Systematic Review and Meta-Analysis

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Efficacy and safety of over-the-counter analgesics for primary dysmenorrhea

A network meta-analysis

Wenbo Nie, MD[a], Ping Xu, MD[a], Chunyan Hao, MD[b], Yingying Chen, MD[a], Yanling Yin, MD[c], Lisheng Wang, PhD[a,*]

Abstract

Background: Primary dysmenorrhea is common and troublesome. The comparative efficacy of over-the-counter analgesics (OTCAs) for dysmenorrhea is unclear. This study was aimed at conducting a network meta-analysis to assess the efficacy and safety of 5 OTCAs – naproxen, ibuprofen,diclofenac, aspirin, and ketoprofen – in patients with primary dysmenorrhea.

Methods: The study was registered with PROSPERO (number: CRD42019133556). The search strategy involved a review of PubMed, Embase, Cochrane Library, Web of Science, and CINAHL for relative randomized controlled trials of the 5 analgesics from the date of database establishment to July 2019. The outputs are presented as odds ratios (ORs), their corresponding 95% confidence intervals (CIs), and the surface under the cumulative ranking area (SUCRA) probabilities.

Results: Thirty-five trials with 4383 participants were included in our study. As for efficacy outcomes, all the included analgesics except aspirin were more effective than placebo in treating dysmenorrhea [naproxen (OR 3.99, 95% CI 2.18–7.30), ibuprofen (OR 10.08, 95% CI 3.29–30.85), diclofenac (OR 11.82, 95% CI 2.66–52.48), and ketoprofen (OR 5.12, 95% CI 1.57–16.69). The OTCAs were superior to the placebo in terms of pain relief in primary dysmenorrhea. Aspirin was less effective than ibuprofen (OR 0.17, 95% CI 0.04–0.73) and diclofenac (OR 1.17, 95% CI 0.02–0.85). The SUCRA curves showed that diclofenac and ibuprofen were the most and second most effective (85.1% and 83.8%, respectively), followed by ketoprofen, naproxen, and aspirin. Regarding safety, there was no significant difference between the 5 OTCAs included and the placebo. Diclofenac versus ibuprofen (OR 4.31, 95% CI 1.18–15.67), ketoprofen versus diclofenac (OR 0.18, 95% CI 0.04–0.78), and ketoprofen versus aspirin (OR 0.41, 95% CI 0.18–0.97) presented statistically significant differences. Ketoprofen and ibuprofen were ranked the best (SUCRA 90.6% and 79.6%), followed by naproxen, aspirin, and diclofenac.

Conclusion: Considering the efficacy and safety, ibuprofen is recommended as the optimal OTCA for primary dysmenorrhea. Further well-designed studies that directly compare these analgesics are needed to support our conclusion.

Abbreviations: CI = confidence interval, COX = cyclooxygenase, NSAID = nonsteroidal anti-inflammatory drug, OR = odds ratio, OTCA = over-the-counter analgesic, SUCRA = surface under the cumulative ranking area.

Keywords: network meta-analysis, over-the-counter analgesic, primary dysmenorrhea

1. Introduction

Dysmenorrhea, also known as annoying monthly menstrual flow, is the most common gynecologic condition and the main reason for short-term absenteeism of teenagers and adolescents from school or work.[1,2] Studies have reported that the prevalence of dysmenorrhea in adolescents ranges from 60% to 93% and that of severe dysmenorrhea from 36% to 52.5%.[3–5] Dysmenorrhea

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[a] School of Nursing, Jilin University, [b] Gynecology and Integrated Care Unit, China-Japan Union Hospital of Jilin University, [c] Dean's Office, Second Hospital of Jilin University, Changchun, China.

[*] Correspondence: Lisheng Wang, 965 Xinjiang Street, Changchun, Jilin 130021, China (e-mail: lishengwang@jlu.edu.cn).

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is commonly categorized into primary dysmenorrhea and secondary dysmenorrhea. When menstrual pelvic pain is not associated with an identifiable pathological condition, it is called primary dysmenorrhea.[5] It usually occurs from the onset of menstruation or after 6 to 12 months. The pain usually lasts for 2 to 3 days.[6]

Effective solutions for primary dysmenorrhea include nonsteroidal anti-inflammatory drugs (NSAIDs),[7] oral contraceptives,[8,9] acupuncture,[10,11] and low levels of topical heat.[12] When choosing a treatment for dysmenorrhea, it is important to consider treatment availability. In most women with dysmenorrhea, the most severe pain occurs within 12 to 14 hours from the onset of menstruation,[13] and some women cannot determine the exact date of menstruation. Therefore, it is necessary to take painkillers at the beginning of menstruation. Since the 1980s, NSAIDs have become a routine treatment option for dysmenorrhea.[14] Currently, there are several types of NSAIDs, because the results of basic research have indicated that prostaglandins are involved in the pathogenesis of primary dysmenorrhea and that NSAIDs act by blocking the production of prostaglandin. As the most common pain relievers in the management of dysmenorrhea, NSAIDs are available as over-the-counter analgesics (OTCAs) in pharmacies in several countries. In China[15] and Italy,[16] naproxen, ibuprofen, aspirin, diclofenac (prescription required in the US), and ketoprofen are common OTCAs.

In several countries, the use of OTCAs for the treatment of dysmenorrhea is common. A survey of 1539 students in 6 Mexican universities showed that 65% of women with dysmenorrhea practiced self-medication, and the most commonly used medications were OTC drugs.[17] Sugumar et al reported that out of 641 respondents with primary dysmenorrhea, 42% self-medicated.[18] Young women are usually confused about various OTC drug choices, and they often do not know the best analgesic for them. Studies have shown that the majority of prevalent self-medication methods among women are inappropriate, and this is attributable to them being poorly informed about appropriate drug selection, the therapeutic dose, and the associated adverse effects.[4,18,19] In some countries, menstruating women are subjected to cultural restrictions. Adolescents are often reluctant to discuss about menstruation and seldom seek for optimal menstrual health.[20] A lack of knowledge about analgesics among women leads to their refusal to take drugs for fear of safety, but most women use non-drug treatment methods, some of which have no obvious effect.[21] Consequently, whether OTCAs should be used to treat dysmenorrhea and, if yes, which OTCA should be recommended for dysmenorrhea have become topics worth exploring for public health service personnel in pain management.

Indeed, the evidence for OTCA recommendations is notably insufficient. Moore et al[22] conducted a meta-analysis to compare ibuprofen and paracetamol at the standard doses for painful conditions, including dysmenorrhea. The results of a clinical trial of the efficacy of diclofenac potassium relative to a placebo for dysmenorrhea were also reported recently.[23] A Cochrane systematic review[24] compared 20 different NSAIDs versus placebo using the standard meta-analysis to elucidate whether NSAIDs are effective and safe in the treatment of primary dysmenorrhea, but the conclusions of this study are mostly about prescription NSAIDs, with limited evidence of pairwise comparison of different drugs. There are no recommendations pertaining to the use of OTCAs for dysmenorrhea. We therefore conducted a systematic review of the efficacy and safety of 5 OTCAs – naproxen, ibuprofen, diclofenac, and ketoprofen – used for primary dysmenorrhea, to provide a self-medication approach for patients with primary dysmenorrhea and provide evidence for clinical staff and pain specialists in health-care settings.

2. Methods

2.1. Protocol registration

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and was registered on June 6, 2019, with the International Prospective Register of Ongoing Systematic Reviews (CRD42019133556).

2.2. Eligibility criteria

Parallel-group or crossover randomized controlled trials of the 5 analgesics (naproxen, ibuprofen, diclofenac, aspirin, and ketoprofen) for the treatment of primary dysmenorrhea were eligible for inclusion, if they met the following criteria:

- Types of participants: Women of reproductive age with primary dysmenorrhea, which was not formally diagnosed with a physical or gynecological examination, were included as long as there were no clinical indications of pelvic pathology.
- Types of interventions: 1 of the 5 analgesics was compared with a placebo; comparison between either 2 of the 5 OTCAs.

The doses of NSAIDs varied, but were within commonly recommended dose range.[24] Average doses for the included OTCAs are shown in Table 1.

- Types of outcomes: Pain relief was measured in terms of percentage of effectiveness as dichotomous data (at least moderate pain relief or pain score reduction of more than 50% were considered indicative of effectiveness). If pain scales were used, we converted these into dichotomous data according to the author's description of the scale. Adverse effects were measured in terms of their incidence.

Table 1

Dosing parameters of the five analgesics included in the study.

Included analgesics	Average doses	Usage	References
Naproxen	250–550 mg	Every 4–8 h, sometimes with a loading dose (twice the normal dose)	[24,25]
Ibuprofen,	200–400 mg	Every 4-6 h, with a maximum dose of 1200 mg/d for up to 10 d	[24–26]
Diclofenac	75–200 mg daily	2–3 divided doses	[24]
Aspirin	650 mg	Every 4 h	[24,25]
Ketoprofen	25–75 mg	Every 6 h, with or without a loading dose of 25–75 mg	[24,27]

2.3. Search strategy

A systematic literature search of PubMed, Embase, Cochrane Library, Web of Science, and CINAHL was performed from the date of inception of the databases to July 21, 2019. There was no restriction on language, date of trial, or setting. The databases were searched using the following medical subject headings or text keywords in 4 elements of PICOs: P (patient/population) –"primary dysmenorrheal" or "dysmenorrhea" or "dysmenorrhoea" or "pelvic pain" or "menstrual cramps" or "menstrual pain" or "pain-pelvic" or "painful menstruations"; I and C (intervention and comparison) – "non-steroidal" or "non steroidal" or "NSAID" or "NSAIDs" or "naproxen" or "naprosyn" or "ibuprofen" or "brufen" or "diclofenac" or "aspirin" or "acetylsalicylic acid" or "ketoprofen" or "profenid"; O (outcome) – "pain" or "adverse effect" or "adverse reaction" or "safety"; and S (study design) – "randomized controlled trial" or "controlled clinical trial" or "randomized" or "placebo" or "randomly" or "trial." Attempts were also made to identify trials from the Website of Clinical Trials Register. In order to identify other potentially overlooked literature, an additional manual search of references in the selected trials included and systematic reviews was performed.

2.4. Study selection

The identified studies were selected by 2 authors independently. Titles and abstracts were scanned initially, and then the full articles were examined according to the inclusion criteria. The authors attempted to contact the authors of these studies, as required, to determine study eligibility. Disagreements were resolved by consensus and by consulting a third reviewer.

2.5. Data extraction

Two reviewers independently performed data extraction using standardized data extraction forms. For each study, data on the general characteristics of the study, research methods, participants, interventions, outcome measures, results, and other information were extracted. Any disagreements were resolved by consensus or discussion with a third reviewer.

2.6. Risk of bias assessment

Two authors independently assessed the risk of bias for each study. According to the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0), 7 quality domains were considered, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. Disagreements between the 2 authors were resolved by consensus and discussion with a third reviewer.

2.7. Data analysis

We used Review Manager 5.3 to evaluate literature quality. Stata 12.0 was used to perform the network meta-analysis. Inconsistency factors and 95% confidence interval (95% CI) were used to assess the consistency of each closed loop. The 95% CI lower limit was equal to 0, and it was regarded as consistent. Otherwise, the closed loop was regarded as obviously inconsistent.[28] Odds ratio (OR) was used to combine the effect sizes, and interval estimation was performed with 95% CIs, where the upper limit was less than 1 or the lower limit was greater than 1, which indicated a statistically significant difference; otherwise the difference was not statistically significant. The surface under the cumulative ranking area (SUCRA) was used to rank the performance of different interventions.[29] The highest SUCRA score was 100%, and a higher SUCRA score indicated better efficacy and safety. Publication bias was evaluated using a funnel plot.

3. Results

3.1. Study identification and selection

According to the retrieval strategy and data collection method, 1278 reports were identified. EndNote X7 document management software was used to eliminate duplicate documents and 692 articles were eligible. By reading the title and abstract, 626 reports were excluded owing to being duplicates or not conforming to the inclusion criteria for participants and intervention measures. Further screening of the full text of 66 reports showed that 9 were not actually non-randomized controlled trials, 4 were not associated with primary dysmenorrhea, 8 were not focused on the drug included, and 5 did not have relevant outcomes. Moreover, 3 studies involved OTCA treatment combined with the application of traditional Chinese medicine and 2 studies involved non-oral treatment administration. Ultimately, 35 articles were included in the meta-analysis (Fig. 1).

3.2. Characteristics and quality of the included studies

Thirty-five randomized controlled trials with 4383 patients were analyzed in our study. The percentage of effectiveness was reported in 27 studies and the incidence of adverse reactions was reported in 28 studies. The characteristics of the included studies are described in Table 2. The quality of these 35 studies is summarized in Figure 2. The 35 studies mentioned the use of random methods, but only 18 studies described the method of randomization. Among the studies included, only 7 described allocation concealment. In addition, only 22 studies reported the withdrawal of enrolled patients and the causes.

Our study involved 6 interventions: naproxen, ibuprofen, diclofenac, aspirin, ketoprofen, and placebo. Figure 3A and 3B show the network plots of treatment comparisons for the efficacy and safety outcomes. Each vertex represents a drug intervention, and the diameter of the vertices represents the total sample size for drug intervention. Every 2 connecting vertices show a direct comparison between 2 interventions. The thickness of line between 2 drug points is indicative of the number of studies directly comparing the 2 drugs; the thicker the line, the higher the number of such studies. Interventions without a connecting line were analyzed through a network meta-analysis.

3.3. Network meta-analysis of efficacy outcome

The results of the network meta-analysis revealed that naproxen (OR 3.99, 95% CI 2.18–7.30), ibuprofen (OR 10.08, 95% CI 3.29–30.85), diclofenac (OR 11.82, 95% CI 2.66–52.48), and ketoprofen (OR 5.12, 95% CI 1.57–16.69) were more effective than placebo in treating dysmenorrhea (Fig. 4A). Aspirin was less effective than ibuprofen (OR 0.17, 95% CI 0.04–0.73) and

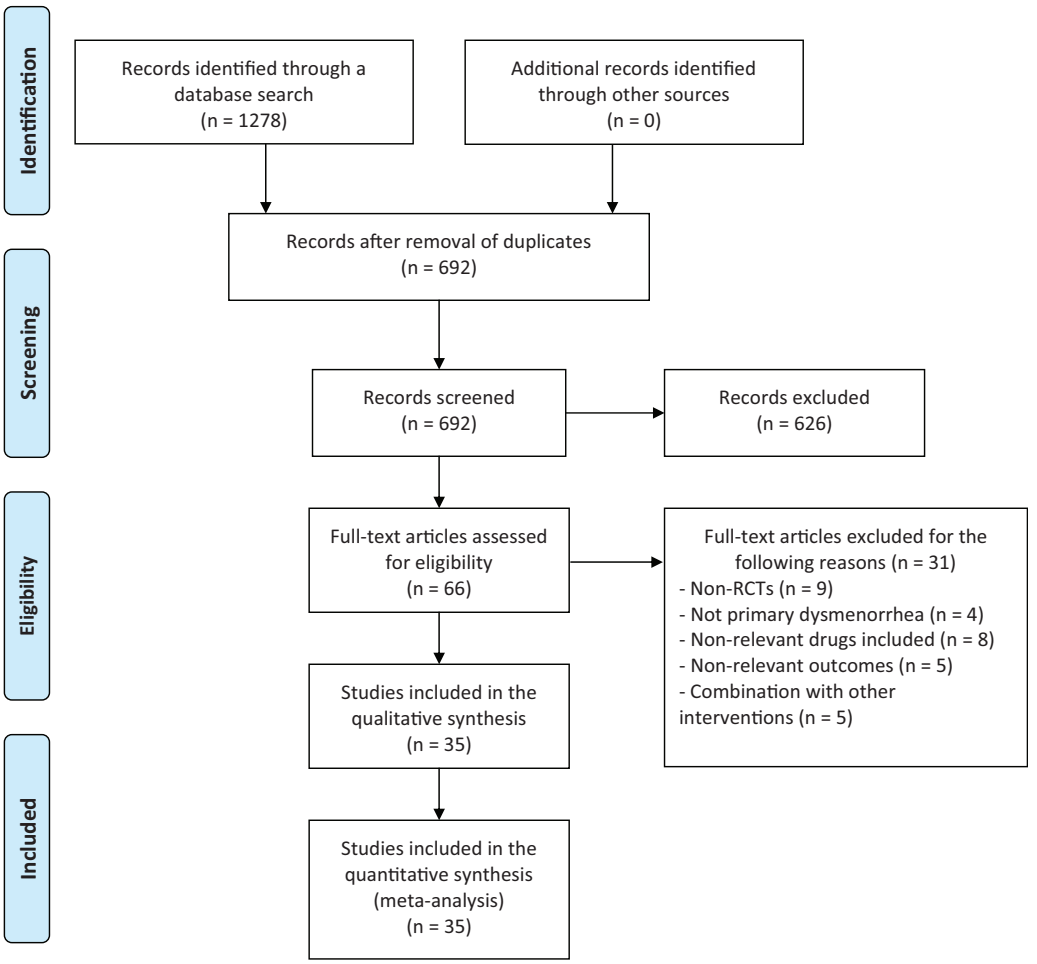

Figure 1. Flow chart of literature selection.

diclofenac (OR 1.17, 95% CI 0.02–0.85). In addition, ranking of efficacy of the various treatments is shown in Table 3. Diclofenac was ranked the best (SUCRA 84.9%), followed by ibuprofen (83.7%), ketoprofen (59.5%), naproxen (48.3%), aspirin (21.0%), and placebo (2.7%).

3.4. Network meta-analysis of the safety outcomes

With respect to adverse effects, there was no significant difference among the 5 OTCAs included and placebo (Fig. 4B). Diclofenac versus ibuprofen (OR 4.31, 95% CI 1.18–15.67), ketoprofen versus diclofenac (OR 0.18, 95% CI 0.04–0.78), and ketoprofen versus aspirin (OR 0.41, 95% CI 0.18–0.97) presented statistically significant differences. Ranking according to safety outcomes of SUCRA curves is shown in Table 4. Ketoprofen was associated with the highest probability of being the safest drug (SUCRA, 90.6%), followed by ibuprofen (79.7%), placebo (61.2%), naproxen (42.8%), aspirin (21.4%), and diclofenac (4.3%).

3.5. Publication bias and data consistency

No obvious publication bias was detected in a visual inspection of funnel-plot symmetries (Fig. 5A, 5B). In terms of network connections regarding efficacy data, 3 closed triangular loops were formed (Fig. 3A). With respect to safety data, there were 6 closed loops (Fig. 3B). Therefore, the node-splitting analysis was conducted to detect if any significant data inconsistency exists. The results demonstrated that all *P* values were more than .05 (Fig. 6A and 6B), indicating that the closed loop consistency was good.

4. Discussion

4.1. Overall analysis of the included studies

Primary dysmenorrhea, a high-frequency disease in women, affects their normal quality of life.[1] There are several types of prescribed NSAIDs, which are used as a first-line treatment,[64] and they act by inhibiting cyclooxygenase (COX) enzymes including COX-1 and COX-2. OTCAs, which are widely used, are certainly effective in relieving the pain of primary dysmenorrhea, but there is no clinical consensus on the best choice. Therefore, the purpose of this network meta-analysis was to develop an optimal treatment strategy with OTCAs through a systematic review and statistical analysis. Although a few studies have been conducted in recent years, the results of our study are valuable, as OTCAs have been widely used to relieve pain in primary dysmenorrhea in the past few decades. In this study, randomized controlled trials of the 5 OTCAs included

Table 2

Characteristics of the included studies.

Included studies	Number of cases		Area	Age of participants (years)	Interventions		Frequency of administration	Intervention duration
	Intervention group	Control group			Intervention Group	Control group		
Akerlund 1989[30]	39	39	Sweden	17–45 (26)	Ketoprofen 100 mg	Naproxen 500 mg	A single dose at severe pelvic pain	2 cycles
Behmanesh2019[31]	56	56	Iran	15–30	Ibuprofen 200 mg	Placebo	3 times daily	2 cycles
Bitner 2004[32]	89	88	USA	≥18	Naproxen 500 mg	Placebo	2 times daily	2 cycles
Chantler 2008[33]	35	39	South Africa	24 ± 4	Diclofenac potassium 50 mg	Placebo	No more than 2 daily	3 cycles
Dandenell 1979[34]	48	49	Sweden	18–40	Naproxen 250 mg	Placebo	According to the need to take, should not exceed 1250 mg daily	2 cycles
Daniels 2002[35]	96	96	USA	18–35	Naproxen 550 mg	Placebo	2 times daily	4 cycles
Daniels 2005[36]	120	120	USA	18–35	Naproxen 550 mg	Placebo	every 8 to 12 h as needed	4 cycles
Daniels 2009[37]	123	122	USA	18–44	Naproxen 550 mg	Placebo	2 times daily	3 cycles
Delia 1982[38]	59	59	USA	16–39	Aspirin 650 mg	Placebo	4 times daily	3 cycles
Dubova 2007[39]	46	42	Mexico	17–25	Ibuprofen 400 mg	Placebo	3 times daily	4 cycles
Ezcurdia 1998[40]	44	44	Spain	18–38 (24.6)	Ketoprofen 50 mg	Placebo	Once every 6 h, up to 4 times daily	4 cycles
Gleeson 1983[41]	27	27	Canada	16–31 (21.7)	Ketoprofen not mentioned	Placebo	Once every 4–6 h, no more than 4 times a day	6 cycles
Hamann 1980[42]	26	26	Denmark	14–45 (25.9)	Naproxen 500 mg Then 250 mg as needed	Placebo	Up to 5 tablets daily	2 cycles
Henzl 1977[43]	12	12	USA	24.4 ± 5.2	Naproxen 550 mg	Placebo	4 times daily	4 cycles
Iacovides 2013[44]	24	24	South Africa	20 ± 2	Diclofenac potassium 50 mg	Placebo	3 times daily	2 cycles
Jacbson 1979[45]	16	18	Sweden	15–40	Naproxen 250–550 mg	Placebo	every 4–6 h daily	2 cycles
Kajanoja 1978[46]	89	90	Finland	17–28 (22.8)	Aspirin 500 mg	Placebo	3 times daily	4~6 cycles
Kapadia 1987[47]	29	27	UK	16–40	Naproxen 550 mg	Ibuprofen 400mg	4 times daily	3 cycles
Kauppila 1986[48]	31	31	Finland	15–41	Naproxen 250 mg	Placebo	every 2–4 h, ≤5 doses per day	2 cycles
Letzel 2006[49]	93	93	Spain	32.8 ± 7.6	Naproxen	Placebo	take medication once pain ≥ 60 mm (moderate to severe pain)	3 cycles
Malmmstrom 2003[50]	73	73	USA	19–45	Naproxen 550 mg	Placebo	Not mentioned	3 cycles
Marchini 1995[51]	56	57	Italy	14–40 (27)	Ibuprofen 400 mg	Placebo	4 times daily	3 cycles
Mehlisch 1988[52]	42 (42)	42	USA	19–43	Ketoprofen 75 mg Ibuprofen 400 mg	Placebo	every 4–6 h daily	3 cycles
Mehlich 1997[53]	53	51	USA	18–45 (32.2)	Naproxen 550 mg	Placebo	≤4 times daily	4 cycles
Milsom 1985[54]	57	57	Sweden	26.1 ± 1.1	Ibuprofen 6*200 mg	Naproxen 4*125mg	3 times daily	2 cycles
Milsom 2002[14]	420 (82)	206	USA	≥ 16	Naproxen 200–400 mg Ibuprofen 200 mg	Placebo	1–2 times daily	2 cycles
Morrison 1980[55]	51	51	USA	Not mentioned	Ibuprofen 200 mg	Placebo	6 times daily	3 cycles
Morrison 1999[56]	122	118	USA	18–44	Naproxen 550 mg	Placebo	2 times daily	3 cycles
Osathanondh 1985[57]	24	24	USA	21–30	Aspirin 650 mg	Placebo	Not more than 4 times daily	4 cycles
Pogmore 1980[58]	41	41	UK	18–40	Aspirin 500 mg	Placebo	4 times daily	4 cycles
Pulkkinen 1979[59]	15	15	USA	26.9 ± 1.7	Ibuprofen 400 mg	Placebo	4 times daily	2 cycles
Riihiluoma 1981[60]	58	57	Finland	21.7 ± 3.2	Diclofenac 25 mg	Placebo	3 times daily	4 cycles
Rosenwaks 1981[61]	23 (23)	23	USA	15–40 (28)	Naproxen 550 mg Aspirin 650 mg	Placebo	4 times daily	2 cycles
Roy 1983[62]	48	48	USA	20–41	Ibuprofen 400 mg	Placebo	Not mentioned	2 cycles
Shapiro 1986[63]	43	43	USA	17–47	Asprin 650 mg	Placebo	4 times daily	4 cycles

(naproxen, ibuprofen, diclofenac, aspirin, and ketoprofen) were selected through careful reading of literature and employing an evaluation methodology without language restriction. In the studies that met the inclusion criteria, different statistics were used for the efficacy outcome indicators of dysmenorrhea and incidence of adverse events. Some studies used dichotomous variables, whereas others used continuous variables; therefore, some data could not be combined. Only binary variable data and the results that can be converted into binary variable data were integrated in our study. The overall quality of the included studies was not very high. This might be because some of the studies on the treatment of primary dysmenorrhea with OTCAs were published several years ago, and they did not adequately focus on the detailed description of research methodology.

4.2. Efficacy of the 5 OTCAs for primary dysmenorrhea

With respect to the effectiveness of the 5 OTCAs, the results of the present network meta-analysis showed that all the included analgesics except aspirin were superior to the placebo in terms of pain relief in primary dysmenorrhea. The results are consistent with those of a systematic review conducted by Zhang[65]; that is, the efficacy of the treatment of primary dysmenorrhea was significant with naproxen (OR = 0.38, 95% CI 0.32–0.44) and ibuprofen (OR = 0.23, 95% CI 0.13–0.41), but the effect of aspirin (OR = 0.79, 95% CI 0.58–1.08) was not obviously better than placebo. Marjoribanks et al[24] analyzed 11 kinds of NSAIDs in the treatment course of primary dysmenorrhea and reported that while NSAIDs are very effective in alleviating dysmenorrhea, studies directly comparing 2 kinds of drugs are limited. They also reported that the size of sample in such studies was small. Hence, it is difficult to decide whether a drug is more effective or safer than another. In our network meta-analysis, most of the results compensate for the limitations of the traditional meta-analysis, by ranking the drugs based on the SUCRA score providing information for more effective treatment. Diclofenac and ibuprofen showed the best efficacy among the 5 OTCAs. Naproxen, the most widely used drug with the highest number of studies, showed moderate efficacy in ranking.

4.3. Safety of the 5 OTCAs for primary dysmenorrhea

In terms of safety, Marjoribanks et al[24] reported that the use of NSAIDs in the treatment course of primary dysmenorrhea was highly effective when compared with placebo (OR = 4.50, 95% CI 3.85–527), but attention should be paid to their adverse reactions (OR = 1.37, 95% CI 1.12–1.66). However, in our study, the 5 OTCAs used for dysmenorrhea did not cause more

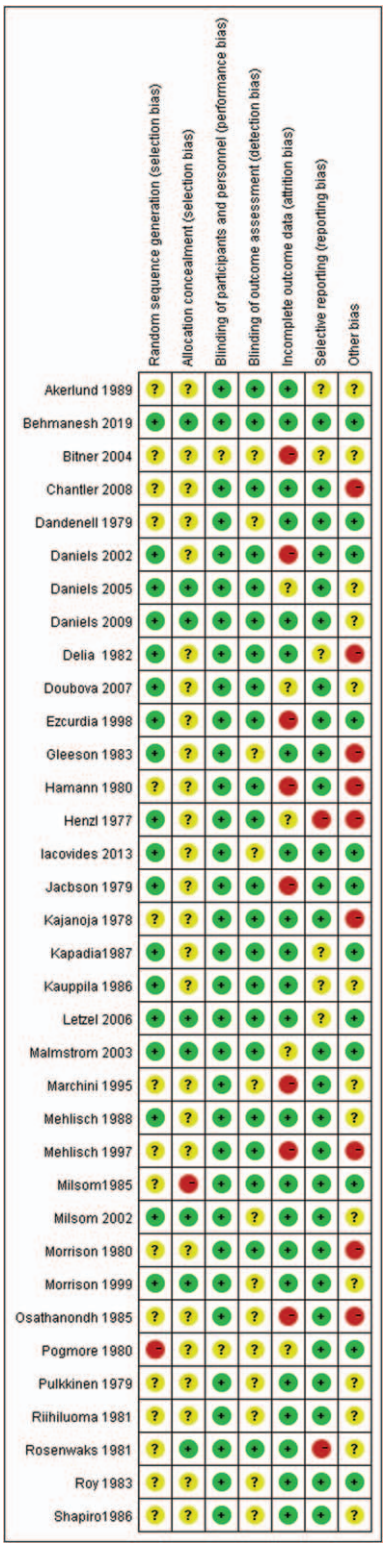

Figure 2. Summary of methodological quality.

adverse effects relative to those associated with placebo. This may be because analgesics for dysmenorrhea are usually needed for only a few days a month, and OTCAs, as drugs that can be purchased and taken by patients themselves, are relatively safe. In all the included studies, no serious adverse reaction was reported. This can be attributed to the fact that the duration of all these studies was no more than 6 months. Our network meta-analysis showed that the OTCAs were well tolerated as a pain-relief option for dysmenorrhea over a period of 6 months. Our safety outcomes obtained using SUCRA curves showed that ketoprofen and ibuprofen were the safest OTCAs, even better than placebo, whereas diclofenac was the worst one.

4.4. Overall completeness and applicability of evidence

Although our network meta-analysis results were relatively comprehensive, there were still some limitations, which may weaken the reliability of the results. First, we only evaluated the efficacy and safety differences among these OTCAs; however, the dosage and frequency of medication were not taken into consideration. Second, although various trials were included in the study, the sample size included was small. Among the 22 studies included, only 8 had a total sample size of more than 100 cases and seldom mentioned the estimation of sample size; therefore, the strength of the data was slightly weakened.

It would be useful to know whether the benefits of OTCAs can be maintained with reduced adverse effects by combining lower doses of OTCAs with codeine, paracetamol, acupuncture, or transcutaneous electrical nerve stimulation.[24] It would also be useful to know whether dysmenorrhea in oral contraceptives or intrauterine contraceptive device users can be treated in a similar way to primary dysmenorrhea. However, these questions are beyond the scope of the present study.

4.5. Relevance for practice

As previously mentioned, dysmenorrhea has been shown to cause repeated short-term pain, which is very serious at some instances. OTCAs have been suggested for pain relief in the treatment of primary dysmenorrhea[64,66]. However, some adolescents use overdoses of OTCAs without guidance, while others who experience intense pain do not seek treatment with painkillers owing to potential serious adverse reactions. Thus, it is important for health-care providers to review pertinent literature and discern available pain practice data[66] and to recommend which type of OTCAs is more effective and safe. The results of our study may serve as a reasonable medication recommendation for the health-care staff in evidence-based pain management interventions and education programs.

5. Conclusions

The results of both effectiveness and safety network meta-analyses showed that diclofenac, as the OTCA with the best effectiveness and worst safety, is similar to a double-edged sword in its application. Therefore, we recommend ibuprofen, which was ranked second in terms of effectiveness and safety, to patients with primary dysmenorrhea. Naproxen, one of the most widely used rugs for dysmenorrhea, did not show higher efficacy or safety in our study. However, the findings are applicable only to choosing a certain type of OTCA for dysmenorrhea. A previous study has shown that pharmacokinetics and pharmacodynamics parameters are significantly affected by drug-manufacturing technique and dosage forms (conventional and chewable tablets, enteric-coated capsule, oral suspensions, and liquid capsules).[67] For instance, the median times to reach the maximum blood

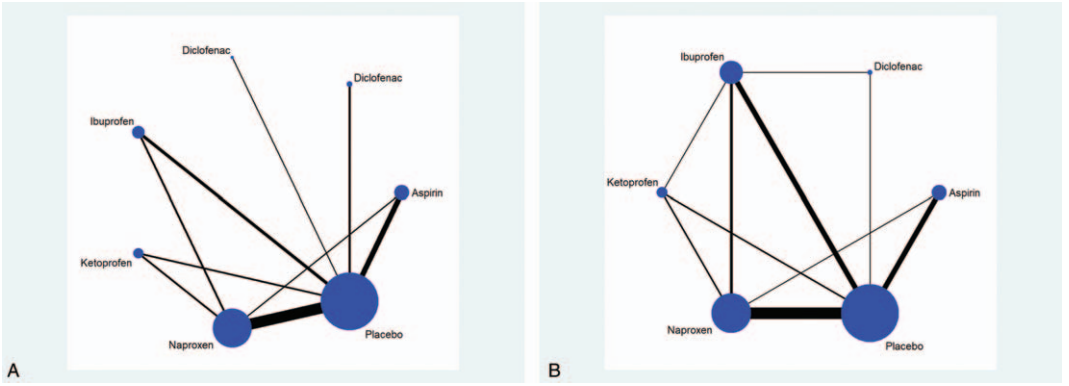

Figure 3. (A) Network connections of the included trials for pain relief. (B) Network connections of the included trials for adverse effects.

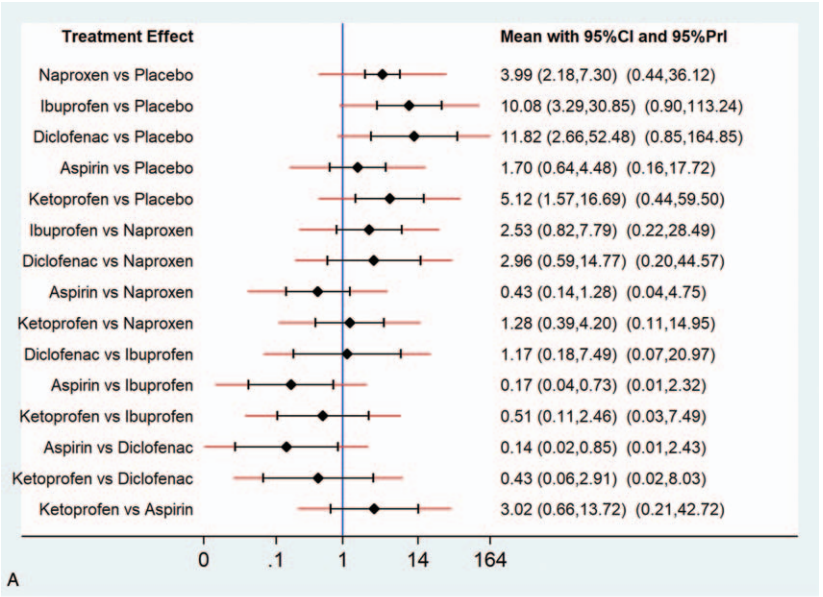

Figure 4. (A) Results of the network meta-analysis for efficacy parameters of the included analgesics. (B) Results of the network meta-analysis for safety parameters of the included analgesics.

Table 3

Ranking according to efficacy outcomes of SUCRA curves.

Treatment	SUCRA	PrBest
Placebo	2.7	0.0
Naproxen	48.3	0.3
Ibuprofen	83.7	40.4
Diclofenac	84.9	51.5
Aspirin	21.0	0.1
Ketoprofen	59.5	7.7

PrBest = the probability that the intervention would be the best treatment, SUCRA = surface under the cumulative ranking curve.

Table 4

Ranking according to safety outcomes of SUCRA curves.

Treatment	SUCRA	PrBest
Placebo	61.2	2.5
Naproxen	42.8	0.2
Ibuprofen	79.7	24.9
Diclofenac	4.3	0.5
Aspirin	21.4	0.1
Ketoprofen	90.6	71.8

PrBest = the probability that the intervention would be the best treatment, SUCRA = surface under the cumulative ranking curve.

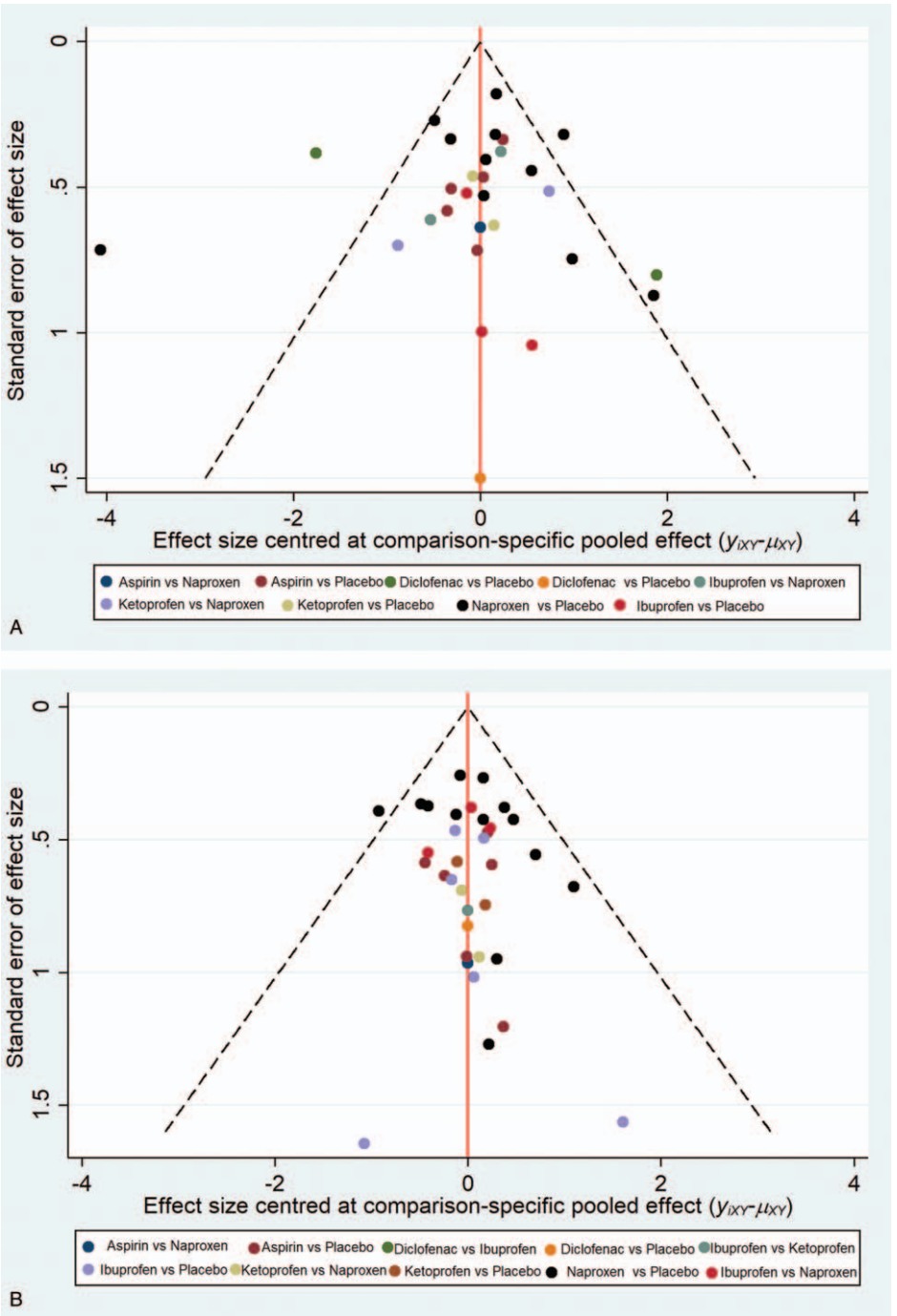

Figure 5. (A) Funnel plot of the efficacy of 5 over-the-counter analgesics and placebo. (B) Funnel plot of the safety of 5 over-the-counter analgesics and placebo.

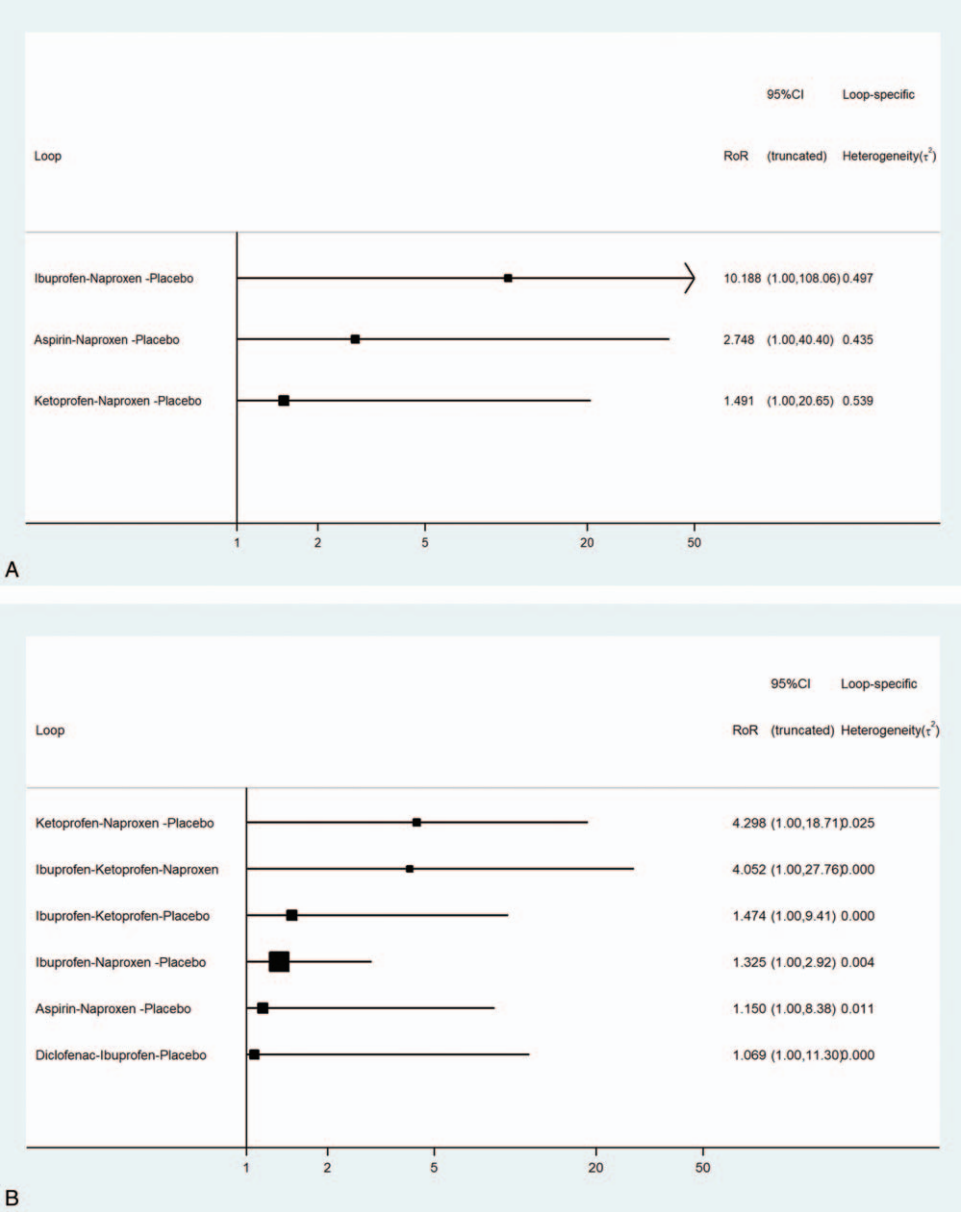

Figure 6. (A) Node-splitting analysis of the network meta-analysis for efficacy outcome. (B) Node-splitting analysis of the network meta-analysis for safety outcome.

concentration after a single oral dose of ibuprofen tablet and enteric-coated ibuprofen capsule (200 mg) were 60 and 240 minutes, respectively.[68] The oral bioavailability of a drug also depends on the dosing vehicle or formulation, physicochemical properties of the compounds, pathway of drug absorption, and physiological conditions.[69] Therefore, our results cannot be used to recommend specific doses of drugs with a specific trade name for the treatment of dysmenorrhea. In future studies, objective outcome parameters reflecting the severity of dysmenorrhea should be included in the evaluations. In addition, it is suggested that clinical nurses and researchers carry out more randomized controlled trials with large samples for direct comparison between OTCAs, in order to more accurately compare the differences in effectiveness, safety, and economy among various non-prescription analgesics.

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Author contributions

All authors provided final approval and agree to be accountable for the work.

Conceptualization: Lisheng Wang.

Data curation: Wenbo Nie, Ping Xu, Chunyan Hao, Yingying Chen, Yanling Yin, Lisheng Wang.

Formal analysis: Ping Xu, Yingying Chen.

Investigation: Yingying Chen, Yanling Yin.
Methodology: Wenbo Nie, Lisheng Wang.
Resources: Chunyan Hao, Yanling Yin.
Software: Wenbo Nie, Ping Xu.
Writing – Original Draft: Wenbo Nie.
Writing – Review & Editing: Lisheng Wang.

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