



## Systematic review and network meta-analysis of different non-steroidal anti-inflammatory drugs for juvenile idiopathic arthritis

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### Abstract

#### BACKGROUND

Various non-steroidal anti-inflammatory drugs (NSAIDs) have been used for juvenile idiopathic arthritis (JIA). However, the optimal method for JIA has not yet been developed.

#### AIM

To perform a systematic review and network meta-analysis to determine the optimal instructions.

#### METHODS

We searched for randomized controlled trials (RCTs) from PubMed, EMBASE, Google Scholar, CNKI, and Wanfang without restriction for publication date or language at August, 2023. Any RCTs that comparing the effectiveness of NSAIDs with each other or placebo for JIA were included in this network meta-analysis. The surface under the cumulative ranking curve (SUCRA) analysis was used to rank the treatments. *P* value less than 0.05 was identified as statistically significant.

#### RESULTS

We included 8 RCTs (1127 patients) comparing 8 different instructions including meloxicam (0.125 qd and 0.250 qd), Celecoxib (3 mg/kg bid and 6 mg/kg bid), piroxicam, Naproxen (5.0 mg/kg/d, 7.5 mg/kg/d and 12.5 mg/kg/d), inuprofen (30-40 mg/kg/d), Aspirin (60-80 mg/kg/d, 75 mg/kg/d, and 55 mg/kg/d), Tolmetin (15 mg/kg/d), Rofecoxib, and placebo. There were no significant differences between any two NSAIDs regarding ACR Pedi 30 response. The SUCRA shows that celecoxib (6 mg/kg bid) ranked first (SUCRA, 88.9%), rofecoxib ranked second (SUCRA, 68.1%), Celecoxib (3 mg/kg bid) ranked third (SUCRA, 51.0%). There were no significant differences between any two NSAIDs regarding adverse events. The SUCRA shows that placebo ranked first (SUCRA, 88.2%), piroxicam ranked second (SUCRA, 60.5%), rofecoxib (0.6 mg/kg qd) ranked third (SUCRA, 56.1%), meloxicam (0.125 mg/kg qd) ranked fourth (SUCRA, 56.1%), and rofecoxib

xib (0.3 mg/kg qd) ranked fifth (SUCRA, 56.1%).

## CONCLUSION

In summary, celecoxib (6 mg/kg bid) was found to be the most effective NSAID for treating JIA. Rofecoxib, piroxicam, and meloxicam may be safer options, but further research is needed to confirm these findings in larger trials with higher quality studies.

**Key Words:** Non-steroidal anti-inflammatory drugs; Juvenile idiopathic arthritis; Network meta-analysis; Systematic review

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**Core Tip:** In summary, celecoxib (6 mg/kg bid) was found to be the most effective non-steroidal anti-inflammatory drug for treating juvenile idiopathic arthritis. Rofecoxib, piroxicam, and meloxicam may be safer options, but further research is needed to confirm these findings in larger trials with higher quality studies.

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## INTRODUCTION

Juvenile idiopathic arthritis (JIA) refers to several types of chronic arthritis that appear before the age of 16[1-3]. JIA affects 294000 children in the United States, which characterized by chronic arthritis[4,5]. The pathogenesis of JIA was unknown. Clinical manifestations of JIA is joint pain, swelling, and morning stiffness[6,7]. Symptoms of JIA often persist into adulthood and are one of the leading causes of joint dysfunction in children[8]. At present, JIA is difficult to cure in the short term. The goal of treatment for JIA is to achieve sustained remission or low disease activity[9].

There are two forms of COX in the human body currently: COX-1 and COX-2[10,11]. Normally, COX-2 expression is low, but in inflammatory conditions, it is dramatically increased and thus causing a high level of inflammation[12]. Non-steroidal anti-inflammatory drugs (NSAIDs) work by blocking COX enzyme synthesis, which in turn inhibits prostaglandin synthesis[13,14]. Thus, NSAIDs have definite pain-relieving and anti-inflammatory properties. Moreover, NSAIDs is well tolerated by children and has fewer side effects. Therefore, NSAIDs are recommended drugs for symptom relief in JIA.

NSAIDs, which include traditional non-selective NSAIDs and selective NSAIDs. There are no direct comparisons of NSAIDs in current research, so it's important to evaluate their effectiveness and safety from the perspectives of healthcare providers and payers. Currently, there is a lack of systematic review and meta-analysis that comparing different NSAIDs for JIA. Network meta-analysis enables comparisons between drugs that have not been directly compared in head-to-head trials, using a common comparator like placebo[15,16]. We will use network meta-analysis to determine the best treatment for JIA and guide clinical decision-making. Our goal is to compare NSAIDs for JIA treatment through network meta-analysis.

## MATERIALS AND METHODS

### Search strategy

Two authors independently searched the electronic literature database of PubMed, EMBASE, Google Scholar, CNKI and Wanfang without restriction for publication date or language at August, 2023. The key words for searching can be seen in Supplement material. Articles and references were searched to prevent overlooking important sources. Previous systematic reviews, meta-analyses, and randomized controlled trials were also reviewed. Any disagreements between authors were resolved with a third independent author. Only studies involving humans were included in the search. As this study is a network meta-analysis, ethical approval was not necessary.

### Inclusion criteria

The inclusion criteria were as follows: (1) Patients were diagnosed with JIA; (2) studies comparing NSAIDs therapies [meloxicam (0.125 qd and 0.250 qd), Celecoxib (3 mg/kg bid and 6 mg/kg bid)], piroxicam, Naproxen (5.0 mg/kg/d, 7.5 mg/kg/d, and 12.5 mg/kg/d), Inuprofen (30-40 mg/kg/d), Aspirin (60-80 mg/kg/d, 75 mg/kg/d, and 55 mg/kg/d), Tolmetin (15 mg/kg/d), Rofecoxib (0.3 mg/kg qd, 0.6 mg/kg), or with placebo; (3) randomized controlled trials (RCTs); and (4) studies reporting ACR Pedi 30 response and adverse events in patients.

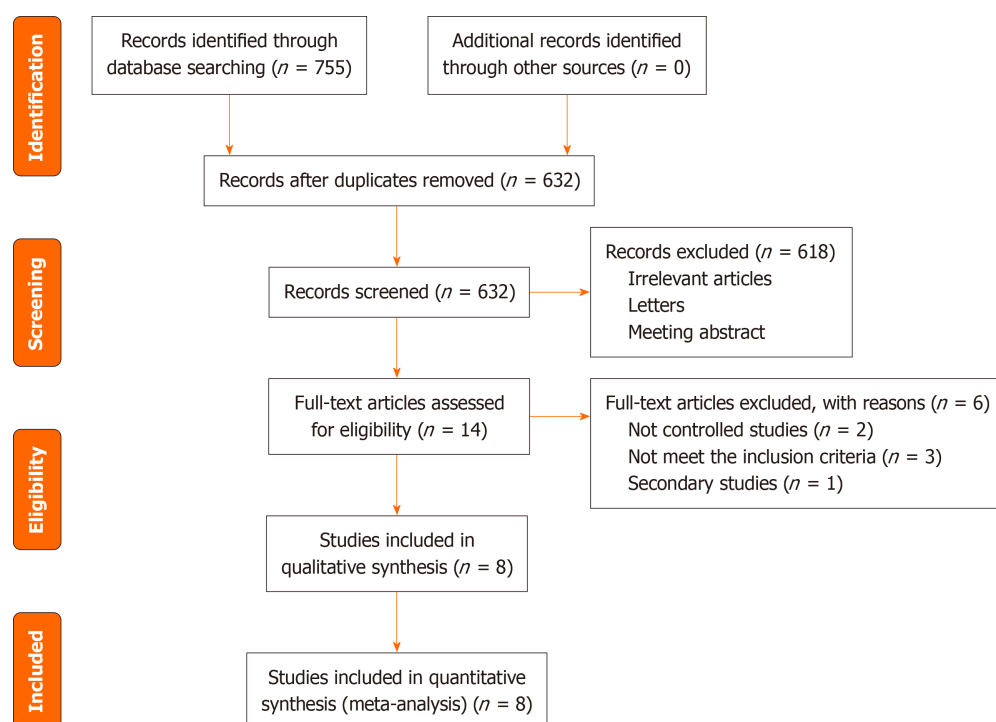


Figure 1 Literature review flow-chart.

The following studies were excluded: (1) Abstract only (insufficient data); (2) repeatedly published studies; (3) repeated studies; (4) not RCT; and (5) secondary research papers (*e.g.*, reviews, meta-analyses).

### Data extraction

Two investigators independently extracted data from included trials using a standardized form, including author, publication year, country, participant characteristics, sample size, follow-up duration, and drugs. Clinical outcomes containing ACR Pedi 30 response and adverse events. In case of inconsistencies, extensive discussions were used for resolution.

### Quality assessment and publication bias assessment

Two assessors evaluated the quality of individual trials based on the Cochrane Handbook, looking at factors like randomization, blinding, and reporting bias. Trials were categorized as “low risk”, “high risk”, or “unclear”.

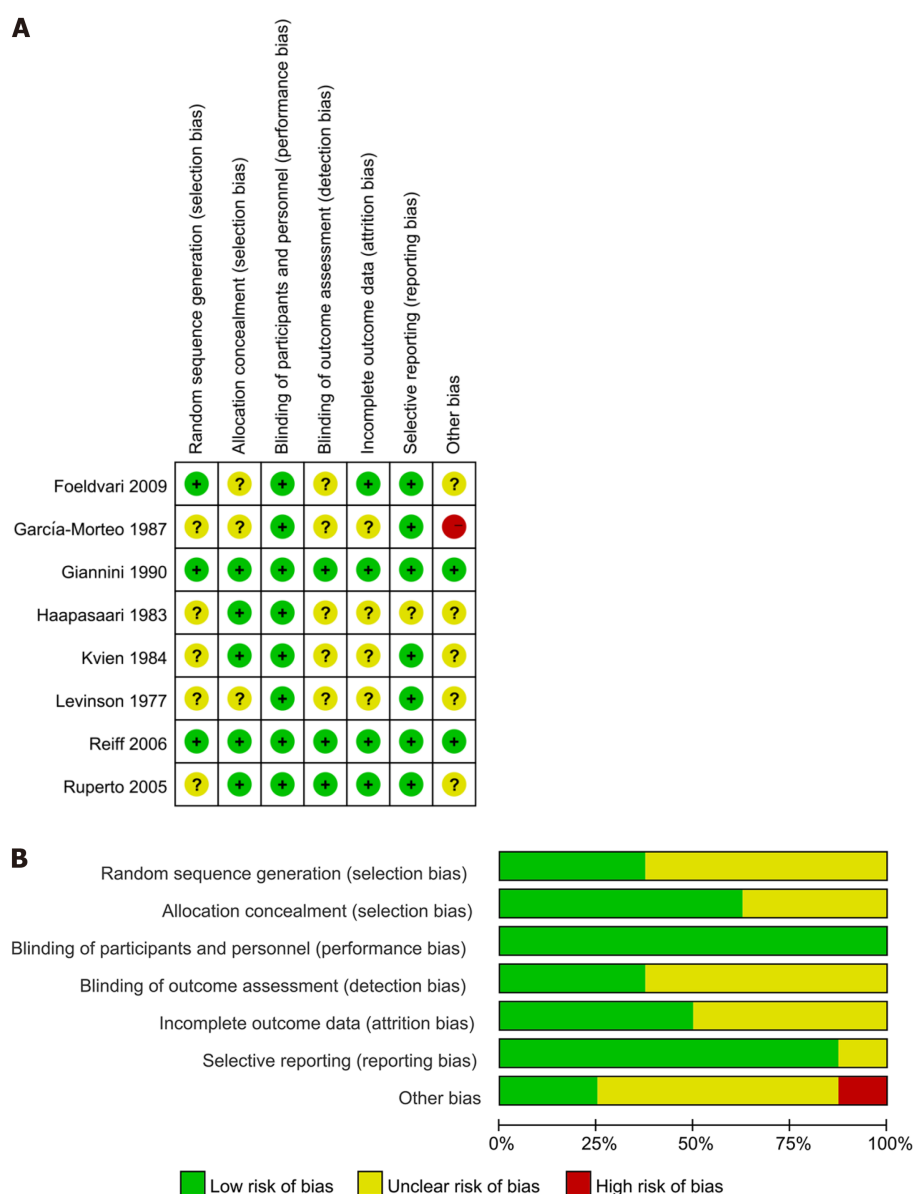
### Statistical analysis

A network meta-analysis was performed to compare various treatments utilizing a random-effect model within a Bayesian framework. The analysis was carried out using the “gemtc” and “rjags” packages in R software version 3.5.1. Convergence was ensured through the implementation of a Markov chain Monte Carlo Bayesian approach with four chains, each consisting of 20000 iterations. Each chain generated 150000 sample iterations, with 10 thinning intervals and 100000 burn-ins. Estimates were based on median values from posterior distributions, with statistically significant differences indicated by 95% confidence intervals excluding 1 for odds ratios and 0 for mean differences. A significance level of  $P < 0.05$  was used. Surface under the cumulative ranking curve (SUCRA) values were used in the network meta-analysis to rank interventions, with higher values indicating greater efficacy. A cluster-ranking plot was used to find the best outcome indicator. Heterogeneity was assessed with the  $I^2$  test, while inconsistency within models was measured with the deviance information criterion. Node-splitting analysis and funnel plots were used to check for local inconsistencies and publication bias respectively.

## RESULTS

### Included studies and risks of bias assessment

The search retrieved a total of 755 articles which were identified from PubMed (322), EMBASE (189), Google Scholar (215), CNKI (20), and Wanfang (9). Of these, 123 were removed as duplicates. Based on our review of the title and abstract, 632 full-text papers were reviewed and 618 were excluded. Then, full-text articles were assessed for eligibility and 6 studies were excluded for reasons. Finally, a total of 8 studies[17-24] met the inclusion criteria and included for analysis (Figure 1).



**Figure 2 Risk of bias summary and bias graph.** A: Risk of bias summary; B: Risk of bias graph.

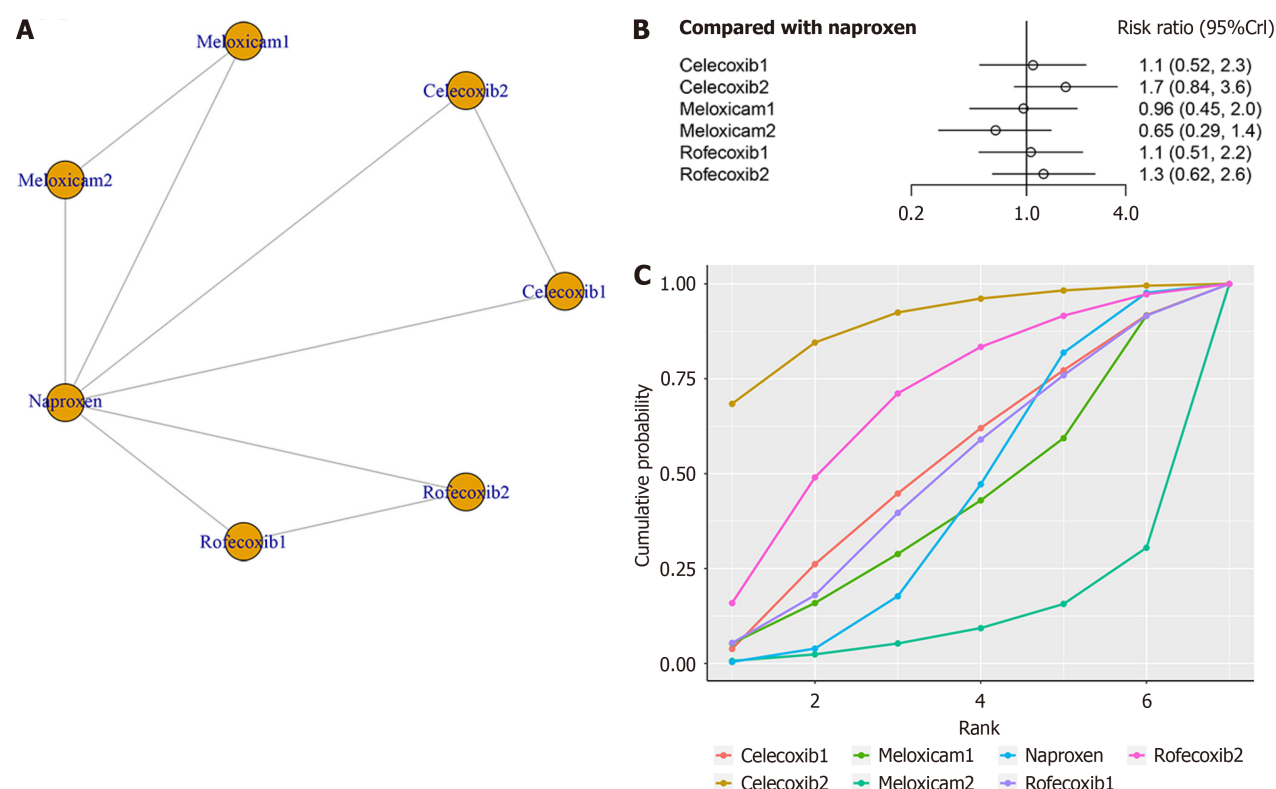
Table 1 displayed the basic characteristics of the included studies. The total sample included 467 patients whose mean or median baseline age of participants ranged from 7.7 to 11.4 years and all of them were published after 1977. Subtype of JIA including polyarticular JIA, oligoarticular JIA and systemic JIA. NSAIDs including meloxicam (0.125 qd and 0.250 qd), Celecoxib (3 mg/kg bid and 6 mg/kg bid), piroxicam, Naproxen (5.0 mg/kg/d, 7.5 mg/kg/d, and 12.5 mg/kg/d), Inuprofen (30-40 mg/kg/d), Aspirin (60-80 mg/kg/d, 75 mg/kg/d, and 55 mg/kg/d), Tolmetin (15 mg/kg/d), Rofecoxib (0.3 mg/kg qd, 0.6 mg/kg), and placebo. Most trials included in the meta-analysis had unclear risk of bias, with 3 studies having adequate random sequence generation and 5 studies reporting adequate allocation concealment. Blinding of participants and personnel was adequate in all included studies, with details shown in Figure 2.

### ACR Pedi 30 response

Three studies, involving a total of 770 patients, evaluated the clinical efficacy of four treatments (meloxicam, celecoxib, naproxen, and rofecoxib) in relation to the ACR Pedi 30 response. The network structure diagrams in Figure 3A illustrate the direct comparisons between these drugs in terms of their impact on the ACR Pedi 30 response. There were no notable differences in ACR Pedi 30 response between NSAIDs (Figure 3B). Celecoxib (6 mg/kg bid) had the highest ranking in SUCRA at 88.9%, followed by rofecoxib at 68.1% and Celecoxib (3 mg/kg bid) at 51.0% (Figure 3C).

### Adverse events

Eight studies with ten treatments (meloxicam, naproxen, piroxicam, placebo, rofecoxib, tolmetin, aspirin, celecoxib, and diclofenac) were analyzed for adverse events (Figure 4A). The network structure diagrams showed direct comparisons between the drugs, revealing no significant differences in adverse events among any two NSAIDs (Figure 4B). The results of the SUCRA indicate that the placebo intervention achieved the highest ranking with a SUCRA value of 88.2%, followed



**Figure 3 ACR Pedi 30 response.** A: The network of evidence of all the trials for ACR Pedi 30 response; B: Forest plot comparing different treatment with naproxen for need for ACR Pedi 30 response; C: Surface under the cumulative ranking curve values of different treatment for need for ACR Pedi 30 response.

by piroxicam with a SUCRA of 60.5%. Rofecoxib at a dosage of 0.600 mg/kg per day ranked third with a SUCRA of 56.1%, while meloxicam at a dosage of 0.125 mg/kg per day and rofecoxib at a dosage of 0.3 mg/kg per day both achieved a SUCRA of 56.1%, placing them in fourth and fifth positions respectively (Figure 4C).

## DISCUSSION

### Main findings

The systematic review found no significant differences in efficacy or safety among NSAIDs. Celecoxib and rofecoxib were ranked highest in terms of efficacy, while piroxicam and rofecoxib were deemed safer compared to other NSAIDs.

### Compared with other meta-analysis

Two relevant pair-wise meta-analyses on the topic have been published[25,26]. Our meta-analysis aligns with previous studies, but offers unique contributions. It is the first network meta-analysis comparing NSAIDs for JIA and includes a protocol for optimal treatment. Thus, our results from this network meta-analysis could help health-care professionals make clinical decisions. NSAIDs remain essential for relieving joint symptoms in JIA patients, despite the shift towards biologics-targeted therapy.

### Study strengths and limitations

This review is the first to systematically analyze and compare NSAIDs in JIA patients, providing a more comprehensive assessment than direct comparisons. At the same time, SUCRA value from network meta-analysis realize the efficacy and safety of each drug global sorting. The study did not find a statistically significant difference in lowering ACR Pedi 30 response between the two drugs. Based on the SUCRA values derived from trials included in our network meta-analysis, celecoxib (6 mg/kg bid) seem to be the most efficacious drug in lowering ACR Pedi 30 response. This was similar to the finding of the previous study, where a no significant difference between NSAIDs for osteoarthritis[27].

Furthermore, NSAIDs are well tolerated and has a good safety record. The most common adverse reactions are gastrointestinal adverse effects, headache, fever rash and impairment of liver function. The main side effects of NSAIDs were gastrointestinal issues, with no serious adverse events reported. The study found no significant difference in side effects between the drugs. Placebo had the highest ranking in terms of safety, followed by piroxicam and rofecoxib. The rate of adverse event after administration NSAIDs varied from 0.7% to 70.5%[28-30]. Currently, there are fewer reports of changes in kidney function among children using NSAIDs, with the most common being reversible acute renal insufficiency. In the early stages of NSAID usage, other potential renal damages, such as nephrotic syndrome and interstitial nephritis, may also manifest.

**Table 1** General characteristic of the included studies

Ref.	Sample size			Mean age			Subtype	t1	t2	t3	DMARDs (%)	Biologic agents (%)	CS (%)	Treatment duration (wk)
	t1	t2	t3	t1	t2	t3								
Ruperto <i>et al</i> [17], 2005	73	74	78	8.9	9.0	7.5	pJIA, oJIA	Meloxicam (0.125 qd)	Meloxicam (0.250 qd)	Naproxen (5.000 mg/kg)	24.7/28.4/37.2	NS	19.3/22.0/14.9	12
Foeldvari <i>et al</i> [18], 2009	77	82	83	10.4	10.2	10.4	pJIA, oJIA	Celecoxib (3.0 mg/kg bid)	Celecoxib (6.0 mg/kg bid)	Naproxen (7.5 mg/kg)	50.6/47.6/51.8	0/3.7/3.6	NS	12
García-Morteo <i>et al</i> [19], 1987	12	14		8.5	8.5		pJIA, oJIA	Piroxicam	Naproxen (12.5 mg/kg/d)		NS	NS	11.5	12
Giannini <i>et al</i> [20], 1990	45	47		7.7	7.7		pJIA, oJIA, sJIA	Inuprofen (30-40 mg/kg/d)	Aspirin (60-80 mg/kg/d)		0	0	NS	12
Haapasaari <i>et al</i> [21], 1983	15	15	15	NS	NS	NS	pJIA, oJIA, sJIA	Diclofenac (2-3 mg/kg/d)	Aspirin (50-100 mg/kg/d)	Placebo	NS	NS	NS	2
Kvien <i>et al</i> [22], 1984	40	40		11.4	9.0		pJIA, oJIA	Naproxen (10 mg/kg/d)	Aspirin (75 mg/kg/d)		0	0	0	24
Levinson <i>et al</i> [23], 1977	53	54		9.4	9.0		pJIA, oJIA, sJIA	Tolmetin (15 mg/kg/d)	Aspirin (55 mg/kg/d)		NS	0	0	12
Reiff <i>et al</i> [24], 2006	109	100	101	9.7	9.4	10.7	pJIA, oJIA	Rofecoxib (0.3 mg/kg qd)	Rofecoxib (0.6 mg/kg)	Naproxen (7.5 mg/kg/d)	53.2/51.0/45.5	NS	19.3/22.0/14.9	12

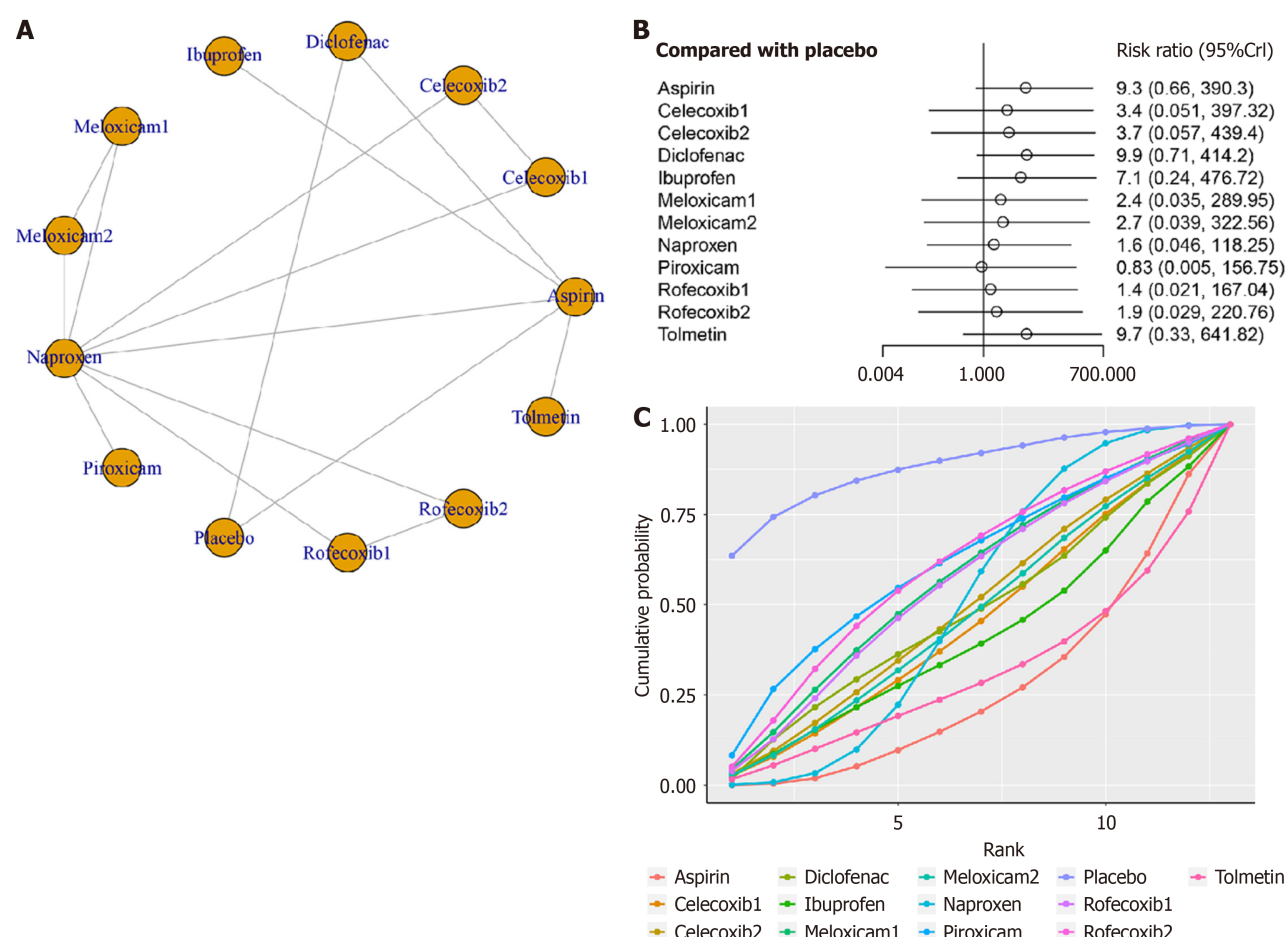
CS: Corticosteroid; pJIA: Polyarticular juvenile idiopathic arthritis; oJIA: Oligoarticular juvenile idiopathic arthritis; sJIA: Systemic juvenile idiopathic arthritis; DMARDs: Disease-modifying anti-rheumatic drugs; NS: Not significant.

Our meta-analysis has limitations, including the lack of randomized controlled trials and a small number of participants, necessitating larger clinical trials. Finally, we were unable to report other outcomes like blood loss, hospital stay relevant to this meta-analysis. The diversity in the study results may be due to differences in study quality, design, and patient characteristics. Incomplete data recording was also noted, which could introduce bias when combining the data. However, our study still offers some valuable insights for clinical use.

## CONCLUSION

In summary, celecoxib (6 mg/kg bid) was found to be the most effective NSAID for treating JIA. Rofecoxib, piroxicam, and meloxicam may be safer options, but further research is needed to confirm these findings in larger trials with higher quality studies.





**Figure 4 Adverse events.** A: The network of evidence of all the trials for adverse events; B: Forest plot comparing different treatment with placebo for need for adverse events; C: Surface under the cumulative ranking curve values of different treatment for need for adverse events.

## ARTICLE HIGHLIGHTS

### Research background

Different non-steroidal anti-inflammatory drugs (NSAIDs) have been used for juvenile idiopathic arthritis (JIA), but the best method has not been determined.

### Research motivation

To perform a systematic review and network meta-analysis to identify the most effective NSAID for JIA patients.

### Research objectives

To perform a systematic review and network meta-analysis to determine the optimal instructions.

### Research methods

We searched for randomized controlled trials (RCTs) from PubMed, EMBASE, Google Scholar, CNKI, and Wanfang without restriction for publication date or language at August, 2022. Any RCTs that comparing the effectiveness of NSAIDs with each other or placebo for JIA were included in this network meta-analysis. The surface under the cumulative ranking curve (SUCRA) analysis was used to rank the treatments. *P* value less than 0.05 was identified as statistically significant.

### Research results

Eight RCTs (1127 patients) compared different instructions for NSAIDs, including meloxicam, Celecoxib, piroxicam, Naproxen, inuprofen, Aspirin, Tolmetin, Rofecoxib, and placebo. No significant differences were found in ACR Pedi 30 response between any two NSAIDs. Celecoxib (6 mg/kg bid) had the highest SUCRA ranking at 88.9%, followed by rofecoxib at 68.1% and Celecoxib (3 mg/kg bid) at 51.0%. There were no notable differences in adverse events between NSAIDs. Placebo had the highest ranking, followed by piroxicam, rofecoxib (0.600 mg/kg qd), meloxicam (0.125 mg/kg qd), and rofecoxib (0.300 mg/kg qd).

## Research conclusions

In summary, celecoxib (6 mg/kg bid) was found to be the most effective NSAID for treating JIA.

## Research perspectives

Rofecoxib, piroxicam, and meloxicam may be safer options, but further research is needed to confirm these findings in larger trials with higher quality studies.

## FOOTNOTES

**Author contributions:** Zeng T and Ye JZ conceived and designed the study; Qin H searched and selected relevant studies; Xu QQ and Zeng T extracted and interpreted data; and all authors critically reviewed and approved the final manuscript.

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