A et al. [22]	2019	51	Lornoxicam 8 mg im Lornoxicam 8 mg	Medication not specified 4 (7.8%) 0 (0%)	No acute AEs	VAS @30 min: 2.1 1.4, P = NS

Table 1. *Continued*

Article	Year	Study size	Groups	Rescue treatment	Side effects	Outcomes
Kanda Swamy GV et al. [23]	2015	100	Diclofenac 75 mg im Piroxicam 40 mg sl	Pentazocine 30 mg 30% 26%, P = NS	No AEs	Total pain relief after 30 min: 16% 18%, P = NS
Porwal A et al. [24]	2012	217	Dexketoprofen 50 mg im + Dicyclomine 20 mg im Diclofenac 50 mg im + Dicyclomine 20 mg im	Not specified	No significant AEs	Difference in VAS not significant until 6 hours post administration. Difference significant in favor of Dexketoprofen @6 h and @8 h
Cevik E et al. [25]	2012	123	Tenoxicam 20 mg Lornoxicam 8 mg Dexketoprofen 50 mg	Fentanyl 0.75 µg/kg 16 (39%) 10 (24%) 8 (19%)	Single	VAS reduction @30 min: 42 mm 57 mm 52 mm
Glina S et al. [26]	2011	340	Parecoxib 40 mg Ketoprofen 100 mg	Morphine 17% 18%, P = NS	Dizziness: 2.9% vs 0.6%	VAS change @30 min 4.3 4.3, P = NS
Altay B et al. [27]	2007	80	Piroxicam 40 mg sl Piroxicam 40 mg im	13% 7%, P = NS	No AEs	Overall efficacy 90% in both groups P = NS
Fraga A et al. [28]	2003	119	Etofenamate 1000 mg im Diclofenac 75 mg im	Centre-dependent. Mostly used: pethidine Etofenamate: 11 (18.6%) Diclofenac: 12 (20.0%)	Mild to moderate side effects 3.4% 5.0%	Both similar in potency. Improvement after 60 min: 84.5% 83.3%
Cohen E et al. [29]	1998	57	Ketorolac 30 im Diclofenac 75 im	Pethidine 75 mg im	No significant differences	VAS @60 min. 2.4 2.2, P = NS
Laerum E et al. [30]	1996	100	Diclofenac 75 mg im Indomethacin 50 mg	Same substance used 11 12 3rd injection needed: 75 mg pethidine im 5 9, P = NS	<5%, Differences not significant	VAS @60 min: 0.7–2.1 1.0–2.5 Probability of pain after 1 h: 37% 52%
			Acetaminophen (Paracetamol) vs Opioid			
Pathan SA et al. [13]	2016	1090	Acetaminophen 1 g Morphine 0.1 mg/kg	Morphine 111 (20%) 126 (23%), P = NS	Acute AEs: Paracetamol 1% Morphine 3%	≥50% pain reduction @30 min: 364 (66%) 335 (61%), P=NS
Azizkhani R et al. [31]	2013	124	Acetaminophen 0.15 mg/kg Morphine 0.1 mg/kg	Not specified	Dizziness 0% vs 24% Vomiting 0% vs 2%	VAS @30min: 2.4 0.7, P <0.001
Serinken M et al. [32]	2012	80	Acetaminophen 1 g Morphine 0.1 mg/kg	Fentanyl 1 µg /kg	5.3% – nausea and vomiting 14% – dizziness, vertigo and nausea	VAS reduction @30 min: 6.4 5.7, P = NS
			Acetaminophen (Paracetamol) vs NSAID			
Cenker, E et al. [33]	2018	200	Acetaminophen 1 g Ibuprofen 800 mg	Fentanyl, 1 µg/kg 10.1% 2%	Adverse events: 6.06% 4.1%	Pain reduction @15 min: 18.3 27.9, P <0.0001
Pathan SA et al. [13]	2016	954	Diclofenac 75 mg im Acetaminophen 1 g	Morphine 63 (12%) 111 (20%)	Acute AEs: Diclofenac: 7 (1%) Paracetamol: 7 (1%)	Reduction in initial pain by ≥50%, at 30 min: 371 (68%) 364 (66%) Median pain score @60 min 0 (0–2) 1 (0–3), P = NS
Al-Terki A et al. [34]	2021	208	Acetaminophen 1 g Parecoxib 40 mg	Morphine 0.1 mg/kg, 36 (35.3%) 27 (26.7%)	Minor adverse events: 2% 3%	VAS reduction @30 min: 7.6 to 3.8 7.8 to 3.4

Table 1. *Continued*

Article	Year	Study size	Groups	Rescue treatment	Side effects	Outcomes
Other Anesthetics (local / dissociative) vs NSAIDS or opioids						
Pouraghaei M et al. [35]	2021	200	Ketamine 1 mg/kg intranasal Morphine 0.1 mg/kg	No information	Ketamine: dizziness – 21.1% Morphine: nausea – 95.5%	Mean pain scores after 15, 30 and 60 min: 4.85, 2.97 and 1.53 5.22, 2.97 and 1.28
Sotoodehnia M et al. [36]	2019	141	Ketorolac 30 mg Ketamine 0.6 mg/kg	Morphine 0.1 mg/kg	Ketorolac: 14% Ketamine: 63%	VAS @15 min. 4.8 4.7 P = NS for this and other time points
Motamed H et al. [37]	2017	90	Lidocaine 1.5 mg/kg Fentanyl 1.5 µg/kg	Morphine sulfate 0.1 mg/kg		Mean VAS @15 min: 5.1 4.1, P = 0.14 Lack of 3-point reduction (treatment failure) @15 min: 44% for Lidocaine 18% for Fentanyl, P = 0.006
Soleimanpour H et al. [38]	2012	240	Lidocaine 1.5 mg/kg Morphine 0.1 mg/kg	Not specified	Nausea 0% vs 7.5% Dizziness 8% vs 2%	0 to 30 min. VAS change: 9.6-> 1.1 9.7-> 2.2, P = 0.0001
Dipyrone/Metamizole						
Sánchez-Carpena J et al. [39]	2007	308	Dexketoprofen 25 mg Dexketoprofen 50 mg Dipyrone 2 g	34% 25% 16%	No significant difference	Mean total pain relief scores 13.5 ±8.6 15.3 ±8.6 15.5 ±8.6, P = 0.16
Stankov G et al. [40]	1994	104	Dipyrone 2.5 g Tramadol 100 mg Butylscopolamine 20 mg	Dipyrone: 1.0 g dipyron; 5 patients (15%) Tramadol: 20 mg butylscopolamine; 13 patients (38%) Butylscopolamine: 100 mg tramadol; 11 patients (34%)	Single cases	Dipyrone significantly more effective than tramadol in reducing pain for the primary endpoint: pain intensity differences at 20, 30, and 50 min.
Other: Magnesium, Desmopressin						
Zolfaghari Sadrabad A et al. [41]	2021	80	Magnesium sulfate 50 mg/kg Morphine 0.1 mg/kg	Ketorolac 30 mg 8 (20%) 10 (25%)	Nausea 12.5% 7.5%	VAS @20 min 3.2 3.6, P = NS
Ghafouri HB et al. [42]	2020	240	Desmopressin 40 µg intranasal Paracetamol 15 mg/kg max 1 g	Morphine max 3 mg 21 (17.5%) 31 (25.8%)		VAS @15 min @30 min: 5 2.0 8 2.2 P <0.001, P = NS
Arhami Dolatabadi A et al. [43]	2017	40	Desmopressin 40 µg intranasal Ketorolac 30 mg	Morphine 5 mg	No side effects	Ketorolac is more potent than desmopressin P <0.001

AEs – adverse events; im – intramuscular, iv – intravenously, NS – nonsignificant, sl – sublingual

included intravenous administration of 0.1 mg/kg. It has been proved an effective therapeutic lowering pain scores from 8–9 to 2.5–3.7. Its safety profile, when used in single therapy, is acceptable, with usually mild symptoms of which nausea and dizziness being the most common (7.5–16%). If the study design provided for the use of rescue therapy, then morphine or another opioid was used in at least 27 studies as well.

Few studies compared morphine intravenously (iv) with another opioid in this indication. Sublingual buprenorphine showed similar speed and strength of pain reduction effect with sublingual route being easier to use [7]. No difference was noticed in therapeutic effects and adverse events between morphine 2mg iv and pethidine 20 mg iv either [9].

NSAIDs is another pharmaceutical group intensively investigated. In our review 26 studies using NSAIDs as single medication were identified. Table 4 specifies NSAIDs analyzed with diclofenac and ketorolac being most commonly chosen. One, but very large study compared diclofenac with morphine.

Table 2. *Studies comparing combination of two or three medications arranged according to the pharmacological groups and dates. Only most important outcomes and adverse events are presented. VAS scores within 30 minutes from administration are presented if available. Intravenous administration if not otherwise specified*

Article	Year	Study size	Groups	Rescue treatment	Side effects	Outcomes
Opioid + NSAID combination						
Safaie A et al. [44]	2022	195	Morphine 5 mg + Ibuprofen 800 mg Morphine 5 mg + Ketorolac 30 mg Morphine 5 mg	Morphine Mean dose significantly higher in Morphine group	AEs: 18.5% 20.0% 13.8%	Mean NRS @30 min: 6.1 5.9 7.5, P <0.001
Nazemian N et al. [45]	2020	220	Ketorolac 60 mg im. + Fentanyl 1 µg/kg **intravenous** Ketorolac 60 mg im. + Fentanyl 2 µg/kg **intranasal**	Morphine	Nausea: 9% vs 8% Pharyngeal irritation: 0% vs 8%	Mean pain score @60 min: 2.5 3.0, P = NS
Hosseininejad SM et al. [11]	2017	300	Morphine 0.1 mg/kg Ketorolac 30 mg iv Ketorolac 30 mg + Morphine 0.1 mg/kg	Morphine @20 min 12% vs 11% vs 10% P = NS @40 min: 20% vs 24% vs 16% P = 0.04	No differences	Mean pain scores @20 min: 4.5 5.3 4.7, P = NS
Safdar B et al. [16]	2006	130	Same doses repeated if needed @20 min: Morphine 5 mg Ketorolac 15 mg Ketorolac 15 mg + Morphine 5 mg	Morphine @40min: 42% 33% 16%	Nausea: 16% vs 2% vs 4% Dizziness: 9% vs 0% vs 2%	Mean pain scores @40 min: 3.7 4.1 2.0, P <0.003
Cordell WH et al. [46]	1996	154	Ketorolac 60 mg Meperdine 50 mg Ketorolac 60 mg + Meperidine 50 mg	Meperidine 64% 89% 66%	Dizziness: 12% vs 10% vs 2% Somnolence: 10% vs 4% vs 3%	Ketorolac and combination groups did not differ significantly in any of the efficacy measures. Note high rate of rescue Meperidine in all groups.
Opioid + Ketamine combination						
Hosseininejad SM et al. [47]	2019	200	Morphine + Ketamine 0.2 mg/kg Morphine 0.1 mg/kg	Morphine 3,5% 9,5%	Nausea 17% vs 15% Dizziness 5,5% vs 11%	Mean pain score @40 min: 2.7 3.1
Abbasi S et al. [48]	2018	106	Morphine 0.1 mg/kg + Ketamine 0.15 mg/kg Morphine 0.1 mg/kg	Morphine @10, 30 and 60 min Total: 12 doses 28 doses P = 0.01	Hypoxia 1 vs 5 pts Nystagmus 4 vs 0 pts Nausea 4 vs 7 pts	Pain scores @10 and @30 min. lower in combination group @60 and @120 min no difference
Opioid + Other (Magnesium sulfate, Lidocaine, Haloperidol, Citalopram, Clonidine) combination						
Esmailian M et al. [49]	2022	200	Morphine 0.1 mg/kg + **Clonidine** 0.2 mg po. Morphine 0.1 mg/kg Ketorolac 30 mg + **Clonidine** 0.2 mg po. Ketorolac 30 mg	Morphine 18% 68% 28% 42% P = <0.001	No differences	No differences between the groups
Masoumi K et al. [50]	2019	140	Morphine + **Haloperidol** 5 mg Morphine 5 mg	Fentanyl	Haloperidol group: 4.3% extrapyramidal side effects Nausea: no difference	Haloperidol is not recommended in treating acute renal colic pain since it failed in reducing the pain, caused extrapyramidal side effects and did not lower the incidence of nausea and vomiting.
Esmailian M et al. [51]	2014	90	Morphine 5 mg Morphine 5 mg + **Citalopram** 20 mg	Not specified	No significant AEs	Mean VAS decrease (0 vs 20 min): From 7.53 ±1.66 to 6.4 ±2.3 From 7.07 ±1.85 to 4.0 ±3.1

Table 2. *Continued*

Article	Year	Study size	Groups	Rescue treatment	Side effects	Outcomes
Majidi A et al. [52]	2019	90	**All received Morphine** 0.1 mg/kg iv. Those with pain > = 6 after 10 min. allocated to: Magnesium 2 ml of 50% solution iv Morphine 0.1 mg/kg iv	Morphine	No AEs	Success rate (reduction of pain by at least 3 points on VAS): 100% in both groups at 30 min. P = NS Pain free @20min: 31 vs 16 pts P = 0.004. @30min. and later no difference
Jokar A et al. [53]	2017	100	Morphine + Ketorolac Magnesium + Morphine + Ketorolac	Morphine 1.6 mg 0.9 mg P = 0.04	No difference	VAS @30min. @60 min: 4 2.5 5 3 P = ?
Firouzian A et al. [54]	2016	110	Morphine + **Lidocaine** 1.5 mg/kg Morphine 0.1 mg/kg	Not specified	Nausea scores lower after Morphine + Lidocaine P = 0.04	Difference not significant; P = 0.15
			NSAID + other (Desmopressin, Ketamine, Lidocaine, Dexamethasone, Nitric oxide gas) combination			
Heydari F et al. [55]	2023	135	**Desmopressin** 40 µg + Ketorolac Ketamine 1 mg/kg + Ketorolac Ketorolac	Morphine 18% 7% 24%	–	Pain scores in each group at 10, 30 and 60 min: (6.7 ±1.8, 4.2 ±2.2, 1.3 ±1.4) (5.6 ±1.2, 3.0 ±1.1, 0.9 ±0.9) (8.2 ±1.1, 5.1 ±2.0, 2.3 ±2.6)
Lopes T et al. [56]	2001	61	**Desmopressin** 40 µg intranasal Diclofenac 75 mg im. Desmopressin + Diclofenac	Pethidine 65% 37% 9%	Single, mild AEs	All three treatments were equally effective at 10 and 20 min.
Pricop C et al. [57]	2016	249	Ketorolac 30 mg im. **Desmopressin** 60 µg sl. Desmopressin 120 µg sl. Ketorolac 30 mg + Desmopressin 60 µg sl.	Tramadol	No severe AEs.	Desmopressin in higher dose and combination therapy decreased pain intensity more effectively than other therapies (p <0.05 and p <0.001)
Masoumi K et al. [58]	2014	120	**Desmopressin** 40 µg intranasal + Diclofenac 75 mg im. Diclofenac 75 mg im.	Morphine 18% 32%	No AEs	VAS scale @15 min: 5.43 6.51, P = 0.02
Motov S et al. [59]	2020	150	**Lidocaine** 1.5 mg/kg Ketorolac 30 mg IV Lidocaine 1.5 mg/kg + Ketorolac	Morphine	No clinically significant adverse effects	Difference in pain score @30 min: Between combination therapy and ketorolac group 0.92 (95% CI: −2.44 to 0.61) P = NS
Metry AA et al. [60]	2019	120	Lornoxicam 8 mg + Ketamine Pethidine 50 mg	Pethidine 10% 27%	Pethidine: sedation at 0 min, 15 min, and 30 min and lower oxygen saturation	VAS scores after 30 min: 0 (0–2.75) 0 (0–40), p = 0.021
Togo K et al. [61]	2022	120	Ketorolac 30 mg + **Dexamethasone** 8 mg Ketorolac 30 mg	Morphine or pethidine 35% 58%	Need for antiemetics after 60 minutes: 7 (12%) 17 (28%)	Adding dexamethasone improved pain control, decreased opioid requirement and antiemetic need
Kariman H et al. [62]	2015	100	Morphine iv + Diclofenac 100 mg supp. **50% nitric oxide and 50% oxygen** ventilation for 30-minutes + Diclofenac 100 mg supp.	6 (54.6%) 5 (45.4%), (p = 0.72)	No AEs	VAS @ 3; 5; 10; 30 min: 8.6; 6.9; 5.0; 2.0 6.4; 5.3; 3.6; 1.8 P <0.001
			Spasmolytics			
Yakoot M et al. [63]	2014	80	Ketoprofen 100 mg and **Hyoscine** butylbromide 10 mg (supp.) Ketorolac 30 mg	Not specified	Not significant	VAS reduction @60 min: 92% 75%, P = 0.046

Table 2. *Continued*

Article	Year	Study size	Groups	Rescue treatment	Side effects	Outcomes
Jones JB et al. [64]	2001	59	Ketorolac 30 mg Ketorolac + sublingual Hyoscyamine	Meperidine 25% 17%	No AEs	No clinically significant difference in pain relief between both groups
Song SW et al. [65]	2012	89	Ketorolac 30 mg + Morphine 5 mg + 20 mg Butylscopolammonium bromide iv. Ketorolac 30 mg + Morphine 5 mg	Morphine 15% 33% P <0.05	No acute AEs	The mean change in pain intensity in BB group: 7.1 cm The mean change in pain intensity in placebo group: 5.9 cm, P = 0.02
Fu W et al. [66]	2014	236	Parecoxib 40 mg Parecoxib 40 mg + 80 mg Phloroglucinol	Tramadol 14% 6% P = 0.04	No differences	VAS mean pain score at 5, 15 and 30 min: 71.4 ±17.5, 58.0 ±24.3, 41.7 ±23.6 68.9 ±21.1, 52.9 ±25.5, 37.2 ±23.2
Snir N et al. [67]	2008	90	Papaverine 120 mg Diclofenac 75 mg im. Papaverine 120 mg + Diclofenac 75 mg im.	Meperidine 14% 2% 8%	Minor AEs only	Pain score reduction @20 min. @40 min: 4.9 3.6 3.6 2.5 4.7 3.0

NSAID – nonsteroidal anti-inflammatory drugs; AEs – adverse events; im – intramuscular, iv – intravenously, NS – nonsignificant, po – per os

In the study by Pathan et al [13] with over 500 patients in each group diclofenac appeared to be significantly more effective in achieving primary outcome (the proportion of participants achieving at least a 50% reduction in initial pain score at 30 min after analgesia) than morphine with fewer adverse events.

Ketorolac 30 iv/im was most frequently tested of all NSAIDs both in direct comparisons and as an element of combined therapy. Trials comparing this substance to morphine, pethidine or meperidine showed similar pain reducing effects and lower AE rates or even small advantage of ketorolac in patients needing rescue treatment [19].

Ketorolac, when compared to ibuprofen 800 mg iv, appeared less potent in terms of complete pain relief [30.8% vs 69.1%] [21]. There is also evidence that ketorolac is as effective as a low dose of ketamine in relieving pain in renal colic, but ketamine presents more side effects, such as a spike in systolic blood pressure [36].

Studies assessing seven other NSAIDs, including selective COX-2 inhibitors, showed no advantage over diclofenac, ibuprofen or ketorolac in direct and indirect comparisons [23, 24, 28, 30].

Three other than opioids and NSAIDs important anesthetics investigated in renal colic are dipyrone/metamizole, acetaminophen and ketamine. Dipyrone/metamizole 1 g or 2 g iv showed similar effects as dexketoprofen with nonsignificant differences in mild AEs, while it was more effective than tramadol 100mg or butylscopolamine 20 mg [39, 40].

We found six studies exploring effects of acetaminophen [paracetamol] [13, 31-34, 42] administered 1 g or 15 mg/kg iv. In four of six studies authors concluded that acetaminophen was as potent as comparator [morphine, parecoxib, diclofenac] and acute AE rate was close to 1%. It appeared less potent than ibuprofen [33] or intranasal desmopressin [42].

Intranasal ketamine 1mg/kg proved to be equivalent to morphine in typical dose in terms of pain reduction [35]. It also proved to be as effective as ketorolac, however with higher rate of AEs [36].

When comparing morphine to lidocaine, it appears that the latter is even more potent, as 90% of tested subjects successfully responded to lidocaine compared to 70% for morphine [38]. However, when comparing lidocaine to fentanyl, the study shows that lidocaine is less effective in the first 15 minutes of treatment [37]. Despite this difference, the mean pain severity in both study groups was not statistically significant.

Two substances: magnesium sulfate [41] and desmopressin [42, 43], were evaluated individually against established therapeutics despite not being analgesics. Both proved to reduce pain significantly with limited or no AEs. Magnesium sulfate showed efficacy comparable to morphine [41].

Thirty-three of the above studies implemented a rescue treatment protocol, while seven did not specify all the details. Side effects were reported in the same number of analyzed trials, with dizziness and nausea being the most frequently occurring adverse effects in morphine-tested subjects. Ketorolac-receiving patients often experienced nausea and vomiting.

Table 3. *Studies comparing non-pharmacological treatments. Arranged according to method used*

Article	Year	Study size	Groups	Rescue treatment	Side effects	Outcomes
Kaynar M et al. [68]	2015	124	Diclofenac 75 mg im. Acetaminophen 1 g Acupuncture	–	No or single mild AEs	VAS @10 and @30 min: 5.2 2.7 7.1 5.0 3.9 3.8
Zhang X et al. [69]	2021	84	Acupuncture Lornoxicam 8 mg im. + sham acupuncture	–	No or single mild AEs	VAS @5, @15, @40 min: 3.0 2.0 2.0 7.0 6.0 2.0
Tu JF et al. [70]	2022	80	Acupuncture + Diclofenac 50 mg im. Diclofenac 50 im. + sham acupuncture	Morphine No statistically significant difference (2.5%, P >.99)	No AEs	Response rates at 10 minutes: 77.5% 10.0% VAS decrease (0 vs 30 min): From 5.1 (2.5) to 0.9 (1.3) From 7.4 (1.5) to 3.1 (1.8)
Beltaief K et al. [71]	2018	119	Morphine iv titrated every 5 minutes Acupuncture 30 min.	–	Acupuncture: 3 (2,6%): itching/rash/bleeding at insertion point, needle blockage Morphine: 42 (35,3%): dizziness, nausea and vomiting, rash, hypotension in morphine group (P <0.001)	VAS @60 min: 2.2 1.0, P = 0.002
Seyhan AU et al. [72]	2021	126	Nerve blockade: Intradermal injection of 2% lidocaine into the spinal segments T10-11-12 and L1-2 Dexketoprofen 50 mg	100 mg tramadol im. No one received rescue therapy	No AEs	VAS @5 @15 @45 min: 5 4 1 7 5 2 P <0.05
Maldonado-Avila M et al. [73]	2017	60	Twelfth intercostal nerve block with 10 cc of 2% lidocaine Diclofenac 75 mg im.	–	No AEs	VAS at 3 min: 4.2 ±2.1 7.2 ±1.7 (p <0.001) VAS at 45 min: 2.3 ±2.6 4.5 ±3.6 (p <0.012)
Ayan M et al. [74]	2013	80	Aromatherapy (rose essential oil) + Diclofenac 75 mg im. Diclofenac 75 mg im.	–	–	VAS @10 and @30 min: 4.2 1.1 5.6 3.7 P <0.05
Irmak Sapmaz H et al. [75]	2015	100	Aromatherapy + Diclofenac 75 mg im. Diclofenac 75 mg im.	–	–	VAS score at 30 minutes post treatment 2.20 ±1.74 2.89 1.96 P = 0.02

AEs – adverse events; im – intramuscular; NS – nonsignificant

Combination treatment assessment

Twenty-six RCTs were identified to evaluate the effectiveness and side effects of various drug combinations (Table 2). The researchers explored combinations of two or three established analgesics with different mechanisms of action, as well as the simultaneous use of an analgesic with a spasmolytic agent or agents from other pharmacological groups. In two trials, two combined therapies were compared (A+B vs C+D or A+D), while in another two trials, combination therapy was tested against a different medication (A+B vs C). Additionally, in two trials, the tested medication was added to a combination of two other drugs (A+B+C vs A+B). Out of the twenty studies, fourteen reported a clear advantage of the tested combinations.

The most frequently studied combinations involved opioids with NSAIDs, ketamine with members of both groups, and NSAIDs with spasmolytics. Atypical drugs that were tested in combination with morphine or NSAIDs included desmopressin, citalopram, clonidine, haloperidol, nitric oxide/oxygen mixture for inhalation, magnesium sulfate, and dexamethasone.

Eleven studies demonstrated either a lack of difference or only minor advantages in single secondary

Table 4. *Pharmacological and non-pharmacological therapies represented in the review. In each group therapies are listed in alphabetical order*

Therapy	Citations
Opioids	
Buprenorphine	[7, 12]
Fentanyl	[37, 45]
Hydromorphone	[10]
Meperidine/Pethidine	[8, 9, 10, 15, 17, 18, 19, 46, 60]
Morphine	[7, 9, 11, 13, 14, 16, 31, 32, 35, 38, 41, 44, 47, 48, 49, 50, 51, 52, 53, 54, 62, 65, 71]
Tramadol	[8, 40]
Non-steroidal anti-inflammatory drugs	
Acetylsalicylic acid	[18]
Dexketoprofen	[15, 24, 25, 39, 72]
Diclofenac	[13, 23, 24, 28, 29, 30, 56, 58, 62, 67, 68, 70, 73, 74, 75]
Etofenamate	[28]
Ibuprofen	[21, 33, 44]
Indomethacin	[14, 18, 30]
Ketoprofen	[26, 63]
Ketorolac	[11, 12, 16, 17, 20, 21, 29, 37, 43, 44, 45, 46, 49, 53, 57, 59, 61, 63, 64, 65]
Lornoxicam	[22, 25, 60]
Parecoxib	[26, 34, 66]
Piroxicam	[23, 27]
Tenoxicam	[25]
Other analgesics	
Acetaminophen (paracetamol)	[13, 31, 32, 33, 34, 42, 68]
Ketamine	[35, 36, 47, 48, 55, 60]
Lidocaine	[37, 38, 54, 59]
Metamizole / Dipyrone	[39, 40]
Nitric oxide (comb.)	[62]
Spasmolytics	
Butylscopolammonium bromide (comb.)	[40, 65]
Dicyclomine (comb.)	[24]
Hyoscine butylbromide (comb.)	[63]
Hyoscyamine sulfate (comb.)	[64]
Papaverine (comb.)	[67]
Phloroglucinol (comb.)	[66]
Other medications	
Citalopram (comb.)	[51]
Clonidine (comb.)	[49]
Desmopressin	[42, 43, 55, 56, 57, 58]
Dexamethasone (comb.)	[61]
Haloperidol (comb.)	[50]
Magnesium sulfate	[41, 52, 53]
Non-pharmacological therapy	
Acupuncture	[69, 70, 71]
Aromatherapy (comb.)	[74, 75]
Nerve block	[72, 73]

comb. – therapy studied only in combination with other medication or non-pharmacological treatment

outcomes. This included two out of five studies on the combination of opioids and NSAIDs, as well as one out of two studies on the combination of opioids and ketamine. All studies investigating the use of magnesium and lidocaine showed either very limited or no advantage. Additionally, the addition of a spasmolytic to an NSAID showed minor or no advantage in four out of five studies. In one trial of desmopressin combined with an NSAID, there was only a reported decrease in the need for rescue treatment, but no advantage in terms of the primary outcome. However, three other studies on this combination showed a clear advantage in terms of pain reduction, speed of action, and reduction of rescue opioids. A clear disadvantage of combined therapy was found only for the administration of morphine with haloperidol, as the latter added pyramidal adverse events without providing any advantage for pain reduction. No combination of morphine and spasmolytics has been found in the literature. Three out of the 26 RCTs did not describe a rescue treatment protocol, nor did they report the rate of additional analgesic use.

Alternative therapies

Eight RCTs were analyzed to form Table 3, with sample sizes ranging from 60 to 126 subjects per study. The most frequently used alternative method was acupuncture, which appeared in four out of eight studies [68–71]. The other alternative therapy analyzed was 12th intercostal nerve and spinal segments blocks [72, 73], and aromatherapy [74, 75]. Only two analyses included rescue treatment protocols that specified the details of possible salvage intervention [70, 72]. In all eight studies, none or minor side effects were noticed.

DISCUSSION

Numerous studies have been conducted to evaluate various forms of therapy for incidents of acute renal colic. Despite concerted efforts and recommendations, the matter remains unresolved [76].

There is substantial evidence supporting the effectiveness of opioids, NSAIDs, metamizole, and acetaminophen when used as individual medications. However, it's important to acknowledge the frequent need for rescue therapy, often involving opioids. If a significant proportion of patients require rescue treatment, it's possible that at certain time points, the effects of the investigated drug combined with the rescue medication might become apparent. The exclusion of patients from the analysis after rescue therapy usage further complicates interpretation. A high rate of rescue therapy administration suggests that the proposed therapeutic approach is inadequate and requires modification, either by altering the treatment regimen or adjusting the dosing scheme. Our review lacks the capacity to definitively recommend any specific substance as the primary therapy option. Other analytical meta-analyses indicate the superiority of NSAIDs over opioids and acetaminophen in this context [77].

Nevertheless, opioids remain a viable choice as either a first or second-line option, particularly when combined with NSAIDs, as they pose a minimal risk of adverse events. Concerns about severe respiratory depression and drug dependency are less relevant when considering the treatment of acute pain in typically healthy patients. Notably, according to one meta-analysis, acetaminophen seems to exhibit greater efficacy than opioids at 30 minutes in specific randomized controlled trials [78].

It is crucial to highlight that the aforementioned studies underscore the heightened potency, efficacy, and rapid action of combination therapies in comparison to single-medication approaches. The success of combined analgesic treatments is well-established. Moreover, investigations into alternative medication combinations, such as desmopressin and clonidine, have demonstrated increased therapeutic efficacy without significant side effects. To achieve even more promising outcomes, further analysis should explore additional combination therapies, including the concurrent use of two analgesic agents and one antispasmodic medication. Notably, these combinations have been underrepresented in RCTs.

Furthermore, the augmentation of standard therapy with alternative approaches like nerve blocks or acupuncture has also exhibited enhanced effectiveness. Acupuncture, in particular, has proven to be a swifter and more efficacious technique for diminishing pain intensity in cases of renal colic. The associated adverse events of these procedures are minimal; however, the limited availability of specialized practitioners poses a constraint. Nerve blocks have demonstrated greater potency compared to conventional methods of pain relief in renal colic and appear to be more feasible within an emergency department setting, albeit necessitating specialized training.

Aromatherapy presents yet another alternative modality for pain management, complementing conventional regimens. It has demonstrated a reduction in pain intensity during the treatment of renal colic, particularly among female subjects. This underscores that not only medications but also environmental factors contribute to alleviating acute pain.

In our opinion, achieving further advancements in identifying the most effective therapy for renal colic necessitates specific modifications in the methodologies employed in trials. A commonly utilized exclusion criterion is the prior use of analgesics before study enrollment. However, this criterion is challenging to fulfill in real-life scenarios, as most patients self-administer oral medications at home, and some receive intramuscular or intravenous injections from paramedics or general practitioners prior to arriving at the emergency department. Given the difficulty in addressing this issue, we recommend reporting prior pharmaceutical usage instead of prohibiting it. Moreover, there should be an increased emphasis on pain severity as an inclusion criterion. To obtain reliable data regarding the treatment of acute renal colic pain, only patients experiencing severe pain should be included. While many studies reported a VAS criterion of >4 or even >3, these thresholds often fall below the mean VAS scores reported post-therapy. However, the mean VAS scores generally ranged between 8 and 9, indicating that the majority of enrolled patients indeed had severe pain at recruitment.

A further consideration regarding inclusion criteria relates to the frequently unequal distribution of male-to-female ratios in studies. Although this predominantly affects men with a 2:1 ratio, efforts should be directed towards achieving a more balanced representation of patients to facilitate valid comparisons and future applicability of the results. Investigating the experience and treatment of colic pain across different age groups could also prove valuable.

Inconsistencies in diagnostic procedures were also observed with respect to inclusion criteria. Not all studies confirmed ureteral obstruction through imaging or urine sampling tests. According to EAU guidelines, non-contrast-enhanced computed tomography stands as the gold standard for diagnosing ureteral stones in cases of severe flank pain in the emergency department or hospital setting. However, some analyses did not incorporate such radiological imaging and instead employed plain ultrasound or radiography.

Arguably, the most pivotal methodological aspect concerns the therapeutic objective for renal colic

pain, which should be achieving a decrease in VAS (or a similar metric) to 0–1/10. The compilation and interpretation of results are often challenging due to instances where patients weren't entirely relieved of pain by the treatments under study. As a result, treatments were deemed successful based on potentially misleading criteria, such as a 3-point reduction or 50% decrease on the scale.

When authors present diverse outcomes in their manuscripts, differing conclusions may be drawn when focusing on specific parameters. For instance, in the study by Forouzanfar et al. [21], comparing ibuprofen with ketorolac using a ≥3-point drop in VAS at 30 or 60 minutes, both medications might be perceived as equally effective (100% vs 100%). However, assessing complete pain relief after 15 and 30 minutes could lead to the conclusion that both therapies are ineffective (0% vs 0% and 1.7% vs 10%, respectively). Nonetheless, pain score changes on the plot reveal a significant effect of both substances, albeit not rapidly – at 15 minutes, pain levels remained around 5/10. Statistical tests indicated a significant advantage for ibuprofen when considering score differences and their changes from baseline at 30 and 60 minutes. The authors based their conclusions on ibuprofen's faster pain reduction, mainly due to the substantial difference in the 3-point VAS drop at 15 minutes (92% vs 12%). We propose that future studies present all data in a uniform manner for ease of future analyses. Additionally, achieving consensus on which outcomes hold clinical relevance is imperative.

Furthermore, many studies lacked detailed information about rescue therapy, and patients receiving rescue analgesia were often excluded from the study. It's crucial to include patients requiring rescue therapy in the final analysis as these instances should be considered treatment failures. Additionally, the final analysis sometimes omitted data on side effects observed during therapy, or specific patient symptoms weren't adequately specified.

CONCLUSIONS

Frequent use of opioids as rescue medications in RCTs undermine their conclusions on effectiness of other therapeutics. Guidelines should promote a more adaptable use of combination therapy, including opioids, based on pain severity. Novel research is essential to develop a swift and effective therapy for treating severe pain that doesn't necessitate the use of additional rescue medications.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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