Systematic Review and Meta-Analysis

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The efficacy of dexketoprofen for migraine attack

A meta-analysis of randomized controlled studies

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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.[1–3] 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.[5–7]

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

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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.[14–17,23]

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 min) of frovatriptan combined with dexketoprofen, while Allais 2014 (1) reports the late use (>30 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 50 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.[27] In a randomized, double-blind, crossover, placebo-controlled, dose-optimization phase II study, 50 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]

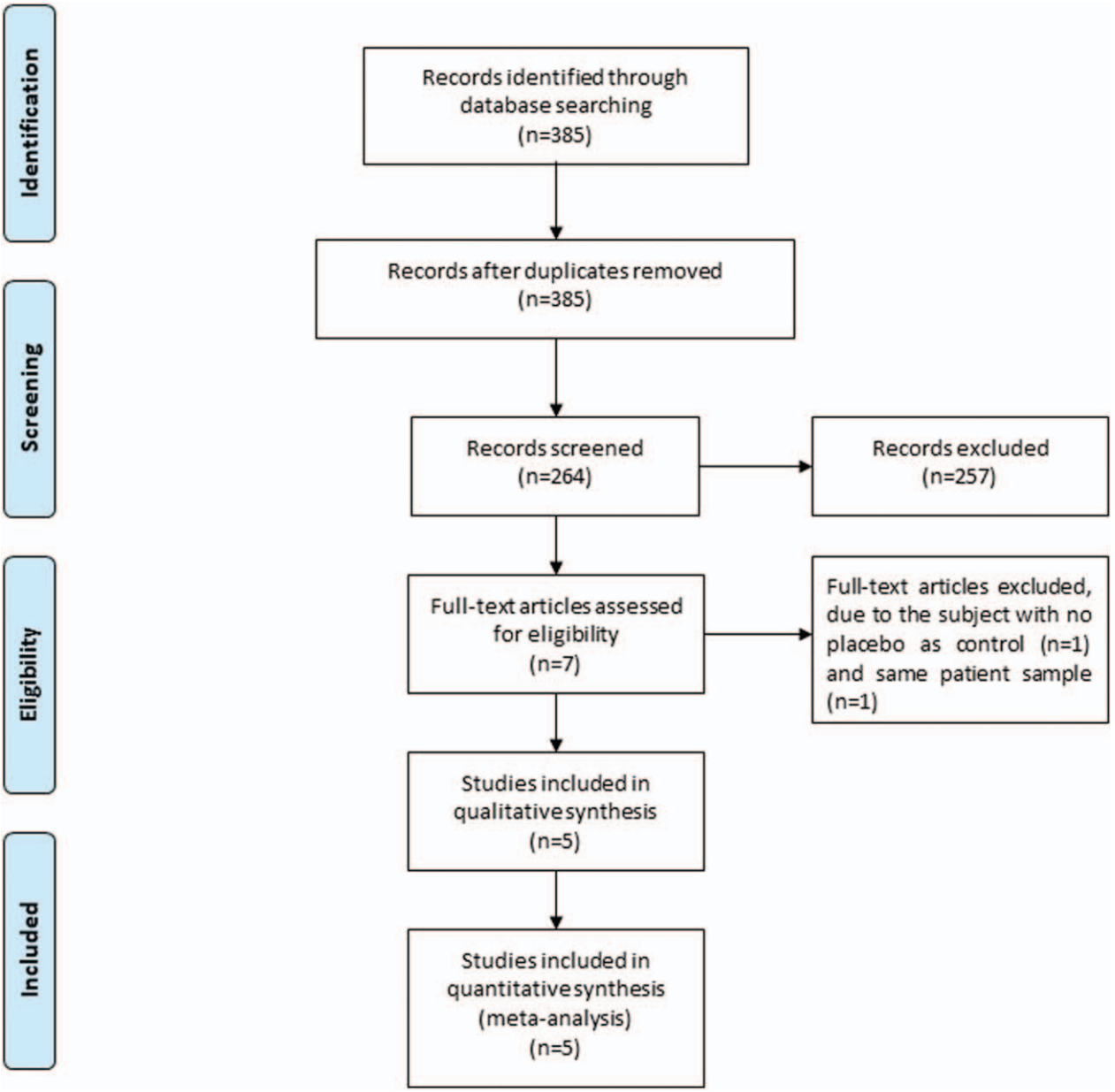

Figure 1. Flow diagram of study searching and selection process.

Table 1

Characteristics of included studies.

		Dexketoprofen group						Control group						
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	–	–	–	50 mg dexketoprofen	112	37±11	–	–	–	Placebo	4
2	Allais 2015	25	37.8±6.9	–	58.0±7.9	25.4±16.9	Frovatriptan 2.5 mg plus dexketoprofen 37.5 mg	28	37.8±7.3	–	57.1±5.7	24.0±16.3	Frovatriptan 2.5 mg plus placebo	4
3	Tullo 2014	91	40±10	75	63.5±12.1	23.1±16.6	Frovatriptan 2.5 mg plus dexketoprofen 37.5 mg	93	38.3±9	89	61.1±8.7	23±16.9	Frovatriptan 2.5 mg plus placebo	5
4	Mainardi 2014	74	40.5±11.0	45	67.8±13.6	–	Dexketoprofen 50 mg	75	40.5±10.9	46	70.4±13.7	–	Placebo	4
5	Allais 2014 (1)	53	40.0±9.	44	63.0±11.2	26.3±10.7	Frovatriptan 2.5 mg plus dexketoprofen 37.5 mg	61	38.5±9.4	58	61.3±8.3	25.6±18.0	Frovatriptan 2.5 mg plus placebo	3
	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.

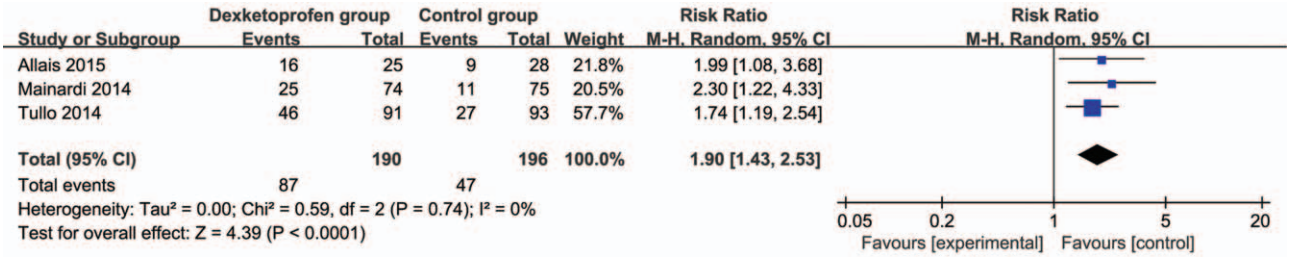

Figure 2. Forest plot for the meta-analysis of pain free at 2 hours.

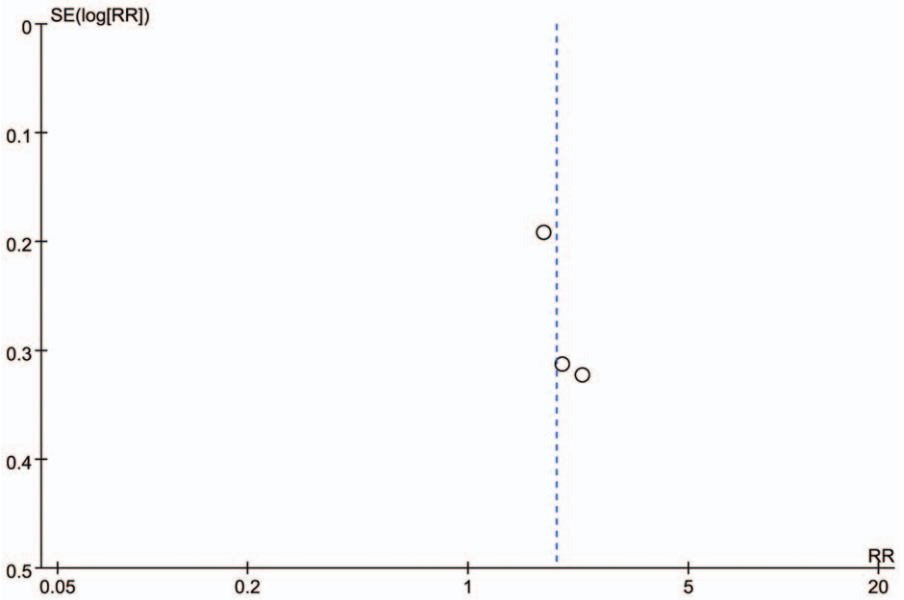

Figure 3. Funnel plot for the outcome of pain free at 2 hours.

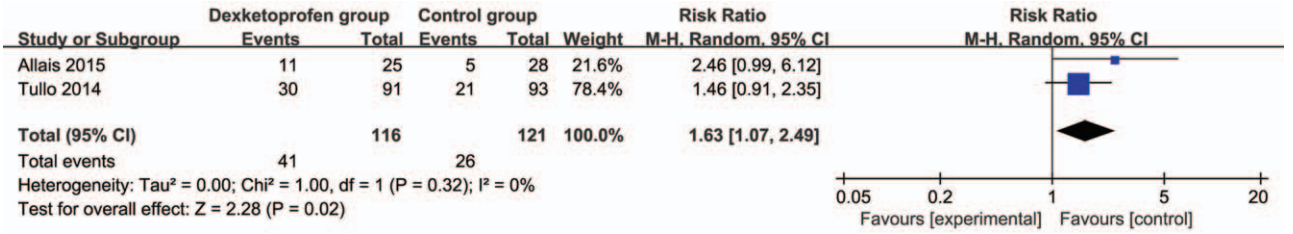

Figure 4. Forest plot for the meta-analysis of pain free at 48 hours.

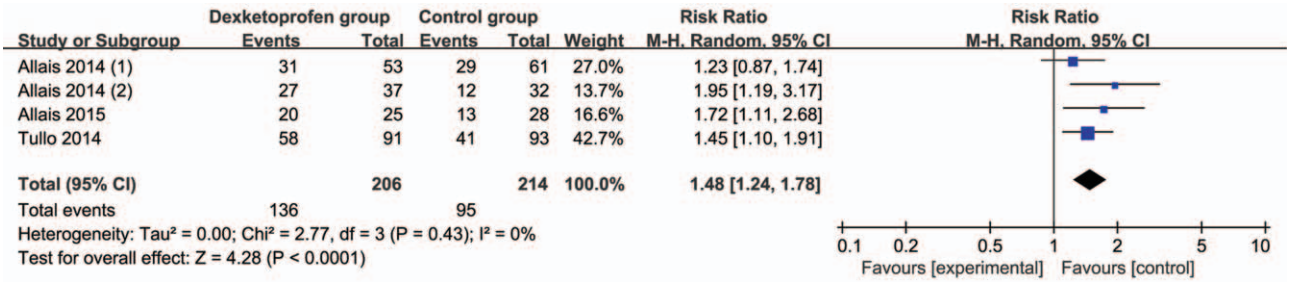

Figure 5. Forest plot for the meta-analysis of good or excellent treatment.

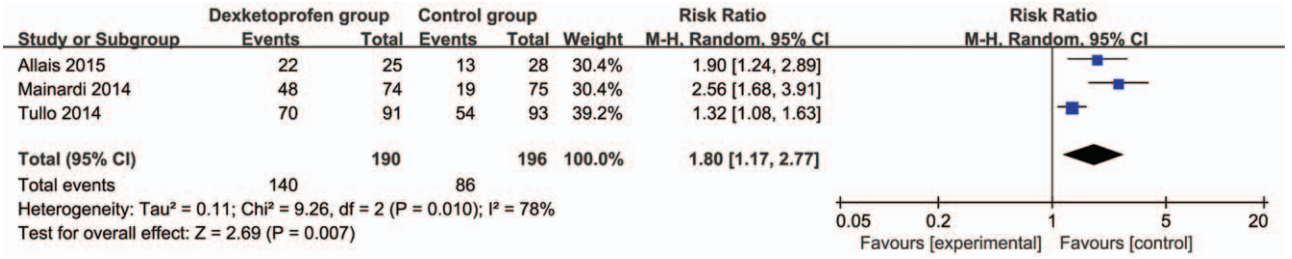

Figure 6. Forest plot for the meta-analysis of pain relief at 2 hours.

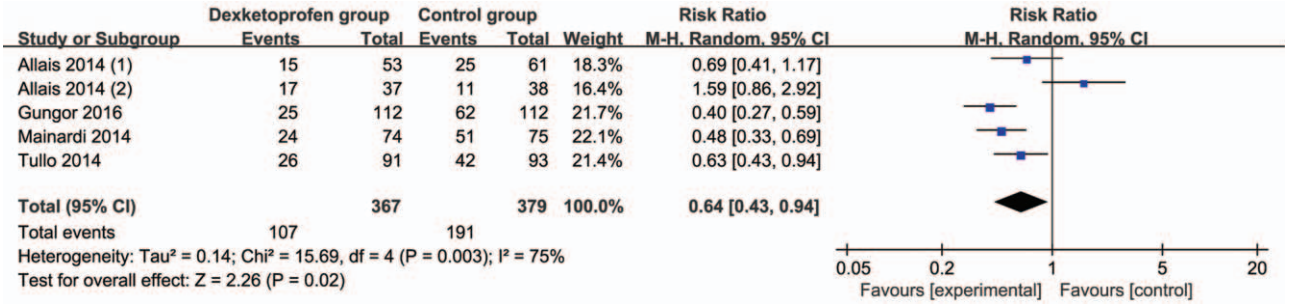

Figure 7. Forest plot for the meta-analysis of the need for rescue drug.

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.[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.[29–31] Frovatriptan is often combined with dexketoprofen to treat migraine attack. For instance, frovatriptan 2.5 mg plus dexketoprofen 37.5 mg 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 2.5 mg.[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.[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.

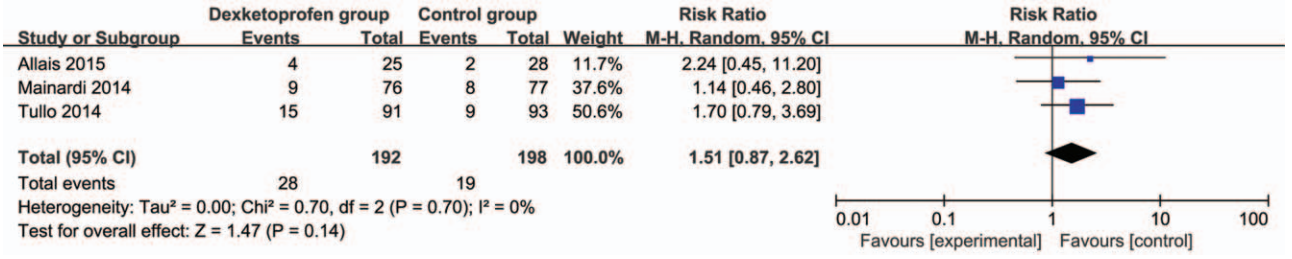

Figure 8. Forest plot for the meta-analysis of adverse events.

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.

References

[1] MacGregor EA. Migraine. Ann Int Med 2017;166:ITC49–64.
[2] Tepper SJ, Diener HC, Ashina M, et al. Erenumab in chronic migraine with medication overuse: subgroup analysis of a randomized trial. Neurology 2019;92:e2309–20.
[3] Golikhatir I, Cheraghmakani H, Bozorgi F, et al. The efficacy and safety of prochlorperazine in patients with acute migraine: a systematic review and meta-analysis. Headache 2019;59:682–700.
[4] Vinson DR. Treatment patterns of isolated benign headache in US emergency departments. Ann Emerg Med 2002;39:215–22.
[5] Maasumi K, Tepper SJ, Kriegler JS. Menstrual migraine and treatment options: review. Headache 2017;57:194–208.
[6] Hindiyeh NA, Kellerman DJ, Schmidt PC. Review of acute treatment of migraine trial results with the new FDA endpoints: design implications for future trials. Headache 2019;59:819–24.
[7] Lipton RB, Munjal S, Brand-Schieber E, et al. DFN-02, sumatriptan 10 mg nasal spray with permeation enhancer, for the acute treatment of migraine: a randomized, double-blind, placebo-controlled study assessing functional disability and subject satisfaction with treatment. CNS Drugs 2019;33:375–82.
[8] Derry CJ, Derry S, Moore RA. Sumatriptan (all routes of administration) for acute migraine attacks in adults – overview of Cochrane reviews. Cochrane Database Syst Rev 2014;CD009108.
[9] Derry S, Rabbie R, Moore RA. Diclofenac with or without an antiemetic for acute migraine headaches in adults. Cochrane Database Syst Rev 2013;CD008783.
[10] Vollesen ALH, Ashina M. PACAP38: emerging drug target in migraine and cluster headache. Headache 2017;57(Suppl 2):56–63.
[11] Etchison AR, Bos L, Ray M, et al. Low-dose ketamine does not improve migraine in the emergency department: a randomized placebo-controlled trial. West J Emerg Med 2018;19:952–60.
[12] Allais G, De Lorenzo C, Airola G, et al. Dexketoprofen trometamol in the treatment of acute migraine attack. Minerva Med 2000;91:153–9.
[13] Caldwell J, Hutt AJ, Fournel-Gigleux S. The metabolic chiral inversion and dispositional enantioselectivity of the 2-arylpropionic acids and their biological consequences. Biochem Pharmacol 1988;37:105–14.
[14] Tullo V, Valguarnera F, Barbanti P, et al. Comparison of frovatriptan plus dexketoprofen (25 mg or 37.5 mg) with frovatriptan alone in the treatment of migraine attacks with or without aura: a randomized study. Cephalalgia 2014;34:434–45.
[15] Gungor F, Akyol KC, Kesapli M, et al. Intravenous dexketoprofen vs placebo for migraine attack in the emergency department: a randomized, placebo-controlled trial. Cephalalgia 2016;36:179–84.
[16] Allais G, Bussone G, Tullo V, et al. Frovatriptan 2.5 mg plus dexketoprofen (25 mg or 37.5 mg) in menstrually related migraine. Subanalysis from a double-blind, randomized trial. Cephalalgia 2015;35:45–50.
[17] Mainardi F, Maggioni F, Pezzola D, et al. Dexketoprofen trometamol in the acute treatment of migraine attack: a phase II, randomized, double-blind, crossover, placebo-controlled, dose optimization study. J Pain 2014;15:388–94.
[18] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;6:b2535.
[19] Higgins J, Thomas J. Cochrane handbook for systematic reviews of interventions version 5.1.0 [updated March 2011]. 2011;The Cochrane Collaboration,
[20] Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17:1–2.
[21] Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. Ann Intern Med 2001;135:982–9.
[22] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–58.
[23] Allais G, Tullo V, Cortelli P, et al. Efficacy of early vs. late use of frovatriptan combined with dexketoprofen vs. frovatriptan alone in the acute treatment of migraine attacks with or without aura. Neurol Sci 2014;35(Suppl 1):107–13.
[24] Kacperski J, Hershey AD. Newly approved agents for the treatment and prevention of pediatric migraine. CNS Drugs 2016;30:837–44.
[25] Pringsheim T, Davenport W, Mackie G, et al. Canadian Headache Society guideline for migraine prophylaxis. Can J Neurol Sci 2012;39: S1–59.
[26] Tfelt-Hansen P, Pascual J, Ramadan N, et al. Guidelines for controlled trials of drugs in migraine: third edition. A guide for investigators. Cephalalgia 2012;32:6–38.
[27] Evers S, Afra J, Frese A, et al. EFNS guideline on the drug treatment of migraine – revised report of an EFNS task force. Eur J Neurol 2009;16:968–81.
[28] Balbisi EA. Frovatriptan succinate, a 5-HT1B/1D receptor agonist for migraine. Int J Clin Pract 2004;58:695–705.
[29] Savi L, Omboni S, Lisotto C, et al. A double-blind, randomized, multicenter, Italian study of frovatriptan versus rizatriptan for the acute treatment of migraine. J Headache Pain 2011;12:219–26.
[30] Bartolini M, Giamberardino MA, Lisotto C, et al. A double-blind, randomized, multicenter, Italian study of frovatriptan versus almotriptan for the acute treatment of migraine. J Headache Pain 2011;12:361–8.
[31] Cortelli P, Allais G, Tullo V, et al. Frovatriptan versus other triptans in the acute treatment of migraine: pooled analysis of three double-blind, randomized, cross-over, multicenter, Italian studies. Neurol Sci 2011;32 (Suppl 1):S95–8.