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Comparison of acetaminophen, ketamine, or ketorolac versus morphine in the treatment of acute renal colic: A network meta-analysis

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ABSTRACT

Background: Renal colic is a disease in which a calculus obstructs the urinary tract, resulting in severe pain do ureteric peristaltic movements. Other symptoms, such as hematuria, nausea, and vomiting, may accompany the pain. This network meta-analysis aimed to compare the efficacy and safety of different analgesic agents for the treatment of acute renal colic.

Methods: Medline, Embase, and CENTRAL databases were searched. Randomized controlled trials (RCTs) that compared different analgesic agents, either alone or in combination were included. For the management of acute renal colic, analgesic agents were selected based on the current standard medical practice. The medications included intravenous acetaminophen, ketamine, ketorolac, and morphine. This study sought to evaluate the pain score on the visual analog scale (VAS) at 15, 30, and 60 min; adverse events; and the utilization of rescue therapy. The efficacy of different analgesic agents was explored through a frequentist network meta-analysis using the Netmeta statistical package in R software. All treatments were ranked using the Netrank function, yielding P-scores.

Results: Twelve RCTs were deemed eligible. As per the P-scores, acetaminophen was the most effective in reducing pain score at 15 min (P-score = 0.74). Ketorolac was the most effective in reducing the pain score at 30 and 60 min (P-score = 0.84) (P-score = 0.99), whereas morphine was the least effective (P-score = 0.07). Moreover, morphine was correlated with the highest odds of adverse events after treatment (P-score = 0.89). Morphine was the most frequently required rescue therapy in cases of suboptimal pain relief (P-score = 0.96).

Conclusion: This network meta-analysis demonstrated that ketorolac and acetaminophen were the most effective analgesic agents according to the pain score. Morphine showed the highest adverse event profile and the highest rate at which rescue therapy was required for the management of acute renal colic.

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1. Introduction

Renal colic is a disease in which a calculus obstructs the urinary tract, resulting in severe pain do ureteric peristaltic movements, and other symptoms such as hematuria, nausea, and vomiting [1]. Over time, the incidence of urolithiasis has gradually increased [2]. According to a study based upon the national health and nutrition examination survey, it was estimated that approximately 19% of males and 9% of females will receive a diagnosis of kidney stone by the time they reach the age of 70 years [3]. In the United States, the overall prevalence of kidney stones was 8.8%, with a higher prevalence of 10.6% among men and 7.1% among women [3]. Opioids are some of the most widely used medications for standard pain management in patients presenting to the emergency department (ED) with acute renal colic [4]. Although opioids are highly potent and can deliver a fast analgesic effect, nonsteroidal anti-inflammatory drugs (NSAIDs) are used as standard analgesics [5-7]. Some studies have supported the use of alternative analgesics, including acetaminophen, and ketamine [8-10]. A recent systematic review comparing acetaminophen and morphine showed that acetaminophen was better than morphine in terms of short-term pain management [8]. However, this systematic review was limited by the small sample size and small number of included studies. Another review showed that NSAIDs and opioids were similar in terms of efficacy; however, NSAIDs had a lower adverse event profile and a lower need for rescue therapy [11]. Many other analgesics have been compared to

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morphine, yet no network meta-analyses have been conducted to pool all available evidence on the different analgesics compared to morphine in the management of acute renal colic.

This systematic review and network meta-analysis aimed to compare the efficacy and safety of intravenous acetaminophen, ketamine, and ketorolac with those of morphine in patients with acute renal colic.

2. Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and extension statement for network meta-analysis were followed. This systematic review and network meta-analysis protocol was registered in PROSPERO (CRD42022357839) [12].

2.1. Study selection

The studies of interest were randomized controlled trials (RCTs) published in English.

The patient population of interest was adults (≥18 years of age) with a chief complaint of acute flank pain and confirmed diagnosis of renal colic with an initial visual analog scale (VAS) of pain intensity of at least 6 out of 10 [13]. The interventions included in the review were: intravenous acetaminophen, ketorolac, and ketamine, either alone or in combination with morphine. The control group was administered intravenous morphine. Studies that included participants with the concurrent use of opioids or different routes of analgesic administration were excluded. The outcomes of interest were pain scores on the VAS scale at 10, 15, 20, 30, 45, 60, 90 and 120 min; adverse events; and the use of rescue therapy. The primary outcome was pain score at 30 min, while the secondary outcomes were pain scores at 15 and 60 min, adverse events, and utilization of rescue therapy.

2.2. Data sources

From database inception to September 3, 2022, we searched Medline, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL). References and citations of included trials were also searched for relevant studies. The complete search strategy is shown in the Supplementary Material. Two independent pairs, in duplicate, screened titles and abstracts, read the full texts, and extracted data from the included studies. A third reviewer subsequently validated data extraction and resolved any discrepancies.

2.3. Data extraction and risk of bias

Data extraction was performed using an Excel spreadsheet, and the following data were extracted from each eligible trial: name of the first author and year of publication, study arms and doses, number of participants in each arm, age, sex, pain score, history of renal colic, history of hematuria, mode of diagnosis (Computed tomography, ultrasound, intravenous urography), method of administration, and the desired outcomes reported by each trial. We used the modified Cochrane Collaboration assessment tool to assess the risk of bias in the eligible studies and classified the studies into the following categories: high risk of bias, some concerns, or low risk of bias [14].

2.4. Network meta-analysis

For each study, binary (event and sample size) and continuous (mean and standard deviation) data were extracted from the intervention and control groups. These binary and continuous data were used to calculate effect sizes, presented as risk ratio (RR), and mean difference (MD), respectively. The significance of the effect sizes was determined using 95% significant level and p-value <0.05 as threshold. The efficacy of analgesic agents, including acetaminophen, ketorolac, ketamine, and morphine, for relieving acute renal colic was explored by frequentist network meta-analysis using the Netmeta statistical package in R. Prior to running the network meta-analysis, the assumptions of transitivity were explored among the included trials. Within-design and between-design inconsistencies were quantified using I2 and Cochran's Q statistic, and a full design-by-treatment interaction random-effects model. A random-effects model was used for all the statistical analyses. Further consistency checks included evaluating the differences between effect estimates based on direct and indirect evidence. Using the dmetar package, a direct evidence plot was constructed to visualize the proportion of direct and indirect evidence for each comparison. All treatments were ranked using the netrank function, yielding P-scores. The ranking of treatments was further corroborated by visualizing a forest plot using morphine as the reference group to check the statistical significance of the treatment ranking.

3. Results

3.1. Study selection and network structure

The search resulted in a total of 1944 articles. After removing duplicates, 1577 remained for screening of titles and abstracts, and 21 articles remained for full-text assessment. Of these, nine were excluded for the reasons listed in the PRISMA flow diagram. Eventually, a total of 12 articles that met the inclusion and exclusion criteria of this review [6,10,15-24] (Fig. 1).

3.2. Characteristics of studies

A total of 2845 participants were included in this review. Of them, 1371 (48.19%) received intravenous morphine. A total of 901 (31.67%) and 208 (12.37%) participants received intravenous acetaminophen and ketorolac, respectively. A total of 144 (5.06%) received intravenous ketorolac synergistically with intravenous morphine. In total, 68 (7.76%) patients received intravenous ketamine. A total of 153 (5.37%) received intravenous ketamine synergistically with intravenous morphine. In terms of sex, 2028 (71.28%) of the included participants were male, 711 (24.99%) were female, and 106 (3.72%) were not reported/missing from the original trials. The median age of participants in the included trials was 35.99 (Table 1).

3.3. Risk of bias assessment

Of the 12 RCTs, eight had an overall low risk of bias, three had some concerns, and one had an overall high risk of bias. Details of the risk of bias in the included trials are shown in Fig. 9.

3.4. Outcome

A network meta-analysis was also performed. The outcomes highlighted were eligible for the meta-analysis were the VAS score at 15, 30, and 60 min; use of rescue therapy; and adverse events. It was not possible to perform a network meta-analysis on the VAS score at 10, 20, 45, 90 and 120 min of the lack of data in the included RCTs.

3.5. Visual analogue scale

Eight studies reported the VAS outcomes among patients undergoing pain relief for acute renal colic. Among these studies, five reported VAS scores at 15 min [6,17,20,21,23], 8 reported VAS scores at 30 min [6,10,15,17,20-23], and six reported VAS scores at 60 min [10,15,20-23]. As per the P-scores for the VAS score at 15 min, acetaminophen yielded the highest reduction in pain score after administration ($P = 0.74$), followed by ketorolac ($P = 0.57$) and morphine ($P = 0.17$). There was a significant within-design inconsistency ($Q = 16.82$, $P = 0.0008$), whereas the between-design inconsistency was 0.

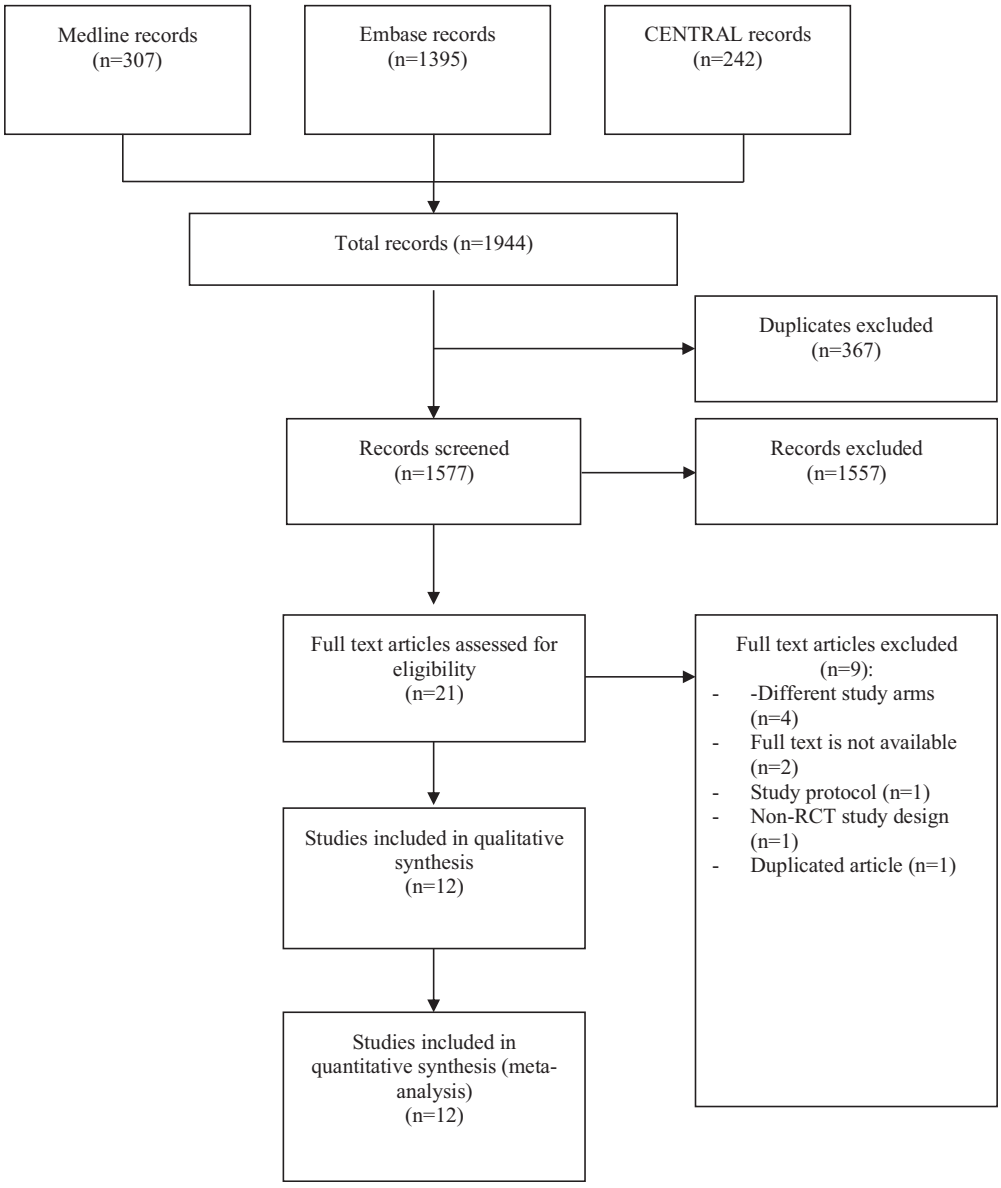

Fig. 1. Study flow diagram.

Although acetaminophen and ketorolac ranked higher than morphine, none of them showed a significant reduction in pain score at 15 min (Fig. 2).

According to per P-scores for the VAS score at 30 min, ketorolac displayed the highest reduction in pain score after administration ($P = 0.84$), followed by ketamine with morphine ($P = 0.64$), acetaminophen ($P = 0.61$), ketamine ($P = 0.30$), and morphine ($P = 0.07$). In comparison to morphine alone, ketorolac (MD = −1.60, 95% CI: −2.82 to −0.38) and acetaminophen (MD = −1.02, 95% CI: −1.76 to −0.29) showed a significant reduction in pain score at 30 min (Fig. 3). There was significant within-design inconsistency ($Q = 18.01$, $P = 0.001$).

As per P-scores for VAS score at 60 min, ketorolac yielded the highest reduction in pain score after administration ($P = 0.99$), followed by ketamine with morphine ($P = 0.52$), acetaminophen ($P = 0.36$), ketamine ($P = 0.35$), and morphine ($P = 0.24$). Compared to morphine alone, ketorolac was the only agent that showed a significant reduction in the pain score at 60 min (MD = −2.90, 95% CI: −4.07 −1.73) (Fig. 4). There was significant within-design inconsistency ($Q = 14.01$, $P = 0.0009$). The proportion of studies reporting direct and indirect evidence for each VAS time interval and bar graph are presented in Supplementary figs. 1–9.

3.6. Risk for adverse effects

A network plot of the adverse effects of analgesic agents on acute renal colic was reported in 10 studies [6,15-18,20-24] (Fig. 5). For per P-scores, morphine yielded the highest event profile of adverse events after administration ($P = 0.89$), followed by ketorolac ($P = 0.78$), acetaminophen ($P = 0.57$), ketamine with morphine ($P = 0.48$), and ketorolac with morphine ($P = 0.25$). Compared to morphine alone, ketorolac with morphine was the only agent that showed a significant reduction in the risk of developing adverse events (RR = 3.96, 95% CI:1.78 to 8.78) (Fig. 6). There were significant within-design ($Q = 51.11$, $p = 0.0001$) and between-design inconsistencies ($Q = 36.57$, $P = 0.0001$). The Forest and bar graphs that present the pooled effect size from both direct and indirect evidence of adverse outcomes are presented in Supplementary figs. 10 and 11.

Table 1
Characteristics of the included studies

Study, Year	Study Ams	Number of partcipants		Gender				Mean age		History of renal colic		Number of patients with hematuria at baseline		Mode of diagnosis (i.e., CT, ultrasound, intravenous urography)		Baseline pain socre		Method of administration		Outcomes measured
		Intervention	Morphine	Intervention		Morphine		Intervention	Morphine	Intervention	Morphine	Intervention	Morphine	Intervention	Morphine	Intervention	Morphine	Intervention	Morphine	
				Male	Female	Male	Female													
Serinken, 2014	Intravenous acetaminophen & morphine	38	35	28	10	23	12	29.1 (±8.2)	31.3 (±9.0)	11 (28.9%)	8 (22.8%)	33 (86.8%)	32 (91.4%)	Ultrasound: 22 (57.9%) CT: 16 (42.1%)	Ultrasound: 24 (68.5%) CT: 11 (31.4%)	VAS (80.1 (±13.3)) - Verbal rating scale (median (IQR) 4 (4–4))	VAS (82.7 ± 10.9)	Paracetamol bolus infusion within 2–4 min (1 g in 100 ml normal saline)	Morphine bolus infusion within 2–4 min (0.1 mg/kg in 100 ml normal saline)	100 mm visual analogue scale, 4-point verbal rating scale, adverse effects.
Pathan, 2016	Intravenous acetaminophen, Intravenous morphine	548	549	446	102	456	93	Median (IQR): 34·4 (28·6–41·5)	Median (IQR): 34·7 (28·8–41·7)	NR	NR	105 (19%)	96 (18%)	CT OR ultrasound: 435 (82%)	CT OR ultrasound: 443 (82%)	Median (IQR): 8 (7–10)	Median (IQR): 8 (7–10)	1 g/100 ml paracetamol administered intravenously over 3–5 min	0·1 mg/kg intravenous morphine over 2–5 min	Pain score on VAS at 30 and 60 min, number of patients required use of rescue therapy, and adverse event rate
Montazer, 2018	Intravenous acetaminophen, Intravenous morphine	152	192	105	47	130	62	41.29 (±12.65)	41.54 (±13.93)	NR	NR	121 (77.60%)	156 (81.2%)	NR	NR	8.21 (±1.26)	8.29 (±1.41)	1 g of IV acetaminophen in 100 ml normal saline for 15 min	0.1 mg/kg IV morphine in 100 ml normal saline for 15 min	Pain score on The Visual Analogue Scale (VAS) at 15, 30, 60, and 120 min, Use of rescue therapy, Number of patients with adverse events.
Safaie, 2022	Intravenous ketorolac with intravenous morphine, Intravenous morphine alone	65	65	37	28	36	29	39.3 (±12.4)	39.8 (±11.5)	11 (16.9%)	9 (13.8%)	NR	NR	CT: 62 (95.3)	CT: 60 (92.3)	Mean (95% CI): 8.4 (8.2–8.6)	Mean (95% CI): 8.4 (8.2–8.6)	5 mg of morphine sulfate in 5 min, 200 ml normal saline intravenously in 30 min, and 30 mg of ketorolac (2 ml) intravenously in 30 s	5 mg morphine sulfate intravenously in 5 min, 200 ml normal saline intravenously in 30 min, and 2 ml distilled water intravenously in 30 s	Pain score on The Visual Analogue Scale (VAS) at 0, 15, 30, 60, and 120 min, Use of rescue therapy, Number of patients with adverse events.
Safdar, 2006	Intravenous ketorolac alone, Intravenous ketorolac with intravenous morphine, Intravenous morphine alone	Intravenous ketorolac alone: 43 Intravenous ketorolac with intravenous morphine: 44	43	Intravenous ketorolac alone: 29 (67%) Intravenous ketorolac with intravenous morphine: 30 (68%)	Intravenous ketorolac alone: 14 (33%) Intravenous ketorolac with intravenous morphine: 14 (32%)	29	14	Intravenous ketorolac alone: 39.3 (±9.9) Intravenous ketorolac with intravenous morphine: 37.8 (±12)	37.3 (±10)	NR	NR	Intravenous ketorolac alone: 24 (83%) Intravenous ketorolac with intravenous morphine: 27 (93%)	25 (83%)	CT scans Positive in intravenous ketorolac alone (CT scans Positive): 25 (86%) CT scans Positive in intravenous ketorolac with intravenous morphine: 26 (89%)	25 (83%)	Intravenous ketorolac alone: 8.8 (±1.6) Intravenous ketorolac with intravenous morphine: 8.9 (±1.4)	8.7 (±1.6)	Intravenous ketorolac alone: Ketorolac 15 mg at time zero and 15 mg at 20 min Intravenous ketorolac with intravenous Morphine: Morphine 5 mg and Ketorolac 15 mg at time zero and Morphine 5 mg and Ketorolac 15 mg at 20 min.	Morphine 5 mg at time zero and 5 mg at 20 min,	Number of patients required use of rescue therapy and adverse event rate

Bektas 2009	Intravenous acetaminophen, Intravenous morphine, Intravenous placebo	46	49	31	15	27	22	35 (±10)	39 (±11)	29 (63%)	25 (51%)	33 (72%)	36 (74%)	CT: 15 (33%) Intravenous urography: 8 (17%) Ultrasonography: 17 (37%) Stone recovery: 5 (11%) Radiography: 1 (2%)	CT: 21 (43%) Intravenous urography: 2 (4%) Ultrasonography: 15 (31%) Stone recovery: 9 (18%) Radiography: 2 (4%)	Median (IQR): 73 (55–87)	Median (IQR): 78 (64–98)	1 g paracetamol in 100 ml normal saline solution	0.1 mg/kg morphine in 100 ml normal saline solution	Pain score on VAS at 15 min, pain score on VAS at 30 min, number of patients required use of rescue therapy, and adverse event rate
Reza Azizkhani, 2013	Intravenous acetaminophen, Intravenous morphine	62	62	42	20	42	20	38.40 (11.60)	39.73 (11.62)	NR	NR	NR	NR	NR	NR	(2.70 ± 1.78)	(5.0 ± 1.04)	15 mg/kg for intravenous acetaminophen	0.1 mg/kg for intravenous morphine	Number of patients with adverse events
Abbasi, 2017	Intravenous morphine with placebo, Intravenous morphine with Intravenous ketamine	53	53	NR	NR	NR	NR	49.42	51.58	NR	NR	NR	NR	NR	NR	7.94	7.9	10 mg/ml and 0.15 mg/kg and was then administered	0.1 mg/kg morphine plus placebo (normal saline)	Pain Score (VAS) at 10 min 30 min 60 min 90 min 120 min, Number of patients with adverse events
Hosseininejad, 2018	Intravenous ketamine with Intravenous morphine, Intravenous morphine	100	100	67	33	70	30	35.29 ± 7.12	35.91 ± 9.13	58	47	Gross 9, micro 22	Gross 23 micro 25	NR	NR	7.98 ± 1.01	8.11 ± 1.01	IV 0.1 mg/kg morphine +0.2 mg/kg IV ketamine	0.1 mg/kg IV morphine	Pain score on The Visual Analogue Scale (VAS) at 20, and 40 min, Use of rescue therapy, Number of patients with adverse effects
Hosseininejad, 2017	Intravenous ketrolac with Intravenous morphine, Intravenous Ketrolac, Intravenous morphine	100/100	100	67/69	33/31	72	28	30.28 ± 10.3/ 29.66 ± 9.7	28.81 ± 9.8	54/39	31	71/80	56	NR	NR	8.36/8.38	8.34	30 mg intravenous injection of ketorolac in combination with 0.1 mg/kg intravenous morphine / as placebo/ third group received 30 mg intravenous injection of ketorolac in combination with placebo.	second group received 0.1 mg/kg intravenous morphine and same amount of intravenous normal saline	Pain VAS at 20, and 40 min, Use of rescue therapy, Number of patients with adverse effects
Kambiz Masoumi, 2014	Intravenous acetaminophen, Intravenous morhpine	55	55	43	12	39	16	36.07 (9.7)	34.96 (8.94)	NR	NR	NR	NR	NR	NR	8.84 (1.37)	9.14 (1.13)	patients received intravenous acetaminophen (England, commissioned by Cobel Daroulran, in 1 g vials) with a dose of 1 g in 100 ml normal saline	0.1 mg/kg morphine in 100 ml normal saline was infused. Both drugs were infused during 5–10 min	Pain on VAS score at 15, 30, 45 and 60 min, Rescue therapy
Forouzan, 2019	Intravenous morphine, Intravenous ketamine	68	68	56	12	54	14	33.36 ± 10.21	33.45 ± 11.3	NR	NR	NR	NR	NR	NR	9.26 ± 1	9.26 ± 1.04	intravenous ketamine (0.3 mg/kg)	intravenous morphine (0.1 mg/kg)	Pain VAS 10 20 30 60 min

NR: Not reported.

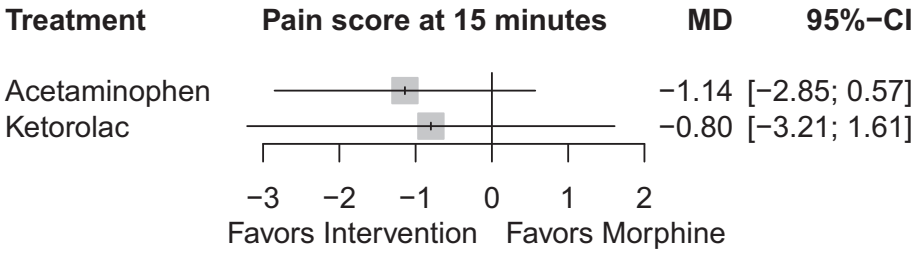

Fig. 2. Forest plot comparing analgesic agents with morphine in VAS at 15 min.

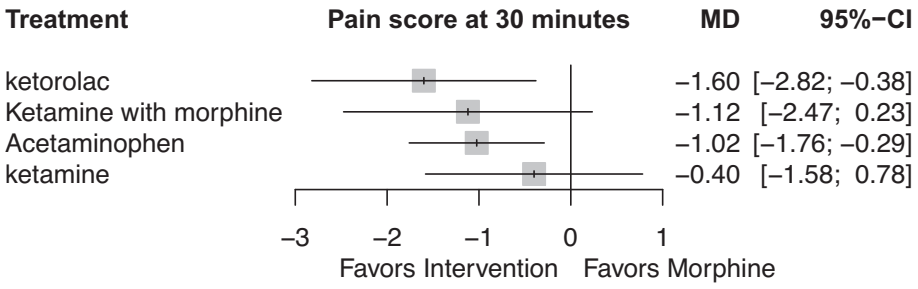

Fig. 3. Forest plot comparing analgesic agents with morphine in VAS at 30 min.

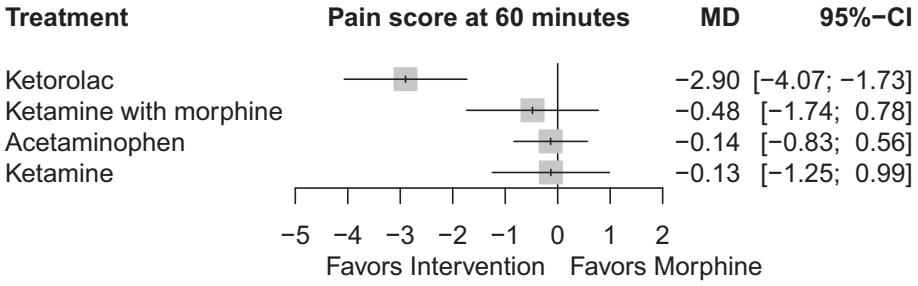

Fig. 4. Forest plot comparing analgesic agents with morphine in VAS at 60 min.

3.7. Utilization of rescue therapy

A network plot of the adverse effects of analgesic agents on acute renal colic was reported in eight studies [6,17-22,24] (Fig. 7). According to P-scores, morphine yielded the highest odds for using rescue therapy ($P = 0.96$), followed by ketamine with morphine ($P = 0.60$), ketorolac ($P = 0.52$), ketorolac with morphine ($P = 0.21$), and acetaminophen ($P = 0.18$). In comparison with morphine, ketorolac (RR = 1.90, 95% CI:1.15 to 3.12), ketorolac with morphine (RR = 2.54, 95% CI:1.53 to 4.20), and acetaminophen (RR = 2.65, 95% CI:1.81 to 3.88) showed significant reduction in the chance of using rescue therapy (Fig. 8). Additionally, there were significant within-design (Q = 27.46, $P = 0.0003$) and between-design inconsistencies (Q = 15.30, $P = 0.0001$). The Forest plot and bar graph that present the pooled effect size from both direct and indirect evidence of adverse outcomes are shown in Supplementary figs. 12 and 13.

4. Discussion

This systematic review and network meta-analysis of 12 RCTs compared the most commonly used analgesic agents for the management of acute renal colic, namely acetaminophen, ketorolac, ketamine, and morphine. The efficacy of different analgesic agents for acute renal colic was determined based on the pain score, while safety was determined based on the adverse event rate and utilization of rescue therapy. This network meta-analysis demonstrated that acetaminophen yielded the highest effectiveness in improving the VAS score at 15 min followed by ketorolac. In addition, ketorolac yielded the highest effectiveness in terms of VAS scores at 30 min and 60 min. The analgesic agent that was most reported for developing higher adverse events was morphine. Moreover, morphine and acetaminophen were associated with the highest and lowest odds of requiring rescue therapy, respectively.

In this study, acetaminophen showed a superior effect on pain relief at 15 min compared to morphine; however, the reduction in pain was not statistically significant. In contrast, acetaminophen resulted in a significant reduction in pain scores at 30 min. Similarly, a meta-analysis conducted by Zhili et al. reported that, compared to morphine for the treatment of renal colic pain, acetaminophen was associated with a significant reduction in pain score at 30 min; however, there was no statistically significant difference observed in pain scores at 15 min or in the need for rescue analgesia between the two treatments [25]. Moreover, several reviews stated that acetaminophen has been found to be either superior or at least equally effective to morphine in providing short-term pain relief to patients experiencing acute renal colic [26,27]. We believe that acetaminophen should be preferred over morphine in the short term because morphine has a higher rate of adverse events than acetaminophen.

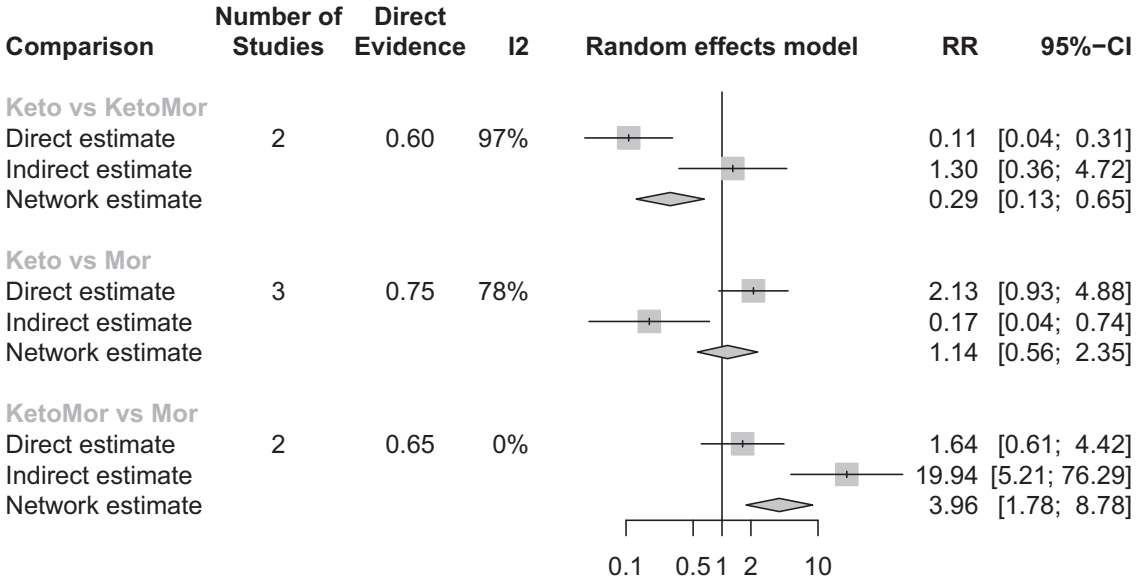

Fig. 5. Forest plot presenting pooled effect size from both direct and indirect evidence for adverse outcomes.

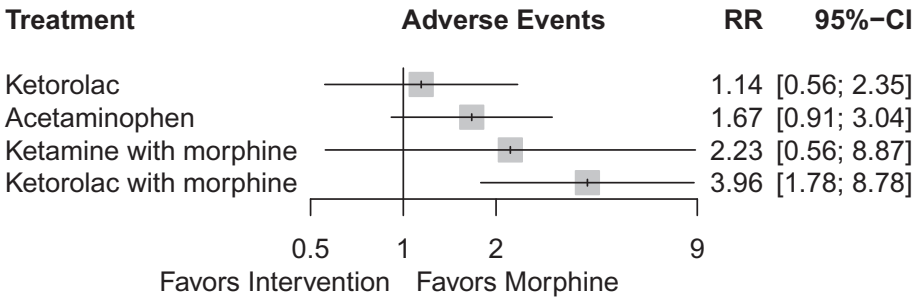

Fig. 6. Forest plot comparing adverse events for analgesic agents with morphine.

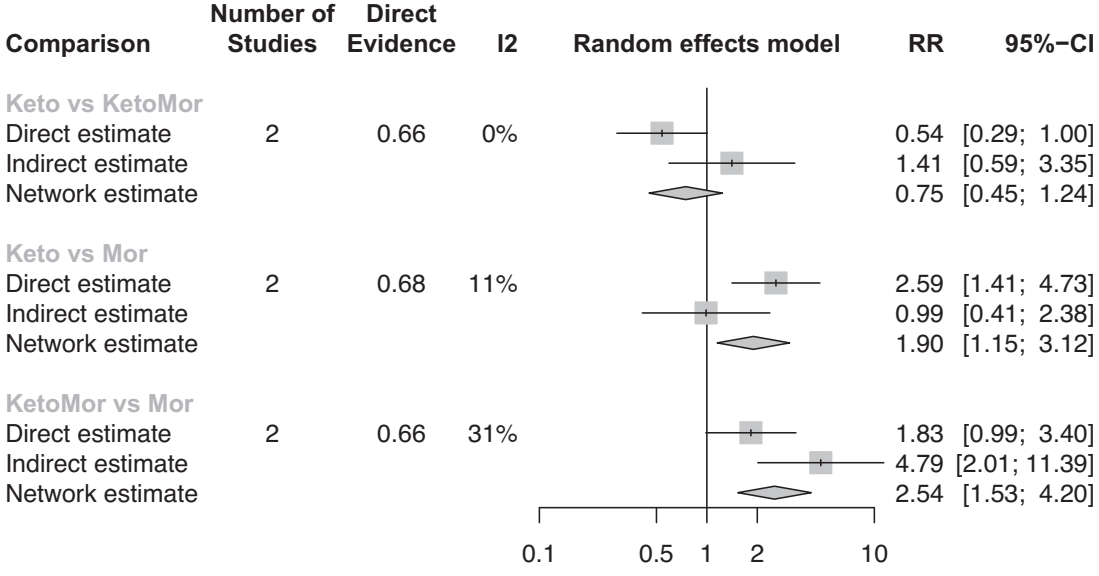

Fig. 7. Forest plot presenting pooled effect size from both direct and indirect evidence for rescue therapy usage.

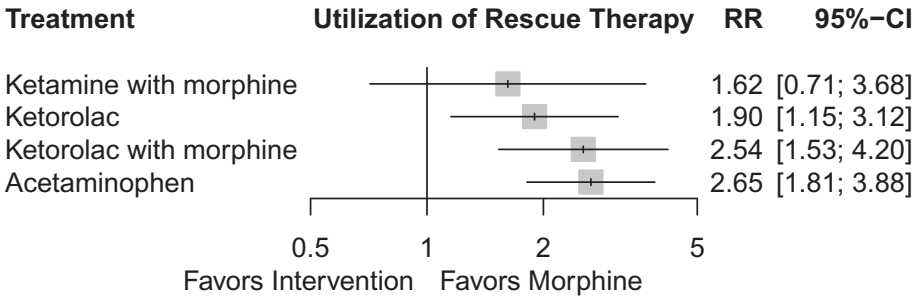

Fig. 8. Forest plot comparing rescue therapy usage for analgesic agents with morphine.

In this study, ketorolac was identified as the most effective analgesic agent based on pain scores at both the 30- and 60-min time points. Notably, a significant reduction in the pain score was observed only at the 30-min time point. One of the major advantages of NSAIDs is that they inhibit prostaglandins, which leads to a decrease in inflammation and pressure of the ureter, leading to more pain relief [28]. A review published by Holdgate et al. stated that NSAIDs cause a slight reduction in pain and are less likely to require further pain relief than opioids [29]. The primary objective of combination therapy for pain management is to enhance the analgesic efficacy of individual drugs while minimizing potential side effects, allowing the administration of lower doses of each agent [30,31]. In the case of opioid analgesics, combination therapy aims to maintain or increase the potent analgesic properties while reducing the adverse effects commonly associated with opioids [32]. This study could not determine the efficacy of ketorolac combination therapy because of differences in time intervals. Some studies have reported that the combined use of ketorolac and morphine results in a superior analgesic effect for pain management in cases of acute renal colic [18,24]. Furthermore, several studies have demonstrated that the use of ketamine, either as a standalone agent or in combination with morphine, can lead to a greater reduction in pain in the short term because of the rapid onset of action of ketamine, which allows for faster pain relief, and the ability of ketamine to reduce the peak effects of morphine [10,15]. All of the included RCTs adopted the administration of morphine as IV bolus. However, it is recommended

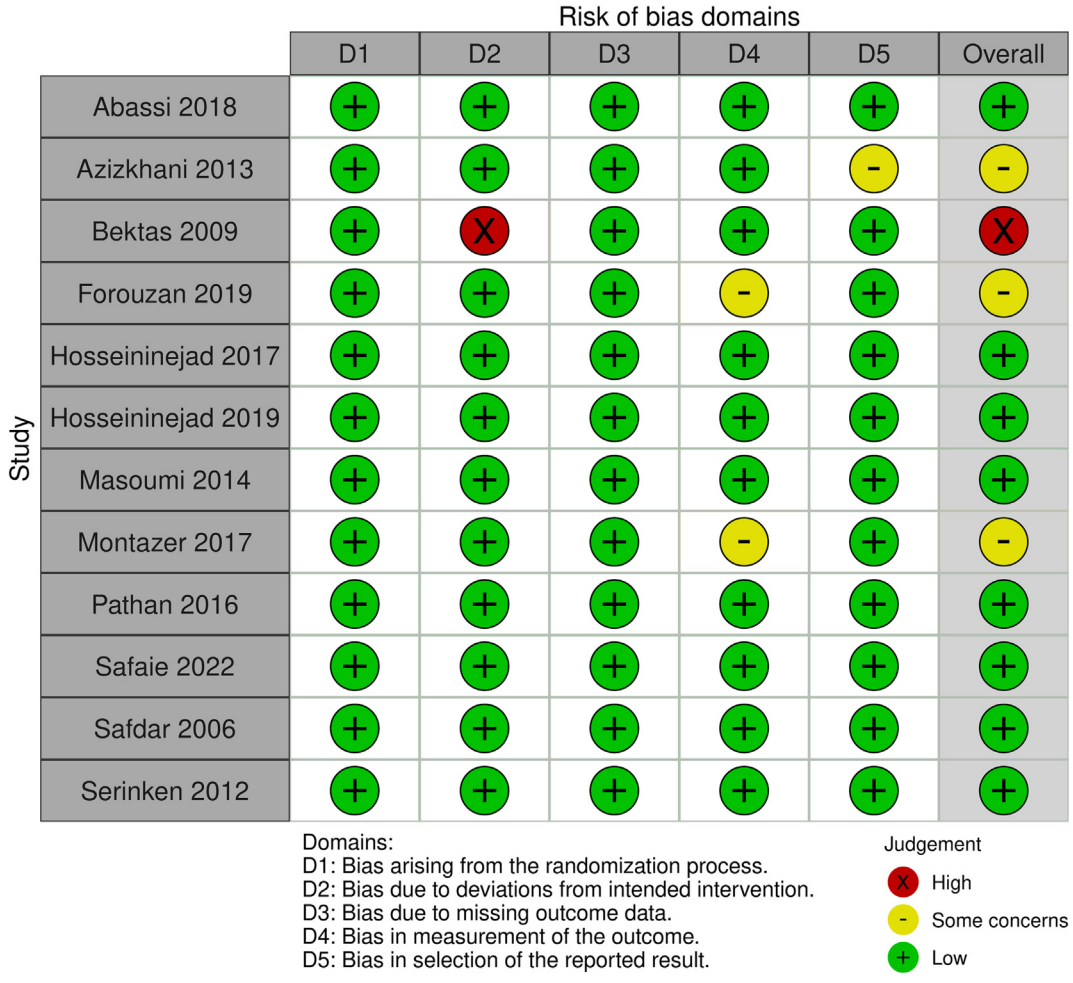

Fig. 9. Risk of bias assessment.

to complement the bolus by gradual titration in order to achieve the desired analgesic effect of morphine. This could explain in part the modest effect of morphine on pain score compared to the other analgesics in this network meta-analysis [33].

With respect to adverse events, morphine had the highest odds for developing adverse events. Notably, ketorolac combined with morphine was the only analgesic that showed a significant reduction in the adverse events. Pathan et al. conducted a review comparing the use of opioids alone with a combination of opioids and NSAIDs and found a lower incidence of adverse events in participants treated with NSAIDs. Specifically, patients treated with NSAIDs were less likely to experience adverse events than those treated with opioids alone [11]. Holdgate et al. reported that opioids have more adverse effects than NSAIDs, while a review by Golzari et al. stated that adverse effects might be greater with NSAIDs than with morphine [29,34]. Notably, one study reported that some adverse effects such as nausea and vomiting might be attributed to renal colic rather than to the agent itself [35]. Remarkably, the results of this study demonstrated that only the combination of ketorolac and morphine resulted in a statistically significant reduction in adverse events. Nonetheless, it is important to note that this finding is derived from a single RCT and should be interpreted with caution [18]. Administration of higher doses of ketamine may lead to serious adverse events. Furthermore, some studies have suggested that low-dose ketamine may not be as effective as morphine in providing pain relief [36,37]. Pathan et al. reported no significant differences in adverse events between acetaminophen and morphine [11]. In terms of the utilization of rescue therapy, the results of this study showed that acetaminophen and ketorolac were associated with the lowest rates of rescue therapy among the analgesic agents studied, although the difference was not statistically significant. Several publications have stated that NSAIDs are less likely to be used as rescue therapy than opioids [11,29]. In a review by Xu et al., no statistically significant difference was observed between morphine and acetaminophen in terms of the number of rescue analgesia required [25].

5. Strength & limitations

This systematic review and network meta-analysis could influence practice change as it compares agents both synergistically and alone to intravenous morphine in patients with acute renal colic. Nevertheless, this review had some limitations. First, the findings of these RCTs showed a high rate of inconsistency. Moreover, other analgesics were not considered. In addition, patients with different routes of administration were excluded from the study. Furthermore, this network meta-analysis compared non-titratable analgesics to titratable ones, which demonstrates a significant challenge in the interpretation of the results. The inherent variability in dosing regimens between these two types of analgesics may affect the comparability and generalizability of the findings.

6. Conclusion

This network meta-analysis showed that ketorolac was the most effective at improving pain scores at 30 and 60 min, whereas acetaminophen was the most effective at 15 min for acute renal colic. Morphine had the highest adverse event profile, whereas acetaminophen had the lowest. Regarding the utilization of rescue therapy, acetaminophen was the least-used analgesic agent in rescue therapy while morphine was the most common. Ketorolac and acetaminophen might be considered as alternative analgesics to morphine for the management of acute renal colic.

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CRediT authorship contribution statement

Yasir A. Alghamdi: Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Roaa E. Morya:** Writing – review & editing, Validation, Methodology. **Dena M. Bahathiq:** Writing – review & editing, Validation, Methodology. **Abdullah F. Bokhari:** Writing – review & editing, Validation, Methodology. **Ahmad K. Alaboud:** Writing – review & editing, Validation, Methodology. **Ahmed S. Abdulhamid:** Writing – review & editing, Validation, Methodology. **Abdullah A. Ghaddaf:** Writing – review & editing, Validation, Software, Formal analysis, Data curation, Conceptualization. **Maan Jamjoom:** Writing – review & editing, Validation, Supervision.

Declaration of Competing Interest

The authors declare no conflicts of interest with respect to the research, authorship, and/or publication of this article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajem.2023.08.029.

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