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Review – Stone Disease

A Systematic Review and Meta-analysis Comparing the Efficacy of Nonsteroidal Anti-inflammatory Drugs, Opioids, and Paracetamol in the Treatment of Acute Renal Colic

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Abstract

Context: Renal colic is a common, acute presentation of urolithiasis that requires immediate pain relief. European Association of Urology guidelines recommend nonsteroidal anti-inflammatory drugs (NSAIDs) as the preferred analgesia. However, the fear of NSAID adverse effects and the uncertainty about superior analgesic effect have maintained the practice of advocating intravenous opioids as the initial analgesia.
Objective: The objective of this systematic review and meta-analysis was to compare the safety and efficacy of NSAIDs with opioids and paracetamol (acetaminophen) for the management of acute renal colic.
Evidence acquisition: Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, World Health Organization International Clinical Trials Registry Platform, Google Scholar, and the reference list of retrieved articles were searched up to December 2016 without language restrictions. Two reviewers independently assessed eligible studies using the Cochrane Collaboration tool for assessing and reporting the risk of bias and abstracted data using predefined data fields.
Evidence synthesis: From 468 potentially relevant studies, 36 randomized controlled trials (RCTs) including 4887 patients, published between 1982 and 2016, were included in this systematic review. The treatment effect observed indicated marginal benefit of NSAIDs over opioids in initial pain reduction at 30 min (11 RCTs, $n = 1985$, mean difference [MD] −5.58, 95% confidence interval [CI] −10.22 to −0.95; heterogeneity $I^2 = 81\%$). In the subgroup analyses by the route of administration, NSAIDs required fewer rescue treatments (seven RCTs, $n = 541$, number needed to treat [NNT] 11, 95% CI 6–75) and had lower vomiting rates compared with opioids (five RCTs, $n = 531$, NNT 5, 95% CI 4–8). Comparisons of NSAIDs with paracetamol showed no difference for both drugs at 30 min (four RCTs, $n = 1325$, MD −5.67, 95% CI −17.52 to 6.18, $p = 0.35$; $I^2 = 89\%$). Patients treated with NSAIDs required fewer rescue treatments (two trials, $n = 1145$, risk ratio 0.56, 95% CI 0.42–0.74, $p < 0.001$; $I^2 = 0\%$).
Conclusions: NSAIDs were equivalent to opioids or paracetamol in the relief of acute renal colic pain at 30 min. There was less vomiting and fewer requirements for rescue analgesia with NSAIDs compared with opioids. Patients treated with NSAIDs required less rescue analgesia compared with paracetamol. Despite observed heterogeneity among the included studies and the overall quality of evidence, the findings of a lower need for rescue analgesia and fewer adverse events, in conjunction with the practical advantages of ease of delivery, suggest that NSAIDs should be the preferred analgesic option for patients presenting to the emergency department with renal colic.
Patient summary: In kidney stone–related acute pain episodes in patients with adequate renal function, treatment with nonsteroidal anti-inflammatory drugs offers effective and most sustained pain relief, with fewer side effects, when compared with opioids or paracetamol.

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1. Introduction

Renal colic is a common abdominal complaint with millions of emergency department visits worldwide due to excruciating pain. The reported prevalence of kidney stone varies widely from 0.1% to 18.5% [1], with a recurrence of stone in about 50% of cases over 5–10 yr.

Acute pain management is the main expectation of patients in severe pain from renal colic. The most important factors deciding the choice of initial analgesia include the safety, efficacy, cost, and availability of a drug, in addition to patient and clinician preferences [2]. Nonsteroidal anti-inflammatory drugs (NSAIDs) have been recommended as the first-line analgesic [3–6] based on the mechanism of action of prostaglandin synthesis inhibition and supported by the evidence of effectiveness [7]. However, NSAID use as the first-line analgesic in clinical practice has repeatedly been challenged, and many clinicians continue to prefer opioid treatment [8,9]. The practice of using opioids as the preferred analgesic in renal colic is advocated based on the advantage of titrating the dose according to pain severity and lack of adverse events such as renal failure and gastrointestinal (GI) bleeding reported with NSAID treatment [8]. Following the last Cochrane review [7] concluding that NSAID treatment achieved higher pain reductions with a superior adverse effect profile compared with opioids, some randomized controlled trials (RCTs) with contrary evidence have been published [10–12]. In addition, alternative analgesics including paracetamol have been studied. Paracetamol (acetaminophen) has been reported to provide equal [13,14] or better [15,16] analgesia than opioids for the treatment of renal colic.

The uncertainty evident in current clinical practice requires an assessment review of the efficacy and safety of analgesics commonly used in renal colic. Therefore, we aimed to compare the efficacy and safety of NSAIDs against opioids or paracetamol for the management of acute renal colic.

2. Evidence acquisition

The protocol for this systematic review was registered on PROSPERO (CRD42016047559), and the detailed methodology was published [17] following the Preferred Reporting Items for Systematic Reviews and Meta-analysis recommendations for reporting of protocols (PRISMA-P).

2.1. Literature search

Previously published Cochrane Collaboration systematic reviews [7,18] served as the foundation for our search methodology. The new search strategy was developed and published online along with the protocol [17]. MEDLINE, EMBASE, Cochrane Renal Group, and Cochrane database for systematic reviews and controlled trials were searched up to December 18, 2016, without language restrictions, to identify relevant literature. To search for unpublished or ongoing studies, the World Health Organization International Clinical Trials Registry Platform was searched through February 2017. Finally, a Google Scholar search and hand search of the reference list of retrieved articles were performed to identify missing trials or reports not published in the mainstream literature.

2.2. Inclusion and exclusion criteria

We performed an electronic literature search in identified databases separately. EndNote X7 reference manager was then used to combine the results and remove duplications. Two reviewers (S.A.P. and B.M.) independently screened the titles, abstracts, and full-text articles to identify potentially eligible studies (Fig. 1). The inclusion criteria were defined prior to the search as all RCTs, published in any language, compared NSAIDs with opioids or NSAIDs with paracetamol, in any dose and by any route, used as analgesia in acute renal colic. We translated non-English, full-text articles with the use of professional translators. The summary information for the included studies and reasoning for the excluded articles are presented in the Supplementary material.

2.3. Data extraction

Two reviewers (S.A.P. and B.M.) independently reviewed manuscripts and abstracted data using predefined data fields. We extracted data on research information (settings, study design, outcome measuring scale, and funding), characteristics of participants (age, sex, eligibility criteria, and stone confirmation method), intervention details (drug type, dose, and route of administration), and outcomes reported. The outcomes studied in this review were as follows: (1) 30-min pain variance based on patient-reported pain score using a visual analog scale (VAS 0–100 mm, VAS 10 cm) or numerical rating scale (NRS-11); (2) proportion of patients with complete pain relief at 30 min; (3) proportion of patients with $\geq$50% reduction in pain at 30 min; (4) acute adverse events such as vomiting, allergic rash, dizziness, hypotension, and respiratory problems; (5) treatment-associated vomiting rates; and (6) serious adverse events such as anaphylaxis, need for dialysis, GI bleeding, or intramuscular complications at the injection site. Long-term side effects such as cardiotoxic effects or drug dependence were not studied, as they were not considered to be relevant to single-dose initial therapy.

2.4. Assessment of risk of bias

After a calibrating exercise using the Cochrane Collaboration tool for assessing and reporting the risk of bias, two reviewers assessed each study independently. Reporting was solely based on the information published in the article and when the information reported was insufficient to make any clear judgment, the risk was reported as "unclear." Any discrepancies during the process of screening, identifying eligible articles, or risk assessments were discussed and resolved by reaching a consensus between

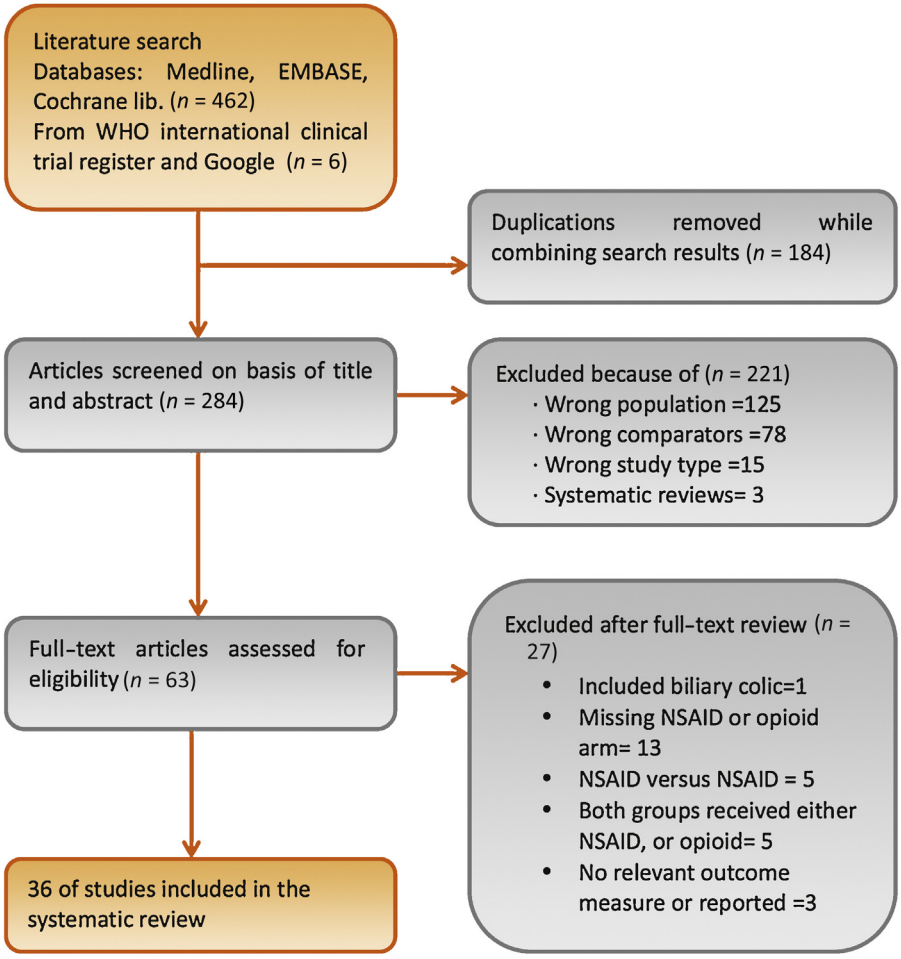

Fig. 1 – Study flow diagram. NSAID = nonsteroidal anti-inflammatory drug; WHO = World Health Organization.

the reviewers before the final reporting and analyses (Supplementary material).

2.5. *Data synthesis and primary analysis*

The VAS or NRS are unidimensional, 10-cm-length scales, which are anchored by "no pain" (score of 0) and "pain as bad as it could be" or "worst imaginable pain" (score of 100 in VAS 100 mm, score of 10 in VAS 10 cm, or score of 10 in NRS-11 points) [19,20]. For pain variance, based on the previous literature and expert opinions, we pooled data from studies reporting VAS 100 mm, VAS 10 cm, and NRS-11 by converting it to a "0–100-pain measure" using an appropriate multiplier. We also analyzed pain variance by reported VAS 100 mm and by NRS-11 or VAS-10 independently (Supplementary material).

We performed all comparison analyses based on the random-effects model using RevMan 5.3 meta-analytic software (The Nordic Cochrane Centre, Copenhagen, Denmark). To assess the statistical significance of pooled results, two-tailed statistical test and probability of type I error of 0.05 was set. Continuous outcomes were analyzed using inverse variance method, and observed treatment effect was reported as mean difference (MD) with 95% confidence intervals (CIs). Categorical outcomes were analyzed using Mantel–Haenszel method, and observed effect size was reported as risk ratios (RRs) with 95% CI.

To assess heterogeneity among the studies included in a pooled analysis, a p value of <0.1 was set, and τ^2 was calculated to represent variance between studies included in a pooled analysis (Table 1). Higgins I^2 statistics was used to quantify the percentage of variance due to heterogeneity rather than due to chance [21]. For all unidirectional pooled results, if significant heterogeneity ($p < 0.1$ or $I^2 \geq 50\%$) was encountered, we recalculated a 95% "prediction interval" (95% PI) to assess certainty of the observed effect in relation to the true effect [22,23].

We also performed subgroup analyses based on an a priori decision to explore the possible sources of heterogeneity. Publication bias was examined visually by funnel plot inspection for any asymmetry around the pooled effect and formally by Egger's test to detect statistical significance. All forest plots and the funnel plots are illustrated in the Supplementary material. Finally, we reported the quality of evidence for each outcome according to the Grading of Recommendation Assessment, Development, and Evaluation (GRADE) methodology.

Table 1 – Effect estimates, heterogeneity, 95% confidence intervals, and prediction intervals

Ref. no.	Comparison by the outcome or subgroup analysis	Studies included	Participants included	Summary estimate	*p* value (for pooled estimate)	95% CI for observed effect	τ^2 [a]	*p* value (heterogeneity—Higgins 2003)	I^2 statistics (%)	95% prediction interval
	Nonsteroidal anti-inflammatory drugs compared with opioids									
1.1	Pain variance [b]	11	1985	MD [c]	0.02	−5.58 (−10.22, −0.95)	44.07	<0.001	81	−5.21 (−18.49, 8.07)
1.2	Pain variance by study quality	11	1985	MD	0.06	−4.94 (−10.17, 0.30)	56.15	<0.001	82	−4.78 (−19.77, 10.21)
1.3	Pain variance by variance estimate	11	1985	MD	0.02	−5.58 (−10.22, −0.95)	44.07	<0.001	81	−5.21 (−18.49, 8.07)
1.4	Pain variance by reported VAS 100 mm	6	426	MD	0.08	−7.89 (−16.76, 0.98)	99.53	<0.001	86	−7.94 (−27.89, 12.01)
1.5	Pain variance by reported NRS-11 or VAS 10 cm	5	1559	MD	0.16	−0.39 (−0.93, 0.16)	0.26	0.002	76	−0.39 (−1.41, 0.63)
1.6	Pain variance by NSAID type	11	1985	MD	0.02	−5.58 (−10.22, −0.95)	44.07	<0.001	81	−5.21 (−18.49, 8.07)
1.7	Pain variance by opioid quality	11	1985	MD	0.02	−5.58 (−10.22, −0.95)	44.07	<0.001	81	−5.21 (−18.49, 8.07)
1.8	Pain variance by route	8	759	MD	0.01	−7.64 (−13.74, −1.54)	59.76	<0.001	82	−7.72 (−23.18, 7.74)
2.1	Failure of complete relief	13	943	RR [d]	0.57	0.96 (0.82, 1.11)	0.02	0.03	49	0.96 (0.72, 1.27)
2.2	Failure of complete relief by study quality	13	943	RR	0.57	0.96 (0.82, 1.11)	0.02	0.03	49	0.96 (0.72, 1.27)
2.3	Failure of complete relief by NSAID type	13	943	RR	0.57	0.96 (0.82, 1.11)	0.02	0.03	49	0.96 (0.72, 1.27)
2.4	Failure of complete relief by opioid type	12	875	RR	0.44	0.93 (0.77, 1.12)	0.04	0.02	49	0.93 (0.62, 1.38)
2.5	Failure of complete relief by route	9	664	RR	0.63	0.97 (0.85, 1.11)	0.01	0.15	34	–
2.6	Failure to achieve ≥50% reduction in initial pain	4	1805	RR	0.26	0.76 (0.47, 1.22)	0.19	<0.001	82	0.76 (0.31, 1.81)
3.1	Need for rescue analgesia	17	2391	RR	0.01	0.73 (0.57, 0.94)	0.1	0.009	52	0.73 (0.38, 1.37)
3.2	Need for rescue analgesia by study quality	17	2391	RR	0.01	0.73 (0.57, 0.94)	0.1	0.009	52	0.73 (0.38, 1.37)
3.3	Need for rescue analgesia by NSAID type	17	2391	RR	0.01	0.73 (0.57, 0.94)	0.1	0.009	52	0.73 (0.38, 1.37)
3.4	Need for rescue analgesia by opioid type	17	2409	RR	0.007	0.73 (0.58, 0.92)	0.09	0.01	49	0.73 (0.4, 1.33)
3.5	Need for rescue analgesia by route	11	1000	RR	0.002	0.75 (0.63, 0.90)	0	0.97	0	–
4.1	Adverse events	23	2703	RR	<0.001	0.53 (0.40, 0.69)	0.19	<0.001	59	0.53 (0.22, 1.26)
4.2	Adverse events by study quality	23	2703	RR	<0.001	0.53 (0.40, 0.69)	0.19	<0.001	59	0.53 (0.22, 1.26)
4.3	Adverse events by NSAID type	23	2703	RR	<0.001	0.53 (0.40, 0.69)	0.19	<0.001	59	0.53 (0.22, 1.26)
4.4	Adverse events by opioid type	23	2721	RR	<0.001	0.55 (0.42, 0.71)	0.19	<0.001	60	0.55 (0.23, 1.31)
4.5	Adverse events by route	16	1201	RR	<0.001	0.56 (0.42, 0.74)	0.15	0.001	60	0.56 (0.25, 1.21)
4.6	Vomiting as adverse event	14	2300	RR	0.009	0.41 (0.24, 0.70)	0.4	0.009	54	0.41 (0.11, 1.45)
4.7	Vomiting as adverse event by opioid type	14	2300	RR	0.001	0.41 (0.24, 0.70)	0.4	0.009	54	0.41 (0.11, 1.45)
4.8	Vomiting as adverse event by route	8	793	RR	<0.001	0.31 (0.20, 0.49)	0	0.8	0	–
	Nonsteroidal anti-inflammatory drugs compared with paracetamol									
5.1	Pain variance	4	1325	MD	0.35	−5.67 (−17.52, 6.18)	125.38	<0.001	89	−5.67 (−28.06, 16.72)
5.2	Need for rescue analgesia	2	1145	RR	<0.001	0.56 (0.42, 0.74)	0.47	0.49	0	–
5.3	Adverse events	4	1325	RR	0.82	1.10 (0.47, 2.58)	0.61	0.92	0	–
5.4	Vomiting as adverse event	2	1195	RR	0.36	0.54 (0.15, 2.00)	0.11	0.74	0	–

CI = confidence interval; MD = mean difference; NRS-11 = numerical rating scale; NSAID = nonsteroidal anti-inflammatory drug; Ref. = reference; RR = risk ratio.
Pain variance, failure to complete pain relief, or ≥50% pain relief was reported for 30 min pain reassessment.

[a] For the RR, τ^2 is reported in log units.

[b] Pain variance denotes pain scores converted to 0–100-pain measure.

[c] MD denotes mean difference (inverse variance method, random effects method, 95% CI).

[d] RR denotes risk ratio (Mantel–Haenszel method, random effects method, 95% CI).

Table 2 – Baseline characteristics of the included studies

Study, author, year (Country)	Groups	Trial size included	Outcome	Note
Comparison 1: NSAIDs with opioids				
Al-Sahlawi et al (1996) [24] (Kuwait)	• Group 1: indomethacin 100 mg IV; 50 (34) • Group 2: pethidine 100 mg IV; 50 (37) • Group 3: lysine acetylsalicylate 1.8 g IV; 50 (31)	100	• Complete pain relief at 30 min • Need for rescue analgesia • Adverse events	Group 3 excluded from the analysis because of the drug type (lysine acetylsalicylate)
Arnau et al (1991) [25] (Spain)	• Group 1: diclofenac 75 mg IM; 116 (63) • Group 2: pethidine 100 mg IM; 118 (61) • Group 3: dipyrone 1 g IM; 116 (67) • Group 4: dipyrone 2 g IM; 101 (57)	234	• Pain score (VAS 10 cm) at 30 min • Need for rescue analgesia • Adverse events	Groups 3 and 4 excluded from the analysis because of the drug type (dipyrone)
Ay et al (2014) [26] (Turkey)	• Group 1: dexketoprofen trometamol 50 mg IV; 26 • Group 2: meperidine HCl 100 mg IV; 26	52	• Pain score (NRS-11) at 30 min • Need for rescue analgesia • Adverse events	
Cordell et al (1994) [27] (USA)	• Group 1: indomethacin 100 mg PR; 31 (18) • Group 2: morphine 5–10 mg IV; 20 (18)	51	• Adverse events	
Cordell et al (1996) [28] (USA)	• Group 1: meperidine 50 mg IV; 35 (28) • Group 2: ketorolac 60 mg IV; 36 (30) • Group 3: combination therapy (both); 35 (25)	71	• Pain score (VAS 100 mm) at 30 min • 50% reduction in initial pain at 30 min • Need for rescue analgesia • Adverse events	Group 3 was combination Analgesia, therefore not included in the analysis
Curry and Kelly (1995) [10] (New Zealand)	• Group 1: tenoxicam 40 mg IV; 17 • Group 2: pethidine 75 mg IV; 24	41	• Pain score (VAS 100 mm) at 30 min • Need for rescue analgesia • Adverse events	
Daljord et al (1983) [29] (Norway)	• Group 1: pethidine 75 mg IV; 16 • Group 2: fortalin 30 mg IV; 16 • Group 3: temgesic 0.3 mg IV; 17 • Group 4: indomethacin 50 mg IV; 18	67	• Complete pain relief at 30 min • Need for rescue analgesia • Adverse events	Groups 1, 2 and 3 were combined as opioid; however, Pethidine data are separately included in opioid subtype analysis
Gonzalez et al (1990) [30] (Spain)	• Group 1: diclofenac 75 mg IM; 20 • Group 2: buprenorphine 0.3 mg IM; 20	40	• Adverse events	
Hetherington and Philp (1986) [32] (UK)	• Group 1: diclofenac 75 mg IM; 30 • Group 2: pethidine 100 mg IM; 28	58	• Need for rescue analgesia • Adverse events	
Hosseini et al (2015) [33] (Iran)	• Group 1: diclofenac 100 mg PR; 266 • Group 2: pethidine 50 mg IM; 275	541	• 50% reduction in initial pain at 30 min	
Indudhara et al (1990) [34] (India)	• Group 1: diclofenac 150 mg PO; 33 • Group 2: pethidine 50 mg IM; 31 • Group 3: Baralgan 2 tablets PO; 30	33	• Adverse events	Third group not included in the analysis because of drug type (Baralgan)
Jonsson et al (1987) [35] (Sweden)	• Group 1: 5 mg oxyconchloride + 50 mg papaverine IV; 26 (24) • Group 2: 50 mg indomethacin IV; 35 (30)	47	• Adverse events	
Khalifa and Sharkawi (1986) [37] (Kuwait)	• Group 1: diclofenac 50 mg IM; 50 (46) • Group 2: (pethidine 50–100 mg and 20 mg hyoscine butyl bromide) IV; 41 (36)	91	• Complete pain relief at 30 min • Adverse events	
Larkin et al (1999) [38] (USA)	• Group 1: ketorolac 60 mg IM; 33 (26) • Group 2: pethidine 100–150 mg IM; 37 (27)	70	• Need for rescue analgesia • Adverse events	
Lehtonen et al (1983) (Finland)	• Group 1: indomethacin 50 mg IV; 93 (69) • Group 2: pethidine 50 mg IV; 31 (26) • Group 3: metamizol 2.5 g IV; 45 (33)	124	• Complete pain relief at 30 min • Need for rescue analgesia • Adverse events	Third group not included in the analysis because of drug type (metamizol)

Table 2 (*Continued*)

Study, author, year (Country)	Groups	Trial size included	Outcome	Note
Lund et al (1986) [40] (Denmark)	• Group 1: indomethacin 50 mg IV; 21 • Group 2: pethidine 75 mg IV; 11	32	• Complete pain relief at 30 min • Adverse events	
Lundstam et al (1982) [41] (Sweden)	• Group 1: diclofenac 50 mg IM; 34 (25) • Group 2: spasmofen 1 ml IM; 32 (25)	66	• Adverse events	
Marthak et al (1991) [11] (India)	• Group 1: diclofenac 75 mg IM; 25 (17) • Group 2: pethidine 75 mg IM; 25 (20)	50	• Pain score (VAS 100 mm) at 30 min • Complete pain relief at 30 min • Adverse events	
Oosterlinck et al (1990) [44] (UK)	• Group 1: Ketorolac 10 mg IM; 45 (32) • Group 2: ketorolac 90 mg IM; 37 (29) • Group 3: pethidine 100 mg IM; 39 (29)	125	• Pain score (VAS 100 mm) at 30 min • Complete pain relief at 30 min • Adverse events	For VAS score analysis, group 2 was chosen as NSAID representative
Pathan et al (2016) [58] (Qatar)	• Group 1: diclofenac 75 mg IM; 547 (460) • Group 2: acetaminophen 1 g IV; 548 (446) • Group 3: morphine 0.1 mg/kg IV (based on measured weight); 549 (456)	1096	• Pain score (NRS-11) at 30 min • 50% reduction in initial pain at 30 min • Need for rescue analgesia • Adverse events	Data for Group 2 (paracetamol) not included in the comparison 1
Persson et al (1985) [45] (Sweden)	• Group 1: indoprofen 400 mg IV; 48 (35) • Group 2: (oxicone 10 mg + papaverine 20 mg) IM; 46 (35)	94	• Adverse events	
Quilez et al (1984) [46] (Spain)	• Group 1: diclofenac 75 mg IM; 24 (14) • Group 2: pentazoxine 30 mg IM; 14 (8) • Group 3: hyoscine N-Butyl Bromide 20 mg IM; 23 (14)	38	• Complete pain relief at 30 min	
Safdar et al (2006) [47] (USA)	• Group 1: morphine 5 mg IV; 43 (29) • Group 2: ketorolac 15 mg IV; 43 (29) • Group 3: combined IV; 44 (30) (the dose was repeated at 20 min in each arm if need)	86	• Need for rescue analgesia • Adverse events	Group 3 was combination analgesia, therefore not included in the analysis
Salameh et al (2011) [48] (Israel)	• Group 1: diclofenac 75 mg IM; 48 (38) • Group 2: tramadol 100 mg IM; 49 (35)	97	• Pain score (VAS 10 cm) at 30 min • Need for rescue analgesia	
Sandhu et al (1994) [49] (UK)	• Group 1: ketorolac 30 mg IM; 76 (59) • Group 2: pethidine 100 mg IM; 78 (58)	154	• Adverse events	
Shirazi et al (2015) [12] (Iran)	• Group 1: tramadol 50 mg IM; 40 (23) • Group 2: indomethacin 100 mg PR; 40 (22) • Group 3: desmopressin 40 μg IN; 40 (25)	80	• Pain score (VAS 10 cm) at 30 min • Complete pain relief at 30 min • Need for rescue analgesia	Third group not included in the analysis because of drug type (desmopressin)
Snir et al (2008) [50] (Israel)	• Group 1: diclofenac 75 mg IM; 30 (26) • Group 2: papaverine 120 mg IV; 29 (22) • Group 3: combined analgesia; 27 (20)	59	• Need for rescue analgesia • Adverse events	Group 3 was combination Analgesia, therefore not included in the analysis
Sommer et al (1989) [51] (Denmark)	• Group 1: diclofenac 75 mg IM; 27 (17) • Group 2: ketogan (containing 7.5 mg ketobemidone HCl) 3 ml IM; 29 (22)	56	• Complete pain relief at 30 min • Adverse events	
Thompson et al (1989) [52] (UK)	• Group 1: pethidine 100 mg + prochlorperazine 12.5 mg injections (?IV ? IM); 29 • Group 2: diclofenac 100 mg PR; 29	58	• Complete pain relief at 30 min • Need for rescue analgesia • Adverse events	

Table 2 (*Continued*)

Study, author, year (Country)	Groups	Trial size included	Outcome	Note
Torralba et al (1999) [43] (Spain)	• Group 1: ketorolac 30 mg IM; 24 • Group 2: tramadol 1 mg/kg SC; 24	48	• Need for rescue analgesia • Adverse events	
Uden et al (1983) [53] (Sweden)	• Group 1: indomethacin 50 mg IV; 25 (20) • Group 2: hydromorphine chloride-atropine 1 ml SC + prochlorperazine 25 mg PR; 25 (22)	50	• Pain score (VAS 100 mm) at 30 min • Complete pain relief at 30 min • Need for rescue analgesia • Adverse events	
Wood et al (2000) [54] (Canada)	• Group 1: ketorolac 30 mg IM; 65 (57) • Group2-50 mg of meperidine with 50 mg of dimenhydrinate; 77 (68)	142	• Pain score (VAS 100 mm) at 30 min	
Zamanian et al (2016) [55] (Iran)	• Group 1: morphine 10 mg PR; 79 (50) • Group 2: indomethacin 100 mg PR; 79 (52)	158	• Pain score (NRS-11) at 30 min • Adverse events	
Comparison 2: NSAIDs with paracetamol				
Grissa et al (2011) [31] (Tunisia)	• Group 1: paracetamol 1 g IV; 50 (20) • Group 2: piroxicam 20 mg IM; 50 (21)	100	• Pain score (VAS 100 mm) at 30 min • Adverse events	
Kaynar et al (2015) [36] (Turkey)	• Group 1: diclofenac 75 mg IM; 40 (26) • Group 2: acetaminophen 1 g IV; 40 (22) • Group 3: acupuncture; 41 (28)	80	• Pain score (VAS 10 cm) at 30 min • Adverse events	Group 3 excluded from analysis given the nature of treatment (acupuncture)
Narci et al (2012) [42] (Turkey)	• Group 1: diclofenac 75 mg IM; 25 (13) • Group 2: acetaminophen 1 g PO; 25 (14) • Group 3: combined analgesia; 25 (15)	50	• Pain score (VAS 100 mm) at 30 min • Need for rescue analgesia • Adverse events	Group 3 was combination analgesia, therefore, not included in the analysis
Pathan et al (2016) [16] (Qatar)	• Group 1: diclofenac 75 mg IM; 547 (460) • Group 2: acetaminophen 1 g IV; 548 (446) • Group 3: morphine 0.1 mg/kg IV (based on measured weight); 549 (456)	1095	• Pain score (NRS-11) at 30 min • 50% reduction in initial pain at 30 min • Need for rescue analgesia • Adverse events	Data for Group 3 (morphine) not included in the comparison 2

IM = intramuscular; IV = intravenous; NRS-11 = numerical rating scale; NSAID = nonsteroidal anti-inflammatory drug; SC = subcutaneous; VAS = visual analog scale.

3. Evidence synthesis

3.1. Quantity of evidence identified

A total of 36 RCTs [10–12,16,24–55] (including 4887 patients), published from 16 countries between 1982 and 2016, were included in this systematic review (Fig. 1). Five articles were published in non-English literature (three in Spanish [30,43,46], one in Norwegian [29], and one in Danish [40]). Of the included studies, 32 trials compared NSAIDs with opioids, three trials compared NSAIDs with paracetamol, and one trial included all three treatments. Only three RCTs [16,25,33] had ≥100 participants per treatment arm (Table 2). Five RCTs [29,31,43,46,52] were open-label trials, and industry sponsorship was declared in nine RCTs [10,25,28,32,39,40,49,53,54].

3.2. Characteristics of the included studies

Three trials were crossover studies [27,35,43], and only data from the pre-crossover period were included in data synthesis. Most trials conducted pain reassessment at 30 min, and rescue analgesia if needed was initiated after 30 min. In five RCTs [35,38,47,50,55], pain reassessment was carried out at 20 and 40 min without any reassessment at 30 min, and the rescue analgesia was initiated as early as 20 min [38,55]. Therefore, mean pain scores at 20 or 40 min from these studies were not included in the pooled analysis. In 17 out of 36 RCTs, for the primary outcome analysis, patients were excluded after the randomization mostly because of failure to confirm the presence of stone. However, the confirmation techniques used in the trials varied significantly from clinical examination alone to computed tomography scan examination.

3.3. Risk of bias assessment of the included studies

Selection bias was judged to be unclear for most of the studies included in this systematic review. The risk was assessed to be low in 13 studies for both performance and detection bias. Of the remaining studies included, all were found to have a high risk of detection or reporting bias (Fig. 2).

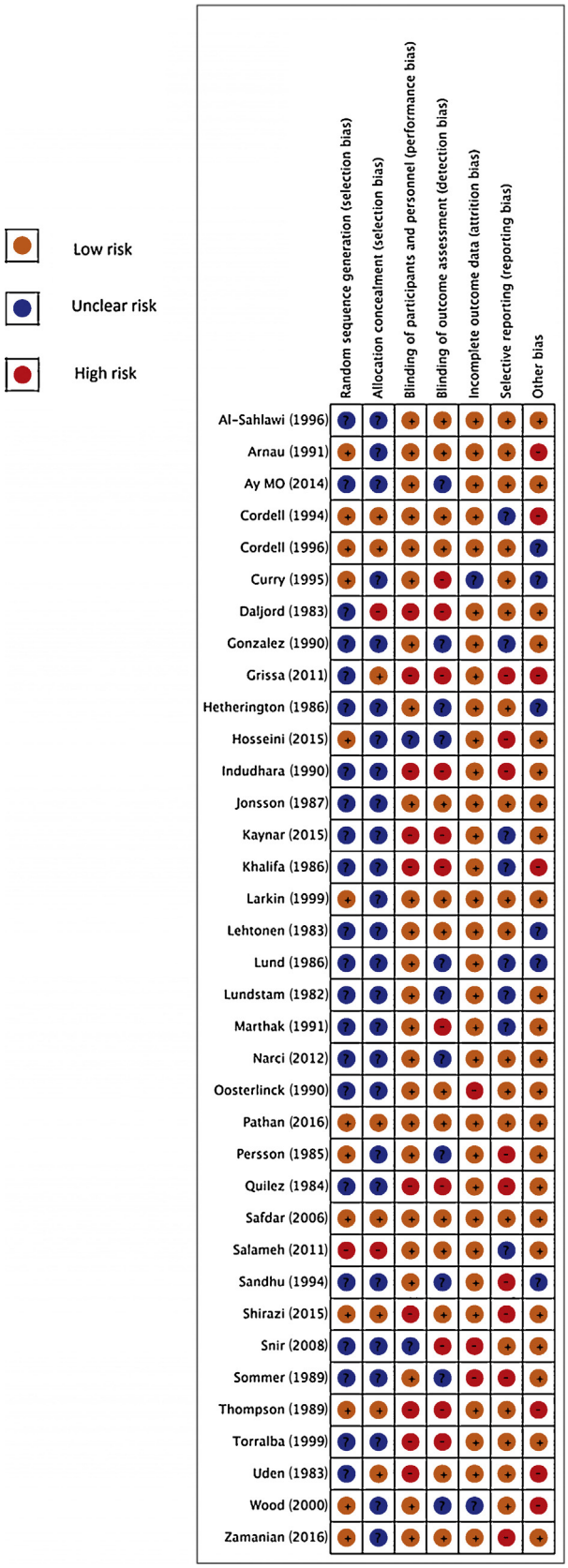

Fig. 2 – Risk of bias summary.

3.4. *Pain variance at 30 min*

Eleven RCTs [10–12,16,25,26,28,44,48,53,54] (including 1985 patients) compared NSAIDs with opioids using 30-min pain variance. After converting patient-reported pain scores into 0–100-pain measure, the treatment effect observed indicated marginal benefit of NSAID treatment over opioids (MD −5.58, 95% CI −10.22 to −0.95, $p = 0.01$); however, significant heterogeneity was observed across the pooled studies ($p \leq 0.001$, $I^2 = 81\%$). Subgroup analyses performed by reported VAS 100 mm, NRS-11, or VAS 10 cm; study quality; variance estimate; NSAID type; opioid type; and the route of administration did not identify the source of this heterogeneity (Table 1). The prediction interval for 30-min pain variance showed no difference between NSAID and opioid treatments (MD −5.58, 95% PI −18.49 to 9.07).

3.5. *Complete and ≥50% pain relief at 30 min*

Thirteen trials[11,12,24,29,37,39,40,44,46,47,51–53] (including 943 patients) compared NSAIDs with opioids, and reported complete pain relief at 30 min or next earliest after the initial treatment. The pooled effect size demonstrated no difference between NSAID treatment and opioids (RR 0.96, 95% CI 0.82–1.11, $p = 0.57$; $I^2 = 49\%$). Four studies [16,28,33,48] ($n = 1805$) comparing NSAIDs with opioids reported the proportion of patients achieving ≥50% reduction in each treatment arms. The pooled results showed no difference of NSAIDs over opioids for this outcome measure (RR 0.76, 95% CI 0.47–1.22, $p = 0.26$; $I^2 = 82\%$).

3.6. *Need for rescue analgesia*

A total of 17 trials [10,12,16,24–26,28,29,32,38,39,43,47,48,50,52,53] compared NSAIDs with opioids (including 2391 patients) and reported rescue analgesia treatment rates. The criteria to use rescue treatment, drug details (type, dose, and route), and the time for recording observation varied significantly among the studies included. The pooled results demonstrated lower requirement for rescue analgesia with NSAID treatment compared with opioids (RR 0.73, 95% CI 0.57–0.94, $p = 0.01$); however, moderate heterogeneity was found across the pooled studies ($p = 0.009$, $I^2 = 52\%$). The data were homogenous for the studies comparing the drugs by intravenous route of administration [10,24,26,28,29,39,47] (seven RCTs, $n = 541$), and showed consistent treatment benefit for NSAIDs requiring fewer rescue treatments compared with opioids (Fig. 3; number needed to treat 11, 95% CI 6–75).

3.7. *Nonspecific acute adverse events*

Twenty-three trials [10,11,16,24,28–30,32,34,35,37–41,43–45,47,49–51,53] (including 2703 patients) compared NSAIDs with opioids and reported the proportion of patients with adverse events. Participants treated with NSAIDs were less likely to have an adverse event than

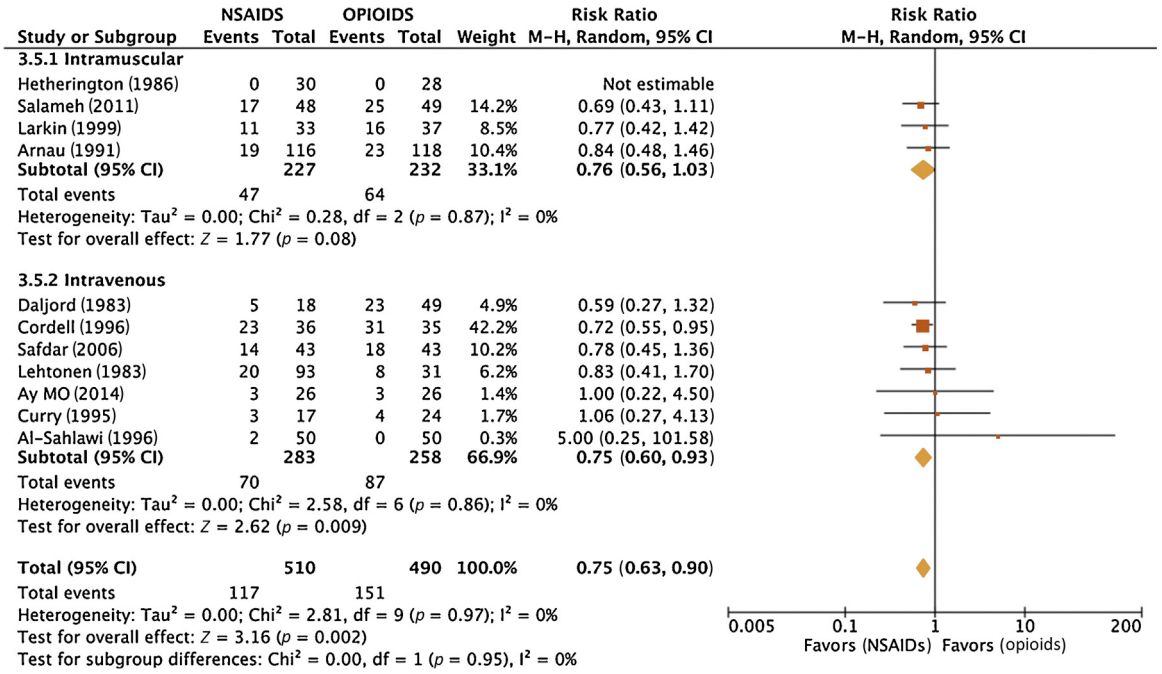

Fig. 3 – Comparison of NSAIDs versus opioids by route for analgesia requirements. CI = confidence interval; df = degree of freedom; M–H = Mantel–Haenszel; NSAID = nonsteroidal anti-inflammatory drug.

those treated with opioids (RR 0.53, 95% CI 0.40–0.69, $p < 0.001$). Study pooling demonstrated moderate heterogeneity ($p < 0.001$, $I^2 = 59\%$), and the prediction interval calculated showed uncertainty about the NSAID benefit over opioids for having fewer adverse events (RR 0.53, 95% PI 0.22–1.26).

3.8. *Vomiting as an adverse event*

Fourteen studies [11,16,25–27,39,41,44,45,47,51–53,55] (including 2300 patients) reported vomiting rates comparing NSAIDs and opioids, and the pooled effect size demonstrated lower vomiting rates with NSAID treatment (RR 0.41, 95% CI 0.24–0.70, $p < 0.009$). Moderate heterogeneity was detected across the included studies ($p = 0.009$, $I^2 = 54\%$), and the prediction interval calculated was 95% PI 0.11–1.45. The data were homogenous for the studies [11,25,41,44,51] comparing the drugs by intramuscular route of administration (five RCTs, $n = 531$) and demonstrated that NSAIDs have lower vomiting rates compared with opioids (Fig. 4; number needed to treat 5, 95% CI 4–8).

3.9. *Serious adverse events*

Only one study [16] reported data on serious adverse events, such as anaphylaxis, renal failure, or GI bleeding over 14 d follow-up, and no event was observed with opioids or NSAIDs.

3.10. *Comparison of NSAIDs versus paracetamol*

Four RCTs [16,31,36,42] (including 1325 patients), published between 2011 and 2016, compared NSAIDs with paracetamol. The treatment effect observed for 30-min pain variance by 0–100 pain measure did not show any difference between NSAIDs and paracetamol (MD −5.67, 95% CI −17.52 to 6.18, $p = 0.35$) and was associated with strong heterogeneity ($p \leq 0.001$, $I^2 = 89\%$). The pooled results showed no difference in treatment-related adverse events (four RCTs, $n = 1325$, RR 1.10, 95% CI 0.47–2.58, $p = 0.82$; $I^2 = 0\%$) or vomiting rates (two trials [16,31], $n = 1195$, RR 0.54, 95% CI 0.15–2.00, $p = 0.36$; $I^2 = 0\%$). However, participants treated with NSAIDs had fewer requirements for rescue analgesia compared with those treated with paracetamol (two RCTs [16,42], $n = 1145$, RR 0.56, 95% CI 0.42–0.74, $p < 0.001$; $I^2 = 0\%$). The number needed to treat with NSAIDs to avoid an additional event of rescue analgesia over paracetamol was 11 with 95% CI 8–21 (Fig. 5).

3.11. *Publication bias and grading the evidence*

Funnel plots generated for pain variance, complete pain relief, need for rescue analgesia, and adverse events—outcomes comparing NSAIDs with opioids—were symmetrical. Egger's test was insignificant, confirming a low risk of publication bias for these outcomes.

The quality of evidence following GRADE methodology was found to be very low for the outcomes such as pain variance, complete relief, or ≥50% reduction at 30 min, mostly owing to the inconsistencies observed in the treatment effect and the quality of studies included. There was low-quality evidence for the requirement of rescue analgesia with NSAID treatment. Evidence for NSAID benefit of lower vomiting rates was of moderate quality. There was high-quality evidence for NSAID benefit over paracetamol for the requirement of rescue treatments.

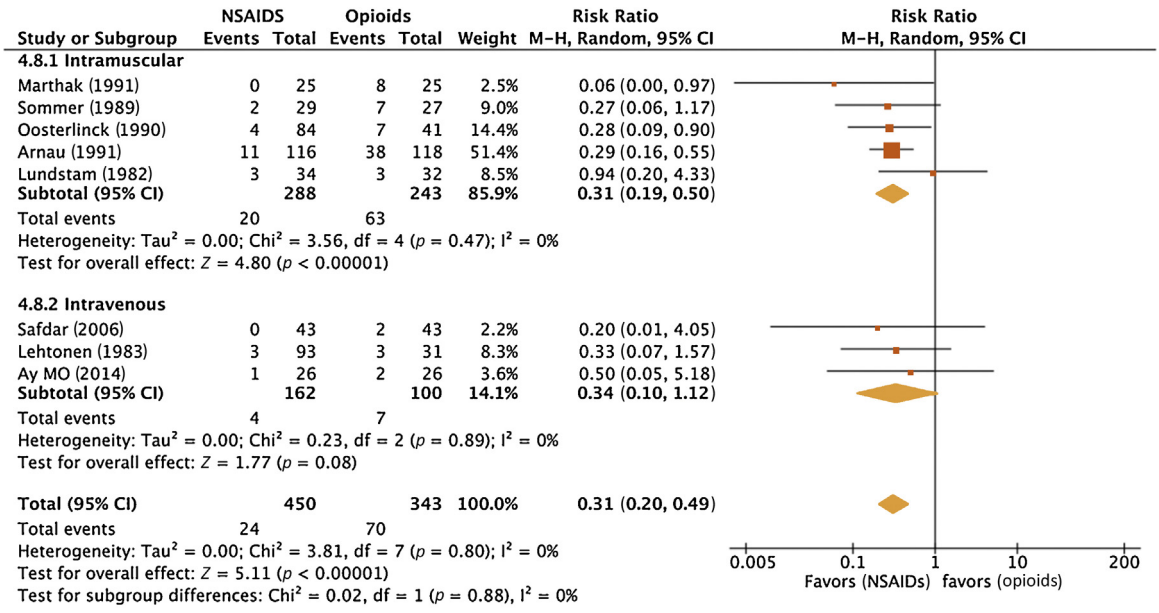

Fig. 4 – Comparison of NSAIDs versus opioids by route for vomiting as the adverse event. CI = confidence interval; df = degree of freedom; M–H = Mantel–Haenszel; NSAID = nonsteroidal anti-inflammatory drug.

3.12. Discussion

The principal finding of this systematic review is that the superiority of NSAIDs over opioids or paracetamol, for 30-min analgesic effect in renal colic, was uncertain. However, NSAIDs were found to have additional superior analgesic characteristics compared with opioids, requiring fewer rescue treatments and having lower vomiting rates. Equivalence of efficacy and adverse effect profile, when combined with the pragmatic benefits of ease of drug administration in the acute care setting and lack of analgesia abuse or addiction properties, establishes NSAIDs as the first-line analgesic agents to treat acute renal colic pain.

End points that are readily understood and expected by patients are the ideal targets to guide therapy. It must be accepted that complete resolution of pain could be due to the natural course of the disease or may not be possible in

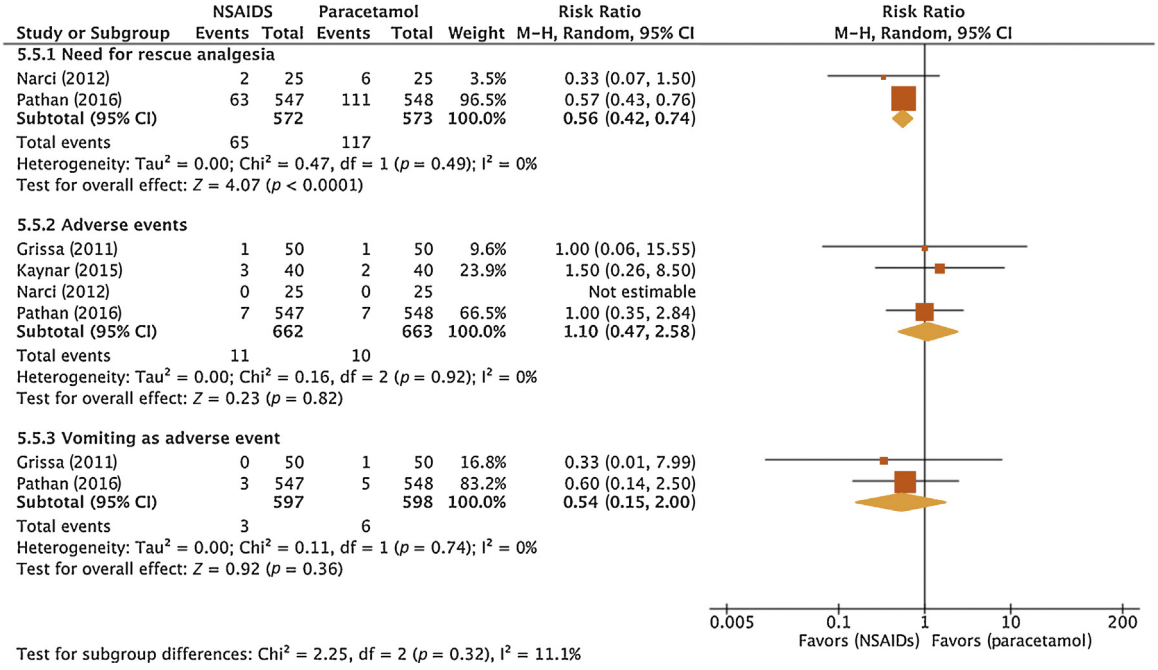

Fig. 5 – Comparison of NSAIDs versus paracetamol, need for rescue analgesia, adverse events, and vomiting as an adverse event. CI = confidence interval; df = degree of freedom; M–H = Mantel–Haenszel; NSAID = nonsteroidal anti-inflammatory drug.

the short term. All three treatments resulted in significant pain reduction in acute renal colic, and this finding was consistent with previous systematic reviews [7,56]. Previous systematic reviews had concluded that NSAIDs achieved greater pain reduction by pain variance (a statistically sensitive measure), but the translation of this benefit to a dichotomous outcome of clinically significant pain reduction (a practically relevant measure) did not support this superiority. The findings also emphasize the importance of reporting patient-centered dichotomous outcomes, such as complete pain relief or at least 50% reduction in pain along with pain variance in future trials [57].

It was interesting to note that NSAID benefit over opioids was route specific for the given outcomes. For rescue analgesia, the additional benefit was limited to the intravenous subgroup comparison, whereas for vomiting rates, the benefit was observed in the intramuscular subgroup comparison only. In renal colic management, intravenous administration of analgesics is believed to be more efficacious and less painful than the intramuscular route; therefore, it is routinely advocated for ease of titration. However, the intramuscular route is advantageous in providing quick and safe analgesia without the need for establishing intravenous access [58]. The per rectal (PR) route of NSAID administration is a common practice in many centers. However, for PR route of NSAID administration, there were insufficient data to pool the results because of a lack of common outcome measures or common routes of drug administration in the studies identified. Therefore, evidence in form of well-designed, large RCTs is needed to assess the efficacy of PR route of NSAID administration. It would seem prudent to carefully consider the route-specific benefits, discomforts, logistics involved, and patient preference while choosing the right analgesic approach.

Significant heterogeneity was noted in the type of opioids or NSAIDs used as well as the route of drug administration. Methodological heterogeneity may partly explain the observed difference in outcome. Recently, there has been a large volume of literature and concern about opioid misuse [59–61]. We did not find any advantage of opioid use as the initial analgesic. However, NSAID use was supported because of its sustained effect and lower adverse effect profile in addition to ease of logistics and speed of administration.

Our systematic review was comprehensive in the scope and search strategy. We adhered to the Cochrane methodology and guide for conducting the review, PRISMA guidelines for reporting of the review findings, and a previously published protocol. The review has several limitations to consider. Heterogeneity among included studies was a major issue in this systematic review [22]. Small study effects, methodological variability, higher proportion of studies with possible risk of selection, and performance or detection bias are known to cause clinical heterogeneity and potentially distort the results of a meta-analysis [62,63]. It is important to interpret meta-analysis results in the light of these considerations by estimating the prediction interval [2,22,23]. In addition, most RCTs included were small studies and had an unclear risk of bias in patient selection. Adverse events and time to assess this outcome were poorly defined in most trials. Characteristics of participants could have varied significantly, as the confirmation methods for stone and adherence to intention to treat were different between the studies. In addition to statistical heterogeneity, clinical heterogeneity was substantial among studies. For example, in the opioid group, 21 out of 33 trials had used pethidine or papaverine, both of which are less commonly used opioids with a worse adverse effect profile, leading to some centers discontinuing their use [64]. Finally, conversion of pain scores measured using different pain scales to a 0–100 pain measure could have led to the loss of some precision; however, we believe that it is clinically insignificant.

4. Conclusions

NSAIDs were at least equivalent to opioids and paracetamol for the relief of acute renal colic pain at 30 min after delivery. There was less vomiting and fewer requirements for rescue analgesia compared with opioids. NSAIDs required less rescue analgesia compared with paracetamol. Despite observed heterogeneity among the included studies and the overall quality of evidence, the findings of lower need for rescue analgesia and fewer adverse events, in conjunction with the practical advantages of ease of delivery, suggest that NSAIDs should be the preferred analgesic option for patients presenting to the emergency department with renal colic.

Author contributions: Sameer A. Pathan had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of data analysis.

Study concept and design: Pathan, Mitra, and Cameron.
Acquisition of data: Pathan.
Analysis and interpretation of data: Pathan, Mitra.
Drafting of the manuscript: Pathan.
Critical revision of the manuscript for important intellectual content: Cameron, Mitra.
Statistical analysis: Pathan, Mitra.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Cameron.
Other: None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2017.11.001.

References

[1] Romero V, Akpinar H, Assimos DG. Kidney stones: a global picture of prevalence, incidence, and associated risk factors. Rev Urol 2010;12:e86–96.

[2] Schriger DL. Pseudo-objectivity in the conduct and reporting of systematic reviews: an example. BMJ 2014;328:1401.

[3] The British Association of Urological Surgeons. Section of endourology: stone guidelines. First published: December 2008; reviewed and updated February 2012. http://www.baus.org.uk/_userfiles/pages/files/Publications/RevisedAcuteStoneMgtGuidelines.pdf.

[4] Turk C, Petrik A, Sarica K, et al. EAU guidelines on diagnosis and conservative management of urolithiasis. Eur Urol 2016;69:468–74.

[5] Managing patients with renal colic in primary care: Know when to hold them. BPJ 2014;60:8–17 In: http://www.bpac.org.nz/BPJ/2014/April/docs/BPJ60-colic.pdf

[6] Emergency Department Management of Renal Colic and Suspected Renal Calculus. Irish Association for Emergency Medicine clinical guidelines 3, version 1; May 2014. http://www.iaem.ie/wp-content/uploads/2015/08/IAEM-CG3-ED-Management-of- Suspected-Renal-Colic-Suspected-Renal-Calculus.pdf.

[7] Holdgate A, Pollock T. Systematic review of the relative efficacy of non-steroidal anti-inflammatory drugs and opioids in the treatment of acute renal colic. Br Med J 2004;328:1401–4.

[8] Dave C, Faraj K, Shetty S. Nephrolithiasis treatment & management. Medscape, Drug & Disease, Urology section, stone articles; Chief Editor: Schwartz BF. Updated 03. 2016. http://emedicine.medscape.com/article/437096-treatment-d7

[9] Badalato G, Leslie SW, Teichman J. American Urological Association, Medical Student Curriculum: Kidney Stones. 2016 July In: http://www.auanet.org/education/educational-programs/medical-student-education/medical-student-curriculum/kidney-stones

[10] Curry C, Kelly AM. Intravenous tenoxicam for the treatment of renal colic. N Z Med J 1995;108:229–30.

[11] Marthak KV, Gokarn AM, Rao AV, et al. A multi-centre comparative study of diclofenac sodium and a dipyrone/spasmolytic combination, and a single-centre comparative study of diclofenac sodium and pethidine in renal colic patients in India. Curr Med Res Opin 1991;12:366–73.

[12] Shirazi M, Salehipour M, Afrasiabi MA, Aminsharifi A. Analgesic effects and safety of desmopressin, tramadol and indomethacin in patients with acute renal colic; a randomized clinical trial. Bull Emerg Trauma 2015;3:41–5.

[13] Bektas F, Eken C, Karadeniz O, Goksu E, Cubuk M, Cete Y. Intravenous paracetamol or morphine for the treatment of renal colic: a randomized, placebo-controlled trial. Ann Emerg Med 2009;54:568–74.

[14] Serinken M, Eken C, Turkcuer I, Elicabuk H, Uyanik E, Schultz CH. Intravenous paracetamol versus morphine for renal colic in the emergency department: a randomised double-blind controlled trial. Emerg Med J 2012;29:902–5.

[15] Masoumi K, Forouzan A, Asgari Darian A, Feli M, Barzegari H, Khavanin A. Comparison of clinical efficacy of intravenous acetaminophen with intravenous morphine in acute renal colic: a randomized, double-blind, controlled trial. Emerg Med Int 2014;2014:571326.

[16] Pathan SA, Mitra B, Straney LD, et al. Delivering safe and effective analgesia for management of renal colic in the emergency department: a double-blind, multigroup, randomised controlled trial. Lancet 2016;387:1999–2007.

[17] Pathan SA, Mitra B, Romero L, Cameron PA. What is the best analgesic option for patients presenting with renal colic to the emergency department? Protocol for a systematic review and meta-analysis. BMJ Open 2017;7:e015002.

[18] Afshar K, Jafari S, Marks AJ, Eftekhari A, MacNeily AE. Nonsteroidal anti-inflammatory drugs (NSAIDs) and non-opioids for acute renal colic. Cochrane Database Syst Rev 2015;6:CD006027.

[19] Huskisson EC. Measurement of pain. Lancet 1974;2:1127–31.

[20] Jensen MP, Karoly P, Braver S. The measurement of clinical pain intensity: a comparison of six methods. Pain 1986;27:117–26.

[21] Higgins JP, Green S, editors. Cochrane handbook for systematic reviews of interventions, Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. 2011 In: www.handbook.cochrane.org

[22] Borenstein M, Higgins JP, Hedges LV, Rothstein HR. Basics of meta-analysis: I2 is not an absolute measure of heterogeneity. Res Synth Methods 2017;8:5–18.

[23] Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. BMJ 2011;342:d549.

[24] Al-Sahlawi KS, Tawfik OM. Comparative study of the efficacy of lysine acetylsalicylate, indomethacin and pethidine in acute renal colic. Eur J Emerg Med 1996;3:183–6.

[25] Arnau JM, Cami J, Garcia-Alonso F, Laporte JR, Palop R. Comparative study of the efficacy of dipyrone, diclofenac sodium and pethidine in acute renal colic. Eur J Clin Pharmacol 1991;40:543–6.

[26] Ay MO, Sebe A, Kozaci N, et al. Comparison of the analgesic efficacy of dexketoprofen trometamol and meperidine HCl in the relief of renal colic. Am J Ther 2014;21:296–303.

[27] Cordell WH, Larson TA, Lingeman JE, et al. Indomethacin suppositories versus intravenously titrated morphine for the treatment of ureteral colic. Ann Emerg Med 1994;23:262–9.

[28] Cordell WH, Wright SW, Wolfson AB, et al. Comparison of intravenous ketorolac, meperidine, and both (balanced analgesia) for renal colic. Ann Emerg Med 1996;28:151–8.

[29] Daljord OA, Barstad S, Norenberg P. Ambulatory treatment of an acute attack in urinary calculi. A randomized study of the effects of petidin, fortralin, temgesic and confortid. Tidsskr Nor Laegeforen 1983;103:1006–8, [In Norwegian].

[30] Gonzalez Ramallo VJ, Muino Miguez A, Rodriguez de Castro E, Lazaro Bermejo C. Intramuscular buprenorphine in the symptomatic treatment of renal colic. Rev Clin Esp 1990;186:414.

[31] Grissa MH, Claessens YE, Bouida W, et al. Paracetamol vs piroxicam to relieve pain in renal colic. Results of a randomized controlled trial. Am J Emerg Med 2011;29:203–6.

[32] Hetherington JW, Philp NH. Diclofenac sodium versus pethidine in acute renal colic. Br Med J (Clin Res Ed) 1986;292:237–8.

[33] Hosseini MM, Yousefi A, Ghahramani L, Rastegari M, Ebrahimi AR. Comparison of the therapeutic effects of rectal diclofenac sodium and intramuscular pethidine injection in the treatment of acute renal colic: a randomized clinical trial. J Clin Trials 2015;5:1000225.

[34] Indudhara R, Vaidyanathan S, Sankaranarayanan A. Oral diclofenac sodium in the treatment of acute renal colic. A prospective randomized study. Clin Trials J 1990;27:295–300.

[35] Jonsson PE, Olsson AM, Petersson BA, Johansson K. Intravenous indomethacin and oxycone–papaverine in the treatment of acute renal colic. A double-blind study. Br J Urol 1987;59:396–400.

[36] Kaynar M, Koyuncu F, Buldu I, et al. Comparison of the efficacy of diclofenac, acupuncture, and acetaminophen in the treatment of renal colic. Am J Emerg Med 2015;33:749–53.

[37] Khalifa MS, Sharkawi MA. Treatment of pain owing to acute ureteral obstruction with prostaglandin-synthetase inhibitor: a prospective randomized study. J Urol 1986;136:393–5.

[38] Larkin GL, Peacock IWF, Pearl SM, Blair GA, D'Amico F. Efficacy of ketorolac tromethamine versus meperidine in the ED treatment of acute renal colic. Am J Emerg Med 1999;17:6–10.

[39] Lehtonen T, Kellokumpu I, Permi J, Sarsila O. Intravenous indomethacin in the treatment of ureteric colic. A clinical multicentre study with pethidine and metamizol as the control preparations. Ann Clin Res 1983;15:197–9.

[40] Lund PG, Jensen SK, Therkildsen MH, Olsen JH. Treatment of acute pain due to ureteral calculi with intravenous indomethacin or pethidine. Ugeskr Laeger 1986;148:1601–4.

[41] Lundstam SO, Leissner KH, Wahlander LA, Kral JG. Prostaglandin-synthetase inhibition with diclofenac sodium in treatment of renal colic: comparison with use of a narcotic analgesic. Lancet 1982;1:1096–7.
[42] Narci H, Uğur M, Uzun H, Yandi M. Combining 1000 mg oral acetaminophen with 75 mg intramuscular diclofenac of analgesic efficacy for acute renal colic treatment. Sci Res Essays 2012;7:2017–21.
[43] Torralba JAN, Rigabert Montiel M, Banon Perez V, Valdelvira Nadal P, Perez Albacete M. Intramuscular ketorolac compared to subcutaneous tramadol in the initial emergency treatment of renal colic. Arch Esp Urol 1999;52:435–7.
[44] Oosterlinck W, Philp NH, Charig C, Gillies G, Hetherington JW, Lloyd J. A double-blind single dose comparison of intramuscular ketorolac tromethamine and pethidine in the treatment of renal colic. J Clin Pharmacol 1990;30:336–41.
[45] Persson NH, Bergqvist D, Melander A, Zederfelt B. Comparison of a narcotic (oxicone) and a non-narcotic anti-inflammatory analgesic (indoprofen) in the treatment of renal colic. Acta Chir Scand 1985;151:105–8.
[46] Quilez C, Perez-Mateo M, Hernandez P, Rubio I. Usefulness of a non-steroid anti-inflammatory, sodium diclofenac, in the treatment of renal colic. Comparative study with a spasmolytic and an opiate analgesic. Med Clin (Barc) 1984;82:754–5.
[47] Safdar B, Degutis LC, Landry K, Vedere SR, Moscovitz HC, D'Onofrio G. Intravenous morphine plus ketorolac is superior to either drug alone for treatment of acute renal colic. Ann Emerg Med 2006;48,173–81, 81.e1e1.
[48] Salameh S, Hiller N, Antopolsky M, Ghanem F, Abramovitz Y, Stalnikowics R. Diclofenac versus tramadol in the treatment of renal colic: a prospective, randomized trial. Open Emerg Med J 2011;4:9–13.
[49] Sandhu DP, Iacovou JW, Fletcher MS, Kaisary AV, Philip NH, Arkell DG. A comparison of intramuscular ketorolac and pethidine in the alleviation of renal colic. Br J Urol 1994;74:690–3.
[50] Snir N, Moskovitz B, Nativ O, et al. Papaverine hydrochloride for the treatment of renal colic: an old drug revisited. A prospective, randomized study. J Urol 2008;179:1411–4.
[51] Sommer P, Kromann-Andersen B, Lendorf A, Lyngdorf P, Moller P. Analgesic effect and tolerance of Voltaren and Ketogan in acute renal or ureteric colic. Br J Urol 1989;63:4–6.
[52] Thompson JF, Pike JM, Chumas PD, Rundle JS. Rectal diclofenac compared with pethidine injection in acute renal colic. BMJ 1989;299:1140–1.
[53] Uden P, Rentzhog L, Berger T. A comparative study on the analgesic effects of indomethacin and hydromorphinechloride-atropine in acute, ureteral-stone pain. Acta Chir Scand 1983;149:497–9.
[54] Wood VM, Christenson JM, Innes GD, Lesperance M, McKnight D. The NARC (nonsteroidal anti-inflammatory in renal colic) trial. Single-dose intravenous ketorolac versus titrated intravenous meperidine in acute renal colic: a randomized clinical trial. CJEM 2000;2:83–9.
[55] Zamanian F, Jalili M, Moradi-Lakeh M, Kia M, Aghili R, Aghili SM. Morphine suppository versus indomethacin suppository in the management of renal colic: randomized clinical trial. Pain Res Treat 2016;2016:4981585.
[56] Labrecque M, Dostaler LP, Rouselle R, Nguyen T, Poirier S. Efficacy of nonsteroidal anti-inflammatory drugs in the treatment of acute renal colic. A meta-analysis. Arch Intern Med 1994;154:1381–7.
[57] Cooper SA, Desjardins PJ, Turk DC, et al. Research design considerations for single-dose analgesic clinical trials in acute pain: IMMPACT recommendations. Pain 2016;157:288–301.
[58] Pathan SA, Mitra B, Cameron PA. Titrated doses are optimal for opioids in pain trials—authors' reply. Lancet 2016;388:961–2.
[59] Philpot LM, Ramar P, Elrashidi MY, Mwangi R, North F, Ebbert JO. Controlled substance agreements for opioids in a primary care practice. J Pharm Policy Pract 2017;10:29.
[60] Cheatle MD. Prescription opioid misuse, abuse, morbidity, and mortality: balancing effective pain management and safety. Pain Med 2015;16(Suppl 1):S3–8.
[61] Florence CS, Zhou C, Luo F, Xu L. The economic burden of prescription opioid overdose, abuse, and dependence in the United States, 2013. Med Care 2016;54:901–6.
[62] Nuesch E, Trelle S, Reichenbach S, et al. Small study effects in meta-analyses of osteoarthritis trials: meta-epidemiological study. BMJ 2010;341:c3515.
[63] Moore RA. Pain and systematic reviews. Acta Anaesthesiol Scand 2001;45:1136–9.
[64] Mitra B, Cameron P. Pethidine in emergency departments: promoting evidence-based prescribing. Med J Aust 2006;184:44, author reply 5.