The efficacy of dexketoprofen for migraine attack
A meta-analysis of randomized controlled studies

Baohua Yang, MD, Zhili Xu, MD, Linglong Chen, MD, Xinguo Chen, MD, Yuequn Xie, MD

Abstract
Background: The efficacy of dexketoprofen for migraine attack remains controversial. We conduct a systematic review and meta-analysis to explore the influence of dexketoprofen supplementation versus placebo on pain control in migraine attack patients.

Methods: We search PubMed, EMBase, Web of science, EBSCO, and Cochrane library databases through March 2019 for randomized controlled trials (RCTs) assessing the effect of dexketoprofen supplementation versus placebo on pain control for migraine attack patients. This meta-analysis is performed using the random-effect model.

Results: Five RCTs involving 794 patients are included in the meta-analysis. Overall, compared with control group for migraine attack, dexketoprofen supplementation is associated with substantially increased pain free at 2 hours (RR = 1.90; 95% CI = 1.43–2.53; P < .0001), pain free at 48 hours (RR = 1.63; 95% CI = 1.07–2.49; P = .02), good or excellent treatment (RR = 1.48; 95% CI = 1.24–1.78; P < .0001) and pain relief at 2 hours (RR = 1.80; 95% CI = 1.17–2.77; P = .007), as well as reduced need for rescue drug (RR = 0.64; 95% CI = 0.43–0.94; P = .02), with no significant increase in adverse events (RR = 1.51; 95% CI = 0.87–2.62; P = .14).

Conclusion: Dexketoprofen supplementation benefits to improve pain control at 48 hours and reduce the need for rescue drug in migraine attack patients.

Abbreviations: CI = confidence interval, RCTs = randomized controlled trials, SMD = standard mean difference.
Keywords: dexketoprofen, migraine attack, pain control, randomized controlled trials

1. Introduction
Migraine is a leading headache etiology in the emergency department (ED) and is regarded as one of their three chief reasons for the ED visit.[1,2,3] Approximately 5.2 million patients have been reported to encounter headache or migraine headache.[4] These patients frequently suffer from the headache pattern similar to former migraine attacks, and they generally require no diagnostic testing in the ED, but require rapid and effective management of their headache.[5,6,7]

Sumatriptan, dopamine antagonists, nonsteroidal anti-inflammatory drugs (NSAIDs), and opioids are widely used for mitigating migraine headaches via diverse routes in the ED, and show the effectiveness in decreasing migraine pain. However, these drugs always lead to various side effects.[8–11] For instance, narcotic analgesics result in common side effects, such as nausea, vomiting, hypotension, and drowsiness. One kind of NSAIDs, dexketoprofen is proved to be effective and very fast in reducing pain intensity of migraine attacks in 42 women, and shows little adverse events.[12]

Dexketoprofen enables to alleviate inflammation and pain by blocking the action of cyclooxygenase and subsequently reducing the production of prostaglandins.[13] Dexketoprofen maximum plasma concentrations can be obtained around 30 minutes after an oral dose. Its elimination half-life is quite short.[14] Recently, several studies have investigated the efficacy of dexketoprofen for migraine attack patients, but the results are conflicting.[14–17] This systematic review and meta-analysis of randomized controlled trials (RCTs) aims to assess the impact of dexketoprofen supplementation on pain control in patients with migraine attack.

2. Materials and methods
This systematic review and meta-analysis are 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.[18,19] No ethical approval and patient consent are required because all analyses are based on previous published studies.

2.1. Literature search and selection criteria
We systematically search several databases including PubMed, EMBase, Web of science, EBSCO, and the Cochrane library from inception to March 2019 with the following keywords: dexketoprofen and migraine. The reference lists of retrieved studies and relevant reviews are also hand-searched and the
process above is performed repeatedly in order to include additional eligible studies.

The inclusion criteria are presented as follows:
(1) study design is RCT,
(2) patients are diagnosed with migraine attack, and
(3) intervention treatments are dexketoprofen (or dexketoprofen supplementation) versus placebo.

2.2. Data extraction and outcome measures
Some baseline information is extracted from the original studies, and they include first author, number of patients, age, weight, migraine disability assessment score, and detail methods in 2 groups. Data are extracted independently by 2 investigators, and discrepancies are resolved by consensus. We have contacted the corresponding author to obtain the data when necessary.

The primary outcome is pain free at 2 hours. Secondary outcomes include pain free at 48 hours, good or excellent treatment, pain relief at 2 hours, the need for rescue drug and adverse events.

2.3. Quality assessment in individual studies
The methodological quality of each RCT is assessed by the Jadad Scale, which consists of 3 evaluation elements: randomization (0–2 points), Blinding (0–2 points), and dropouts and withdrawals (0–1 points).[20] One point would be allocated to each element, if they have been conducted and mentioned appropriately in the original article. The score of Jadad Scale varies from 0 to 5 points. An article with Jadad score ≤ 2 is considered to be of low quality. The study is thought to be of high quality if Jadad score ≥ 3.[21]

2.4. Statistical analysis
We assess the risk ratios (RR) with 95% confidence intervals (CIs) for dichotomous outcomes (pain free at 2 hours and 48 hours, good or excellent treatment, pain relief at 2 hours, the need for rescue drug and adverse events). Heterogeneity is evaluated using the $I^2$ statistic, and $I^2 > 50\%$ indicates significant heterogeneity.[22] The random-effects model is used for all meta-analysis. We search for potential sources of heterogeneity for significant heterogeneity. Sensitivity analysis is performed to detect the influence of a single study on the overall estimate by omitting 1 study in turn or performing the subgroup analysis. Publication bias is assessed by Begg’s test and Egger’s regression test. Results are considered as statistically significant for $P < .05$. All statistical analyses are performed using Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

3. Results
3.1. Literature search, study characteristics, and quality assessment
Figure 1 shows the detailed flowchart of the search and selection results. Three hundred eighty five potentially relevant articles are identified initially. Finally, 5 RCTs are included in the meta-analysis.[14–17] The baseline characteristics of 5 included RCTs are shown in Table 1. These studies are published between 2014 and 2016, and the total sample size is 794. Allais 2014 (1) reports the early use ($\leq 30\text{min}$) of frovatriptan combined with dexketoprofen, while Allais 2014 (1) reports the late use ($> 30\text{min}$) of frovatriptan combined with dexketoprofen.[23] Three studies involve the combination of frovatriptan with dexketoprofen versus frovatriptan plus placebo,[14,16,23] and 2 studies involve the only dexketoprofen versus placebo.[15,17] The doses of dexketoprofen are 30 mg or 37.5 mg. Jadad scores of the 5 included studies vary from 3 to 5, and all 5 studies have high quality based on the quality assessment.

3.2. Primary outcomes: pain free at 2 hours
The random-effect model is used for the analysis of primary outcomes. The results find that compared to control group for migraine attack patients, dexketoprofen supplementation can significantly increase the number of pain free at 2 hours (RR = 1.90; 95% CI = 1.43–2.53; $P < .0001$) with no heterogeneity among the studies ($I^2 = 0\%$, heterogeneity $P = .74$, Fig. 2). The funnel plot is relatively symmetrical, and all studies fall within the 95% CI axis for a given standard error. There is little evidence of publication bias (Fig. 3).

3.3. Sensitivity analysis
There is no heterogeneity for the primary outcomes, and thus we do not perform sensitivity analysis by omitting one study in turn to detect the heterogeneity.

3.4. Secondary outcomes
In comparison with control intervention for migraine attack patients, dexketoprofen supplementation is associated with significantly increased pain free at 48 hours (RR = 1.63; 95% CI = 1.07–2.49; $P = .02$; Fig. 4), good or excellent treatment (RR = 1.48; 95% CI = 1.24–1.78; $P < .0001$; Fig. 5) and pain relief at 2 hours (RR = 1.80; 95% CI = 1.17–2.77; $P = .007$; Fig. 6), as well as reduced need for rescue drug (RR = 0.64; 95% CI = 0.43–0.94; $P = .02$; Fig. 7), but has no remarkable impact on adverse events (RR = 1.51; 95% CI = 0.87–2.62; $P = .14$; Fig. 8).

3.5. Publication bias
No significant publication bias is observed ($P = .412$) based on Begg’s test and Egger’s regression test.

4. Discussion
There are many pharmacologic classes of first-line drugs for the treatment of migraine attacks.[24–26] The guidelines published by the European Federation of Neurological Societies state that triptans, acetylsalicylic acid, naproxen, ibuprofen, diclofenac, and paracetamol are regarded as the first-line recommendation.[15] In a randomized, double-blind, crossover, placebo-controlled, dose-optimization phase II study, 30 mg dexketoprofen trometamol is reported to significantly improve headache relief and the absence of functional disability for acute migraine treatment.[17] In addition, another RCT also confirms the efficacy of 50 mg dexketoprofen for migraine attack, and results in the reduced rescue medication requirement compared to placebo (22.3% vs 55.4%).[15]
Table 1

Characteristics of included studies.

| No. | Author          | Number | Age (years) | Female (n) | Weight (kg) | MIDAS score | Methods                      | Number | Age (years) | Female (n) | Weight (kg) | MIDAS score | Methods                      | Jadad scores |
|-----|-----------------|--------|-------------|------------|-------------|--------------|-----------------------------|--------|-------------|------------|-------------|--------------|-----------------------------|--------------|
| 1   | Gungor 2016     | 112    | 37±11       | –          | 58.6±7.9    | 25.4±16.9    | 50 mg dexketoprofen          | 112    | 37±11       | –          | 57.1±5.7    | 24.9±16.3    | Placebo                                    | 4            |
| 2   | Allais 2015     | 28     | 37.8±6.9    | –          | 53.5±7.2    | 23.1±16.6    | Frovatipran 2.5 mg plus dexketoprofen 37.5 mg | 28     | 37.8±7.3    | –          | 57.1±5.7    | 24.9±16.3    | Placebo                                    | 4            |
| 3   | Tullo 2014      | 91     | 40±10       | 75         | 63.5±12.1   | 23.1±16.6    | Frovatipran 2.5 mg plus dexketoprofen 37.5 mg | 93     | 38.3±9      | 89         | 61.1±8.7   | 23.1±16.6    | Placebo                                    | 5            |
| 4   | Mainardi 2014   | 74     | 40.5±11.0   | 45         | 67.8±13.6   | –            | Frovatipran 50 mg plus dexketoprofen 37.5 mg | 46     | 70.4±13.7   | –          | 61.3±8.3    | 25.6±18.0    | Placebo                                    | 4            |
| 5   | Allais 2014 (1) | 53     | 40.0±9.9    | 44         | 63.0±11.2   | 26.3±10.7    | Frovatipran 2.5 mg plus dexketoprofen 37.5 mg | 58     | 61.3±8.3    | 58         | 61.3±8.3    | 25.6±18.0    | Placebo                                    | 4            |
| 6   | Allais 2014 (2) | 38     | 41.6±10.9   | 30         | 64.2±13.6   | 21.3±12.5    |                             | 32     | 39.6±8.0    | 30         | 60.6±9.6    | 18.2±14.0    |                             |              |

MIDAS = migraine disability assessment.
Figure 2. Forest plot for the meta-analysis of pain free at 2 hours.

Figure 3. Funnel plot for the outcome of pain free at 2 hours.

Figure 4. Forest plot for the meta-analysis of pain free at 48 hours.

Figure 5. Forest plot for the meta-analysis of good or excellent treatment.
Frovatriptan serves as one of the newest triptans and has a long duration of action, a low likelihood of side effects and drug interactions because of the distinct pharmacokinetic and pharmacodynamics profile.\cite{28} The elimination half-life of frovatriptan is 5 times than that of other triptans, but the time to maximum concentration is similar to other triptans.\cite{29–31}

Frovatriptan is often combined with dexketoprofen to treat migraine attack. For instance, frovatriptan 2.5mg plus dexketoprofen 37.5mg are used for migraine attack patients, and the results reveal the increase in pain free at 2 hours and 24 hours, with similar occurrence of total and drug-related adverse events compared to frovatriptan 2.5mg.\cite{14}

Our meta-analysis includes 5 RCTs involving 794 patients, and the results find that dexketoprofen supplementation shows favorably positive influence on pain free at 2 hours and 48 hours, good or excellent treatment, pain relief at 2 hours, and the need for rescue drug for migraine attack patients. No heterogeneity and publication bias is observed in this meta-analysis. Nausea and vomiting are known as the common side effects of NSAIDs. Dexketoprofen and NSAIDs are relatively safe drugs for migraine attacks. The incidence of adverse events is found to have no statistical difference between dexketoprofen supplementation and placebo. Dexketoprofen is reported to shorten the length of ED stays in migraine patients by approximately 30 minutes compared to placebo.\cite{15}

4.1. Limitations

Several limitations exist in this meta-analysis. Firstly, our analysis is based on only 5 RCTs, and more RCTs with large sample size should be conducted to explore this issue. Next, although there is no obvious heterogeneity, only dexketoprofen or its combination with frovatriptan may have some impact on the pooling results. Finally, the ideal dose and combination methods of dexketoprofen remain unclear.

4.2. Future directions

More RCTs with large sample size should be performed to investigate the efficacy of dexketoprofen for migraine attack, especially focusing on the ideal dose and combination methods of dexketoprofen.
5. Conclusion
Dexketoprofen supplementation can enhance pain control at 48 hours and reduce the need for rescue drug in patients with migraine attack.

Author contributions
Conceptualization: Yuequn Xie.
Methodology: Yuequn Xie.
Visualization: Yuequn Xie.
Writing – original draft: Yuequn Xie.
Writing – review & editing: Yuequn Xie.

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