Comparison of Ibuprofen with Ketorolac on the Control of Renal Colic Pain: A Meta-Analysis of Randomized Controlled Studies

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Abstract

Introduction: The comparison of ibuprofen with ketorolac remains controversial for the pain control of renal colic. We therefore conduct this meta-analysis to compare the analgesic efficacy of ibuprofen with ketorolac for renal colic.

Methods: We have searched PubMed, EMbase, Web of science, EBSCO, and Cochrane library databases through December 2022 for randomized controlled trials (RCTs) assessing the analgesic efficacy of ibuprofen in comparison with ketorolac for renal colic. This meta-analysis was performed using the random-effect or fixed-effect model based on the heterogeneity.

Results: Four RCTs were included in the meta-analysis. In patients with renal colic

pain, intravenous ibuprofen and ketorolac produced comparable pain scores at 15 min (MD=-0.46; 95% CI=-1.24 to 0.31; P=0.24), 30 min (MD=-0.81; 95% CI=-1.75 to 0.31; P=0.09), 60 min (MD=-0.63; 95% CI=-1.40 to 0.13; P=0.10) and 120 min (MD=-0.74; 95% CI=-2.18 to 0.70; P=0.31), as well as adverse events (OR=0.95; 95% CI=0.61 to 1.49; P=0.83).

Conclusions: Ibuprofen can obtain the comparable analgesic efficacy to ketorolac for renal colic pain.

Key words: renal colic pain, ibuprofen, ketorolac, pain control, randomized controlled trials.

Introduction

Renal colic caused by nephrolithiasis has become one of the most commonly factors of acute pain [1-3]. It is estimated that 11% of men and 7% of women suffer from renal colic pain [4]. The ureteric obstruction by stones lead to increase intraluminal pressure and stimulate the nerves in lamina propria, followed by the increase in pain intensity [5, 6]. The pathophysiology of renal colic pain included local synthesis of eicosanoids (e.g. prostaglandin E2 and prostacyclin 2) and nitric oxide [7]. Renal colic pain mainly results from the contraction in urethral smooth muscle, alteration in local blood flow rate and the increase in urinary tract pressure [8].

Current analgesic drugs for renal colic pain included non-steroidal anti-inflammatory drugs (NSAIDs) and opioid analgesics [9, 10]. Opioids have important benefits to indirectly alleviate pain intensity, while NSAIDs are used to control renal colic pain by attenuating the production of prostaglandins [11, 12]. However, opioids may be associated with some serious events including hypotension, respiratory depression, apnea and even intolerance or addictions [13]. The most frequently used NSAIDs for renal colin is ketorolac, which is a non-selectively cyclooxygenase (COX) inhibitor that acts as dual COX-1/COX-2 inhibitor [14]. Ibuprofen may have higher analgesic efficacy and lower incidence of adverse effects in controlling renal colic pain compared to ketorolac treatment [4].

Several studies have compared ibuprofen with ketorolac for the pain relief of renal colic, but the results are not well establish [4, 15, 16]. This meta-analysis of RCTs aims to

compare the analgesic efficacy of ibuprofen with ketorolac in the control of renal colic.

Materials and methods

This systematic review and meta-analysis were performed based on the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement and Cochrane Handbook for Systematic Reviews of Interventions [17, 18]. No ethical approval and patient consent were required because all analyses were based on previous published studies.

Literature search and selection criteria

We have systematically searched several databases including PubMed, EMbase, Web of science, EBSCO, and the Cochrane library from inception to November 2022 with the following keywords: “ibuprofen” and “ketorolac” and “renal colic”. The reference lists of retrieved studies and relevant reviews were also hand-searched and the process above was performed repeatedly in order to include additional eligible studies.

The inclusion criteria were presented as follows: (1) study design was RCT, (2) patients were diagnosed with renal colic, and (3) intervention treatments aimed to compare ibuprofen with ketorolac.

Data extraction and outcome measures

Some baseline information was extracted from the original studies, and they included first author, number of patients, age, female, history of renal stone, baseline pain intensity and detail methods in two groups. Data were extracted independently by two investigators, and discrepancies are resolved by consensus. The primary outcomes were pain scores at 15 min and 30 min after the drug administration. Secondary outcomes included pain scores at 60 min and 120 min, as well as adverse events.

Quality assessment in individual studies

The methodological quality of each RCT was assessed by the Jadad Scale which consisted of three evaluation elements: randomization (0-2 points), blinding (0-2 points), dropouts and withdrawals (0-1 points) [19]. One point would be allocated to

each element if they were conducted and mentioned appropriately in the original article. The score of Jadad Scale varied from 0 to 5 points. An article with Jadad score ≤2 was considered to be of low quality. The study had high quality if Jadad score≥3 [20, 21].

Statistical analysis

We assessed mean difference (MD) with 95% confidence interval (CI) for continuous outcomes and odd ratio (OR) with 95% CIs for dichotomous outcomes. Heterogeneity was evaluated using the I^2 statistic, and $I^2 > 50\%$ indicated significant heterogeneity [21, 22]. The random-effect model was used when encountering significant heterogeneity, and otherwise fixed-effect model was applied. We searched for potential sources of heterogeneity for significant heterogeneity. Sensitivity analysis was performed to detect the influence of a single study on the overall estimate via omitting one study in turn or performing the subgroup analysis. Results were considered as statistically significant for $P<0.05$. All statistical analyses were performed using Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

Results

Literature search, study characteristics and quality assessment

Figure 1 showed the detail flowchart of the search and selection results. 114 potentially relevant articles were identified initially. Finally, four RCTs were included in the meta-analysis [4, 15, 16, 23]. The baseline characteristics of four included RCTs were shown in Table 1. These studies were published between 2018 and 2022, and the total sample size was 571. Among the included RCTs, intravenous ibuprofen was administered at the dose of 800 mg, while intravenous ketorolac was used at the dose of 30 mg.

Among the four included RCTs, three studies reported pain scores at 15 min,30 min and 60 min [4, 15, 16], two studies reported pain scores at 120 min [4, 15], and three studies reported adverse events [15, 16, 23]. Jadad scores of the four included studies varied from 3 to 5, and all studies had high quality based on the quality assessment.

Primary outcomes: pain scores at 15 min and 30 min

The random-effect model was used for the analysis of primary outcomes. The results found that compared to ketorolac group for renal colic pain, ibuprofen showed similar pain scores at 15 min (MD=-0.46; 95% CI=-1.24 to 0.31; P=0.24) with significant heterogeneity among the studies (I^2=96%, heterogeneity P<0.00001, Figure 2) and pain scores at 30 min (MD=-0.81; 95% CI=-1.75 to 0.31; P=0.09) with significant heterogeneity among the studies (I^2=96%, heterogeneity P<0.00001, Figure 3). The funnel plots (Figure 4) were not symmetrical, suggesting some publication bias.

Sensitivity analysis

Significant heterogeneity remained for primary outcomes. However, there was still substantial heterogeneity when performing the sensitivity analysis by omitting one study in turn.

Secondary outcomes

In comparison with ketorolac group for renal colic pain, ibuprofen resulted in comparable pain scores at 60 min (MD=-0.63; 95% CI=-1.40 to 0.13; P=0.10; Figure 5) and 120 min (MD=-0.74; 95% CI=-2.18 to 0.70; P=0.31; Figure 6). There was no statistical difference of adverse events between two groups (OR=0.95; 95% CI=0.61 to 1.49; P=0.83; Figure 7).

Discussion

Our meta-analysis included four RCTs and 571 patients with renal colic pain. The results found that ibuprofen obtains comparable analgesic efficacy to ketorolac treatment in renal colic patients, as evidenced by the similar pain scores at 15 min, 30 min, 60 min and 120 min between two groups. In addition, the incidence of adverse events such as nausea and vomiting were similar between ibuprofen and ketorolac.

Both ibuprofen and ketorolac are dual COX-1/COX-2 inhibitors. COX-1 is constitutively located in wide range of cells particularly in platelets and gastrointestinal tract, while COX-2 expression is induced in the presence of inflammation [24-27]. Ibuprofen is able to inhibit COX-1 2.5 times less than COX-2, while ketorolac has lower binding capacity to COX-2 than ibuprofen. These suggests that ibuprofen theoretically provided better analgesic efficacy and lower risk

of adverse events [28].

However, our meta-analysis found that ibuprofen obtains the comparable efficacy to ketorolac for the pain relief of patients with renal colic, and these two drugs had similar incidence of adverse events mainly including nausea and vomiting. Considering the heterogeneity, there was still significant heterogeneity when performing the sensitivity analysis by omitting one study in turn. Three factors may account for it. Firstly, the pain intensity may differ in various patient samples. Secondly, history of renal stone may affect the assessment of analgesic efficacy. Thirdly, the different combination methods of drug administration may cause some bias.

Several limitations exist in this meta-analysis. Firstly, our analysis is based on only four RCTs, and more RCTs with large sample size should be conducted to explore this issue. Secondly, there is significant heterogeneity for the primary outcomes, which may result from different methods of drug administration and baseline pain intensity. Finally, it is not feasible to perform the analysis of some important outcomes such as the requirement of additional analgesics.

Conclusion

Ibuprofen may be equally effective for the relief of renal pain compared to ketorolac.

Compliance with Ethical Standards

Disclosure of potential conflicts of interest

The authors declare no conflict of interest.

Research involving human participants and/or animals

Not applicable.

Table 1 Characteristics of included studies

NO. Author	Ibuprofen group						Ketorolac group						Jadad scores
	Number	Age	Female (n)	History of renal stone (n)	Baseline pain intensity	Methods	Number	Age	Female (n)	History of renal stone (n)	Baseline pain intensity	Methods	

1	Safaie 2022	65	39.5±12.5	19	14	8.4±0.8	intravenous 800 mg ibuprofen	65	39.3±12.4	18	11	8.4±0.8	intravenous 30 mg ketorolac	4
2	Yazdani 2021	62	35.2±7.63	15	-	8.93±0.38	intravenous 800 mg ibuprofen	59	35.29±6.66	19	-	9.06±0.46	intravenous 30 mg ketorolac	4
3	Forouzanfar 2019	120	38.7 ± 11.6	39	33	7.8±1.2	intravenous 800 mg ibuprofen	120	38.7 ± 13.0	41	39	8.0±1.2	intravenous 30 mg ketorolac	5
4	Shaker 2018	35	38.29 ± 11.71	7	22	-	intravenous 800 mg ibuprofen	35	36.51 ± 11.64	4	18	-	intravenous 30 mg ketorolac	3

Figure legend

Figure. 1 Flow diagram of study searching and selection process.

Figure. 2 Forest plot for the meta-analysis of pain scores at 15 min.

Figure. 3 Forest plot for the meta-analysis of pain scores at 30 min.

Figure. 4 Funnel plot for the meta-analysis of pain scores at 15 min (A) and pain scores at 30 min (B).

Figure. 5 Forest plot for the meta-analysis of pain scores at 60 min.

Figure. 6 Forest plot for the meta-analysis of pain scores at 120 min.

Figure. 7 Forest plot for the meta-analysis of adverse events.

Figures

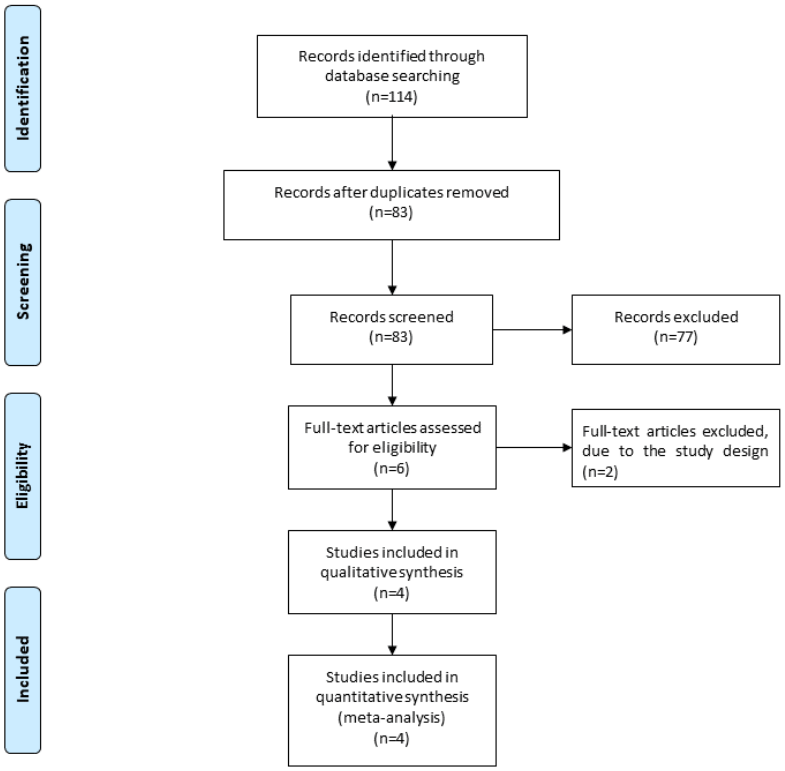


Figure. 1

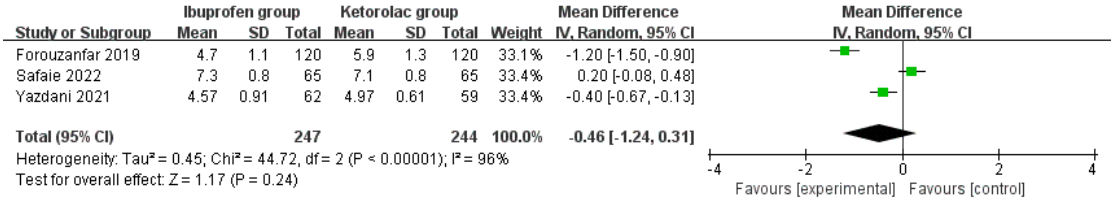


Figure. 2

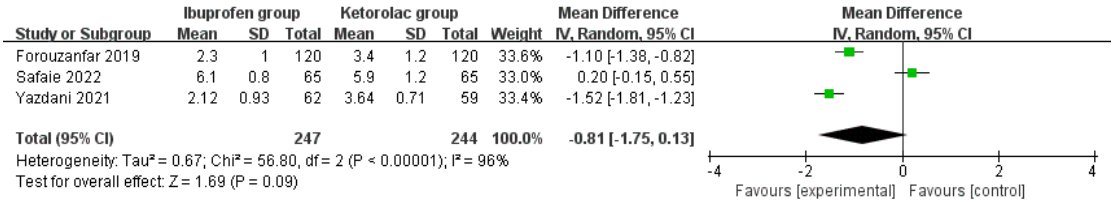


Figure. 3

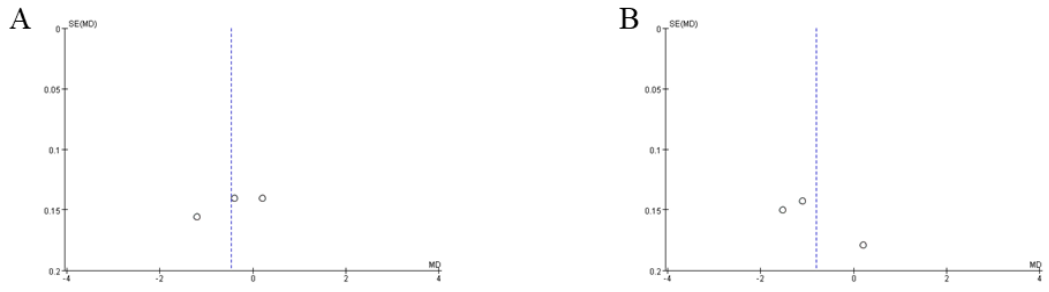


Figure. 4

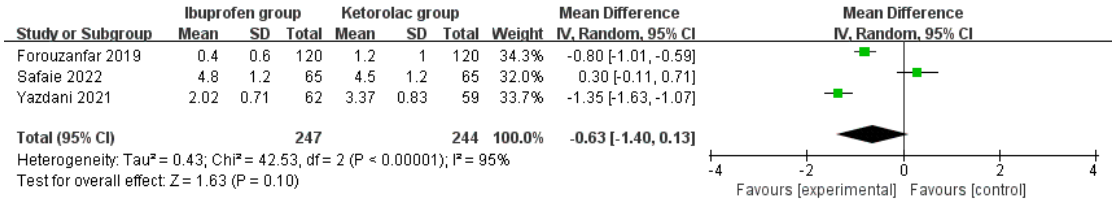
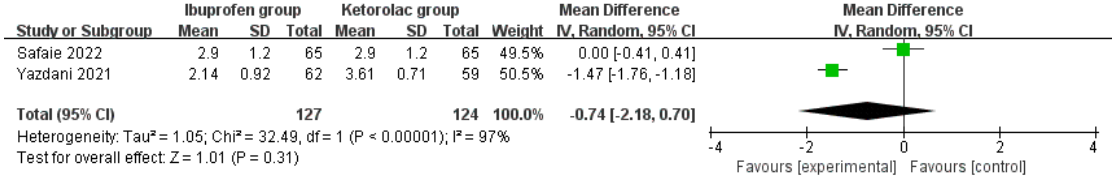


Figure. 5



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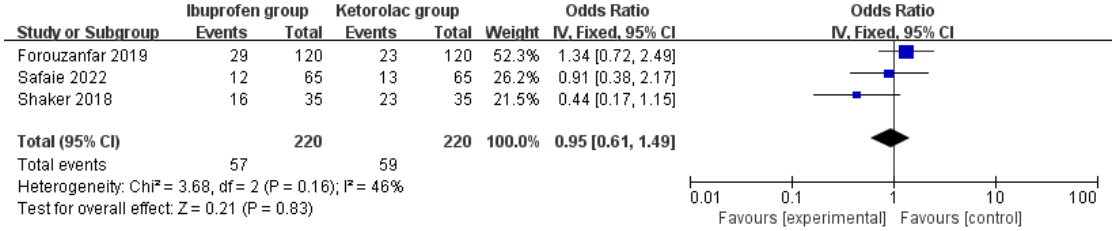

Figure. 7

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