JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1347057
J Contemp Med 2023;13(5):871-878

Original Article / Orijinal Araştırma

A Systematic Review and Meta-Analysis: Acute Migraine Treatment in Pediatric and Adolescent Populations

Sistematik Bir İnceleme ve Meta-Analiz: Pediatrik ve Ergen Popülasyonlarda Akut Migren Tedavisi

Emine Özdemir Kaçer, Can Ateş

[1]Department of Pediatrics, Faculty of Medicine, Aksaray University, Aksaray, Turkey
[2]Department of Biostatistics, Faculty of Medicine, Aksaray University, Aksaray, Turkey

Abstract

Aim: The array of medications used to treat acute migraine in adults is extensive, with several now authorized for use in children and adolescents in outpatient settings. The aim of this meta-analysis was to evaluate the impact of pharmacological interventions, regardless of the method of delivery, compared to placebo, in treating migraine among individuals aged 18 years or younger.

Material and Method: We searched PubMed, EMBASE, and Cochrane Library for comparative RCTs published 30 years before May 2023. We included prospective randomized controlled clinical trials of children and adolescents with migraine, comparing acute symptom-relieving migraine medications with a placebo.

Results: Twelve clinical trials were included in this meta-analysis. The migraine treatment choice and the proportion of patients with complete pain relief at 2 hours post-treatment were analyzed. Ibuprofen (n=2), sumatriptan (n=3), zolmitriptan (n=3), and rizatriptan (n=4) were used for the analysis. Notably, sumatriptan did not exhibit significant differences compared to placebo, despite mixed individual study outcomes (OR:1.35; 95% CI 0.81, 2.27). Rizatriptan displayed varying efficacies across age groups, showing no significant difference in adolescents aged 12-17 years (p>0.05). Zolmitriptan showed dose-dependent effectiveness, with higher doses yielding better outcomes (OR:2.18; 95% CI 1.45,3.28). Ibuprofen emerged as the sole non-triptan medication to demonstrate efficacy in achieving pain-free status at 2 hours, with a favorable safety profile (OR:2.54; 95% CI 1.20, 5.37).

Conclusion: These findings suggest that ibuprofen, zolmitriptan, and rizatriptan are potential treatment options for rapidly relieving migraine in children and adolescents. However, ibuprofen may have advantages over triptans, owing to its convenience and cost-effectiveness.

Keywords: Acute migraine treatment, adolescent, meta-analysis, pediatric, pharmacological interventions, randomized controlled trials

Öz

Amaç: Yetişkinlerde akut migreni tedavi etmek için kullanılan ilaç çeşitleri oldukça geniştir ve birçoğunun artık ayakta tedavi ortamlarında çocuklarda ve ergenlerde kullanılmasına izin verilmiştir. Bu meta-analizin amacı, 18 yaş ve altındaki bireylerde migren tedavisinde, uygulama yöntemine bakılmaksızın, plaseboya kıyasla farmakolojik müdahalelerin etkisini değerlendirmekti.

Gereç ve Yöntem: Mayıs 2023'ten 30 yıl önce yayınlanan karşılaştırmalı RCT'ler için PubMed, EMBASE ve Cochrane Library'yi araştırdık. Migrenli çocuk ve ergenlerde akut semptomları hafifleten migren ilaçlarını plaseboyla karşılaştıran prospektif randomize kontrollü klinik araştırmaları dahil ettik.

Bulgular: Bu meta-analize 12 klinik çalışma dahil edildi. Migren tedavisi seçimi ve tedaviden 2 saat sonra ağrıları tamamen geçen hastaların oranı analiz edildi. Analizde ibuprofen (n=2), sumatriptan (n=3), zolmitriptan (n=3) ve rizatriptan (n=4) kullanıldı. Karışık bireysel çalışma sonuçlarına rağmen (OR:1,35; %95 CI 0,81, 2,27), sumatriptan plaseboya kıyasla anlamlı farklılıklar sergilemedi. Rizatriptanın etkinliği yaş grupları arasında değişkenlik gösterdi ve 12-17 yaş arası ergenlerde anlamlı bir fark görülmedi (p>0,05). Zolmitriptan doza bağımlı etkinlik gösterdi ve daha yüksek dozlar daha iyi sonuçlar verdi (OR:2,18; %95 CI 1,45,3,28). İbuprofen, olumlu bir güvenlik profiliyle (OR:2,54; %95 CI 1,20, 5,37) 2 saatte ağrısız duruma ulaşmada etkinliğini gösteren, triptan olmayan tek ilaç olarak ortaya çıktı.

Sonuç: Bu bulgular ibuprofen, zolmitriptan ve rizatriptanın çocuk ve ergenlerde migreni hızlı bir şekilde hafifletmek için potansiyel tedavi seçenekleri olduğunu göstermektedir. Ancak ibuprofenin kullanışlılığı ve maliyet etkinliği nedeniyle triptanlara göre avantajları olabilir.

Anahtar Kelimeler: Akut migren tedavisi, ergen, meta-analiz, pediatrik, farmakolojik müdahaleler, randomize kontrollü çalışmalar

Corresponding *(İletişim)*: Emine Özdemir Kaçer, Department of Pediatrics, Faculty of Medicine, Aksaray University, Aksaray, Turkey
E-mail *(E-posta)*: dremineozdemir@hotmail.com
Received *(Geliş Tarihi)*: 21.08.2023 **Accepted *(Kabul Tarihi)*:** 20.09.2023

INTRODUCTION

Migraine is a common primary headache disorder affecting both children and adolescents. According to the International Classification of Headache Disorders (ICHD), the prevalence of headaches ranges from 3% to 11% in this age group. Before puberty, boys are slightly more likely to have migraine than girls; however, after puberty, girls have a higher incidence and prevalence of migraine than boys. By the age of 11, one in every 10 girls suffers from recurrent headaches caused by migraine.[1-5] Migraine is a leading cause of morbidity worldwide and can significantly impair school performance and quality of life. Moreover, most adults with migraine have their first headache during childhood or adolescence.[6] In fact, 18% of patients in the pediatric emergency department are diagnosed with migraine.[7]

Migraine in children and adolescents is clinically diagnosed based on the ICHD criteria. The management of migraine involves behavioral and lifestyle changes as well as acute and preventive treatments. The choice of acute treatment depends on the timing, duration, and severity of the headache as well as the patient's needs and treatment goals. The most common drug treatments for acute migraine in children and adolescents are oral analgesics such as paracetamol and ibuprofen.[8] Other agents such as ergot derivatives (e.g., dihydroergotamine) and serotonin 1b/1d receptor agonists (triptans) have been approved by the US Food and Drug Administration for adolescent migraines and are widely used in adults. However, there is a lack of randomized controlled trials (RCTs) that have evaluated the efficacy and safety of these symptomatic therapies for migraine in children and adolescents.

Objective

We performed a meta-analysis to compare and rank the acceptability, safety, and efficacy of different drugs for the treatment of acute migraine in children and adolescents. This meta-analysis focused exclusively on RCTs that investigated symptomatic migraine treatment in children under 18 years of age.

MATERIALS AND METHODS

We conducted this meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines.[9] The PICO method was used as follows:

- Population (P) = Children with migraine
- Intervention (I) = Random onset controlled migraine therapy
- Comparison (C) = Conventional initiation controlled migraine therapy
- Outcome (O) = Drugs and outcomes

We searched PubMed, EMBASE, and the Cochrane Library for comparative RCTs published 30 years prior to May 29, 2023. The studies had to diagnose episodic migraine (with or without aura) according to the International Headache Society criteria or use similar criteria for migraine diagnosis. We used a comprehensive set of keywords, such as "acute," "headache," "migraine," "child," "youth," "teenage," "adolescent," " p(a)ediatric," and "treatment," and their spelling variations. We limited our search to human studies and texts in English.

We identified studies that compared acute migraine therapy outcomes between drugs and placebos, and extracted data on the outcomes of interest. **Figure 1** shows the search strategy and included studies.

Data extraction

Two reviewers (E.Ö.K. and İ.K.) independently reviewed the studies identified in the electronic database search. The primary screening was completed by reviewing the titles and abstracts of each study. They then reviewed the full texts of studies that passed the primary screening based on the inclusion criteria. They manually reviewed the reference lists of these studies to identify additional papers. The data extracted from each study included the first author, publication year, country, study design, and study period. They also extracted quantitative evaluation data, such as age, sex, and intervention (type and dosage of medicines) that were used in the treatment. A customized data-extraction form, as described in the Cochrane Handbook for Systematic Reviews of Interventions was used to record the duration of the trial, sample size, dropouts, and effect of interventions. Each study was evaluated according to inclusion and exclusion criteria. Any disputes were resolved through consensus or, if necessary, consultation with a third reviewer (C.A.).

Inclusion and exclusion criteria

We included all comparative RCTs that evaluated drugs for the treatment of children with migraine. The articles had to be full-length English texts. The participants were required to have episodic migraine (with or without aura) diagnosed according to the International Headache Society criteria or similar migraine diagnostic criteria. Studies and case reports that did not compare the drugs used in the treatment were excluded. We also excluded studies with patients older than 18 years, case series, case reports, and trials with patients with migraines associated with other neurological disorders. **Table 1** presents the demographic characteristics of the included studies.

Outcomes of interest

We were interested in the primary outcomes of migraine treatment choice and pain-free status at 2 h after treatment. We were also interested in the secondary outcomes of the treatment choice and pain reduction at 2 hours, the ability to sleep, the relief of other symptoms, and the decrease in pain frequency and intensity.

Table 1. Characteristics of included studies, listed according to year of publication.

	Study design	Study population	Headache severity scale	Interventions	Outcomes	Mean age	% Female
Hämäläinen et al. 1997	Randomized, double-blind, placebo-controlled, 3-way cross-over trial of ibuprofen, paracetamol, and placebo	< 18 years	5-faces pain scale	Each participant treated 1 of 3 migraine attacks with either oral paracetamol (15 mg/kg), oral ibuprofen (10 mg/kg), or placebo.	Headache relief at 2 h	10,7	50
Lewis et al. 2002	Randomized, double-blind, placebo-controlled, parallel-group trial of oral ibuprofen	6-12 years of age	4-point scale	Each participant treated 1 migraine with liquid ibuprofen suspension (7.5 mg/kg) or placebo	Headache relief (defined as a reduction from moderate or severe to mild or no headache) at 2 h	9	ND
Winner et al. 2002	Randomized, double-blind, placebo-controlled, parallel-group trial of oral rizatriptan	12-17 years of age	4-point scale	Each participant was instructed to take the study medication (rizatriptan 5 mg or placebo) within 30 min of onset of a moderate or severe migraine	Pain-free at 2 h	14	54
Ahonen et al. 2004	Randomized, double-blind, placebo-controlled, two-way cross-over trial of sumatriptan nasal spray	8-17 years of age	5-faces pain scale	Sumatriptan nasal spray 10 mg (weight 20 to 39 kg) or 20 mg (>40 kg) versus placebo.	Headache relief at 2 h (defined as severe or moderate (a grade of ^ 3) to at least 2 grades lower or fell asleep during these 2 h and was pain-free on awakening)	12,4	46
Visser et al. 2004	Randomized, double-blind, placebo-controlled, parallel-group single-attack trial of oral rizatriptan	12-17 years of age	4-point scale	Each participant treated 1 migraine with oral rizatriptan (5 mg) or placebo within 30 minutes of onset.	Headache relief at 2 h	14,2	55
Ahonen et al. 2006	Randomized, placebo-controlled, double-blind, 3-way cross-over trial of oral rizatriptan	6 - 17 years of age	5-faces pain scale	Rizatriptan 5 mg (weight 20 to 39 kg) or rizatriptan 10 mg (weight >40 kg) and placebo.	Headache relief at 2 h (defined as severe or moderate (a grade of ^ 3) to at least 2 grades lower or fell asleep during these 2 h and was pain-free on awakening)	12	54
Winner et al. 2006	Randomized, double-blind, placebo-controlled, parallel-group, multicenter, single-attack, outpatient study of intranasal sumatriptan	12-17 years of age	4-point scale	Sumatriptan 5 mg nasal spray; sumatriptan 20 mg nasal spray; or placebo	Headache relief at 2 h	14,3	55
Lewis et al. 2007	Multicenter, randomized, double-blind, placebo-controlled, 2-way, 2-attack, cross-over study of zolmitriptan nasal spray with a single-blind 'placebo challenge' or 'enrichment' phase	12-17 years of age	4-point scale	Each participant treated 1 migraine attack with zolmitriptan 5 mg nasal spray and another with matching placebo within a 12-week period.	Headache relief (decrease from moderate or severe to mild or no headache) at 2 h (1 h was used as the primary outcome in the study)	14,2	57
Ho et al. 2012	Randomized, double-blind, placebo-controlled, parallel group trial of oral rizatriptan with an enrichment design	6 - 17 years of age	4-point scale	Oral-disintegrating tablet of rizatriptan 5 mg (< 40 kg) or 10 mg (> 40 kg) or placebo.	Pain-free at 2 h	ND	44
Fujita et al. 2014	Randomized, double-blind, placebo-controlled, parallel group trial of oral sumatriptan	10 - 17 years of age	5-grade scale	Oral sumatriptan 25 mg (1 tablet and 1 matching placebo), sumatriptan 50 mg (2 tablets), or placebo (2 tablets) taken as soon as possible (within 30 minutes) after the development of a migraine with grade 3 or more pain	Headache relief (reduction of 2 grades) at 2 h	14,1	58
Winner et al. 2016	Randomized, double-blind, placebo-controlled, parallel group trial of zolmitriptan nasal spray	12-17 years of age	4-point scale	Zolmitriptan 0.5, 2.5, 5 mg nasal spray	Pain-free at 2 h	14	ND
Yonker et al. 2022	Randomized, double-blind, placebo-controlled, crossover trial	6 to 11 years of age	4-point scale	Zolmitriptan nasal spray followed by matching placebo	Headache relief at 2 h	11	57

Quality Assessment and Assessing Bias

Critical appraisals of the included studies were conducted using the Cochrane risk-of-bias tool for RCTs.[10] Two reviewers evaluated each study independently. Any conflicts were resolved through consensus or consultation with a third reviewer if necessary.

Statistical analysis

Effect size serves as a critical metric in meta-analysis, quantifying the magnitude of the relationship between variables across multiple studies. A common effect size measure of our study is odds ratio (OR). Consequently, all estimated OR's and corresponding 95% confidence intervals (CI) for a given outcome were pooled. The I^2 statistic and chi-squared test of heterogeneity were used to assess the heterogeneity of treatment effects between studies. The degree of heterogeneity (I^2) was categorized as low (25%), moderate (25–75%), or high (>75%). According to these heterogeneity statistics, we used Random Effects Model which stands out as an approach that accommodates heterogeneity and provides a more comprehensive understanding of the overall effect size. To visualize our results Forest Plots were used which clearly shows the results of individual studies, combining those studies with corresponding confidence intervals (CIs). Sensitivity analyzes and subgroups analyzes are also used to see the changes in the results. Data were analyzed using Review Manager (RevMan) version 5.4.1, and results were regarded as statistically significant if $p<0.05$.

RESULTS

The literature search yielded 138 unique citations, of which 42 full-text articles were assessed for eligibility. Some of our data requests to manufacturers were met with referrals to trial registry websites, or data were not made available. Between 1993 and 2023, a total of 12 randomized placebo-controlled trials of acute drug therapy for migraine met our inclusion criteria.[11-22] **Figure 1** shows the PRISMA flowchart, which illustrates how we selected the studies. There was complete agreement between the two reviewers regarding data extraction. Data on the study population, interventions, controls, and outcomes were extracted. The 2-hour posttreatment endpoint was chosen as this was the only consistent time interval used in the trials. Headache relief is generally quantified based on changes in pain scales. The characteristics of included studies are shown in **Table 1**.

Risk of Bias Included Studies

The risk of bias in the included studies is illustrated in **Figures 2** and **3**.

Allocation

Investigators described all studies as randomized (low risk of bias in random sequence generation), but the method of randomization was unclear in 4 studies (unclear risk of bias). The authors often used vague terms to describe sequence generation, such as 'randomized 1:1' or 'block randomization to two age groups.' Eight studies reported adequate allocation concealment, and we assessed them as having a low risk of bias in allocation concealment.

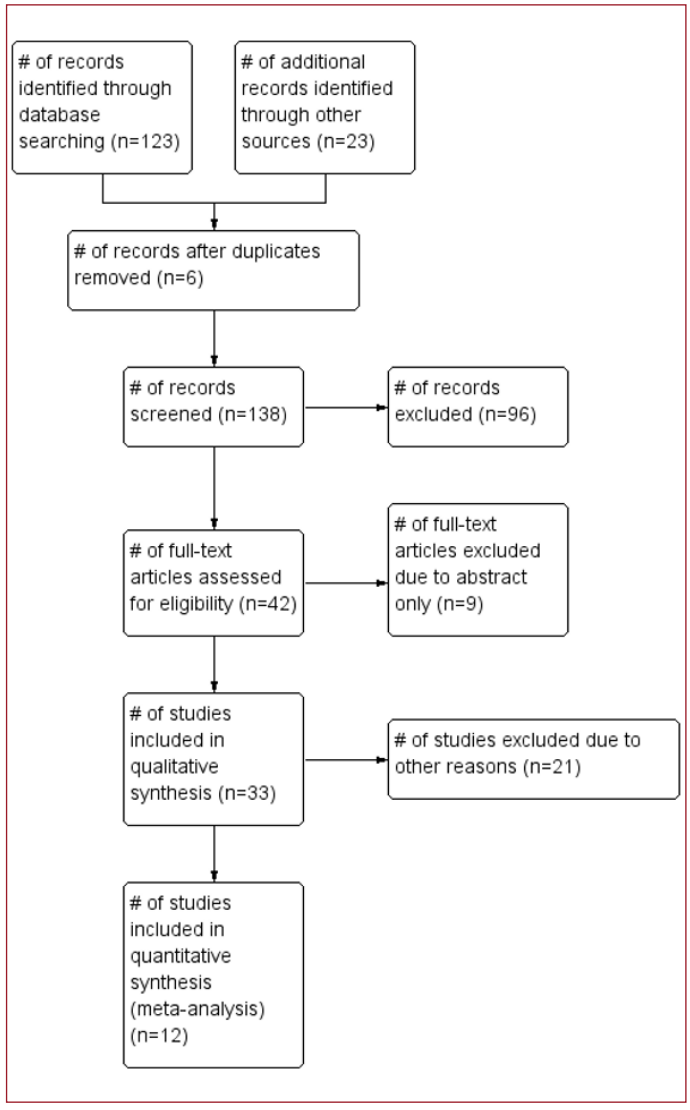

Figure 1. Study flow diagram

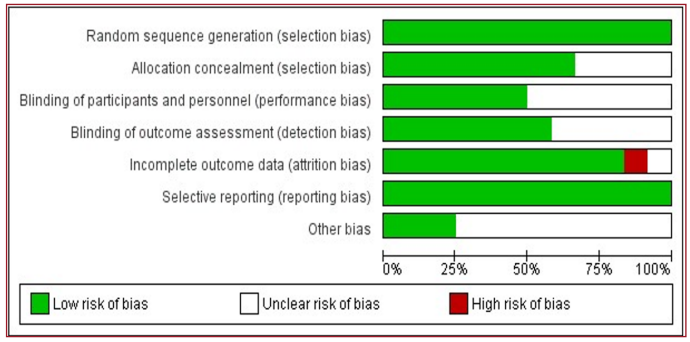

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

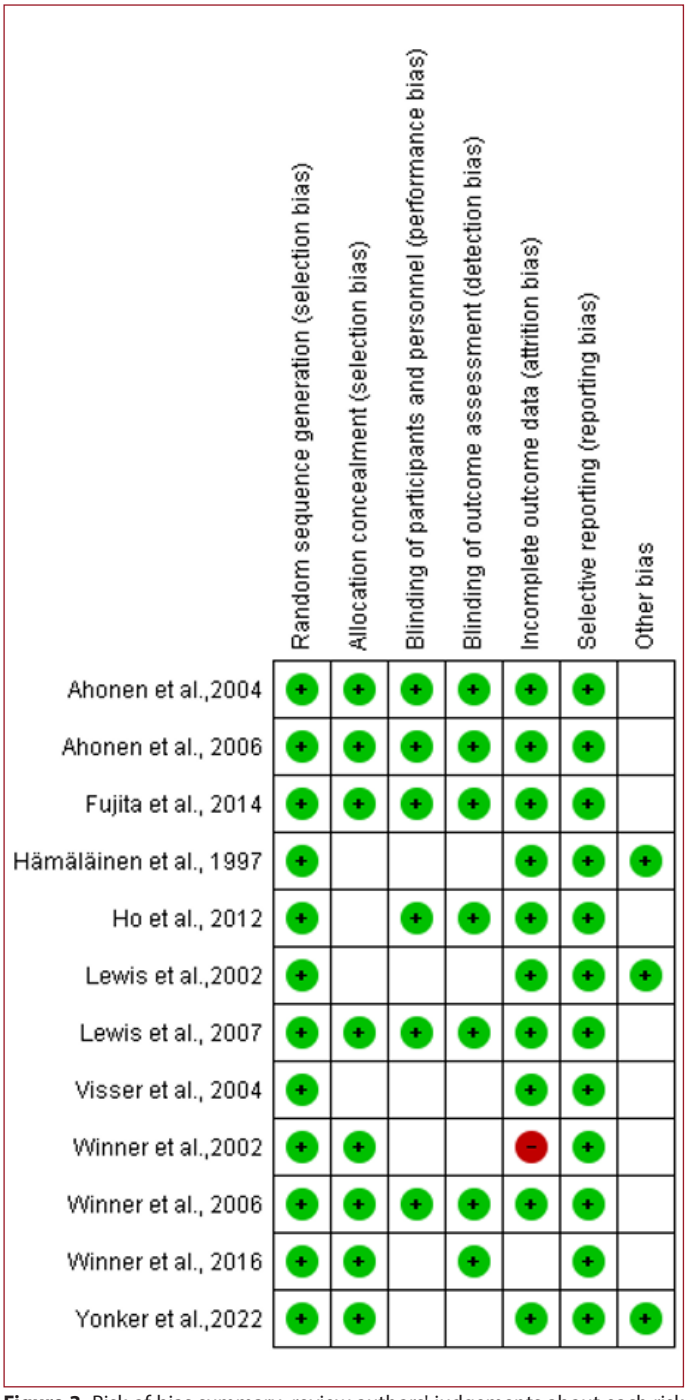

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Blinding

Generally, the authors described all studies as double-blind, but the method for blinding of participants and personnel was unclear in 6 studies (unclear risk of bias). We assessed six studies as having a low risk of bias in blinding the participants and personnel. The method for blinding the outcome assessment was unclear in five studies (unclear risk of bias). Seven studies had a low risk of bias in the blinding outcome assessment.

Incomplete Outcome Data

We rated one study as having a high risk of bias and 1 study as having an unclear risk of bias due to incomplete reporting of outcome data. We rated the remaining 10 studies as low risk.

Selective Reporting

Two studies were accessible only in the sponsors' clinical trial report registry and had no full publications, whereas one study was accessible only in the sponsor's clinical trial report registry. All the included studies reported pain-free primary efficacy outcomes. We considered the remaining studies to be of low risk.

Other Potential Sources of Bias

We evaluated publication bias based on pain-free outcomes for all triptans versus placebo in adolescents, excluding Yonger et al.[21] Although most of the published clinical trial data had low bias, we could not access the unpublished data of 9 studies (unclear risk of bias).

Effects of Interventions

We describe the measures of the effects for each intervention below.

Rizatriptan

Four studies were included in the investigation of rizatriptan's efficacy (5 mg and 10 mg orally) compared with placebo. Two of these RCTs focused on patients aged 12-17 years,[15,16] whereas the other two involved patients aged 6-17 years.[13,14] The rizatriptan dose in patients receiving acute treatment was adjusted based on their weight.

In the analysis, two RCTs,[15,16] examined the efficacy of 5 mg oral rizatriptan compared with placebo in outpatients aged 12-17 years. However, the difference in pain-free status after 2 h of treatment between the rizatriptan and placebo groups was not statistically significant ($p > 0.05$).

In a study involving patients aged 6-17 years,[13] which utilized a three-way crossover design with two doses of rizatriptan and placebo, rizatriptan was more effective than placebo ($p = 0.015$ for rizatriptan first vs. placebo; $p = 0.037$ for rizatriptan second vs. placebo). Another study involving patients of the same age range also found that rizatriptan was more effective than placebo ($p = 0.025$; OR:1.55; 95% CI:1.06 to 2.26).[14]

Upon combining all the studies, the analysis demonstrated that rizatriptan provided relief from headaches after 2 hours (OR: 1.51; 95% CI: 1.22, 1.88) (**Figure 4**). In summary, oral rizatriptan was found to be effective in treating migraine attacks and was well tolerated by patients.

Sumatriptan

This meta-analysis included three RCTs focusing on sumatriptan treatment for pediatric migraine attacks. Among these studies, two utilized nasal sprays, while one involved the oral administration of sumatriptan. The age range of the participants was 8-17 years.

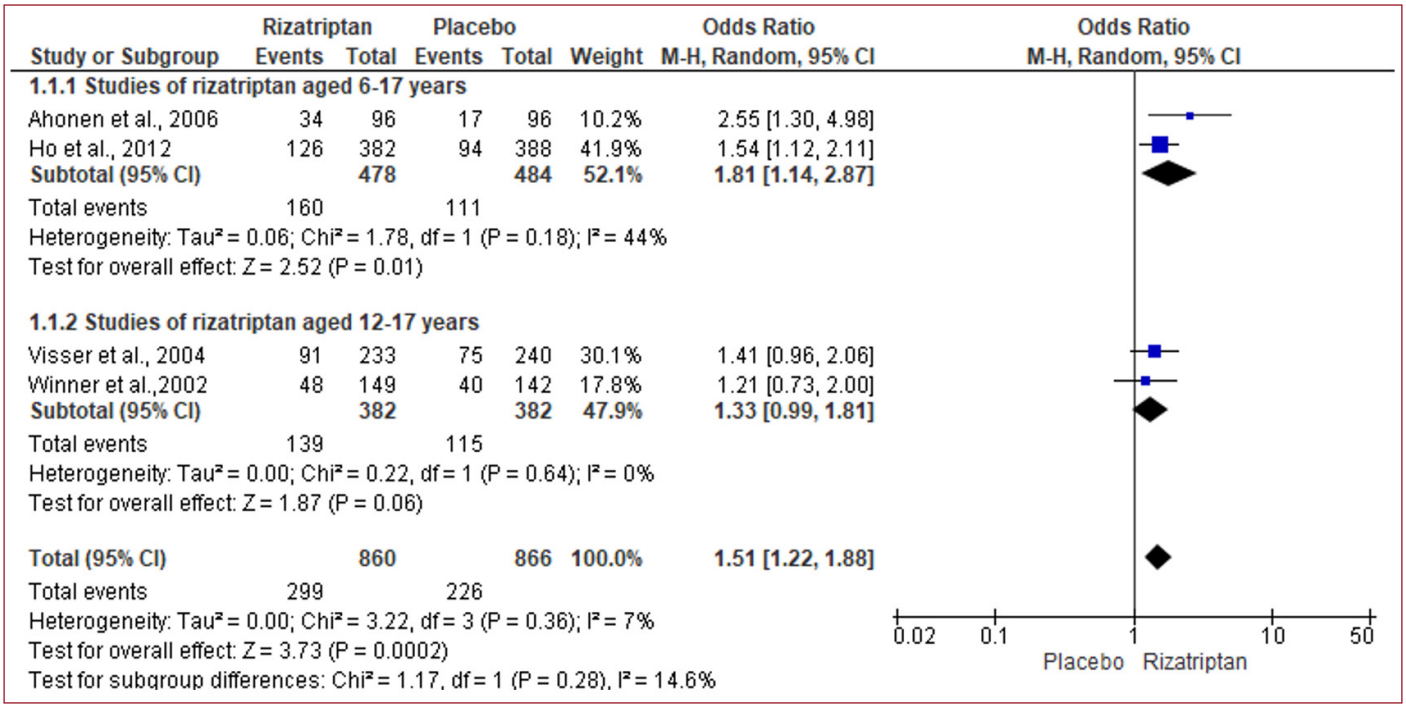

Figure 4. Forest plot of comparison: Rizatriptan vs placebo

In a study where oral sumatriptan was compared to a placebo group, no statistically significant difference was found between the two groups. Therefore, based on the available data, the oral use of sumatriptan did not significantly affect the treatment of pediatric migraine attacks.

In contrast, studies using nasal sumatriptan reported positive results. Nasal sumatriptan has been found to be an effective and well-tolerated treatment for pediatric migraine attacks.[19] However, it is worth noting that one of the studies on nasal sumatriptan had a limited number of patients, which might affect the extent of safety documentation in this specific age group.

Based on the findings from the three RCTs, oral sumatriptan did not show statistically significant efficacy compared to placebo in the treatment of pediatric migraines (OR: 1.35; 95% CI 0.81, 2.27) (**Figure 5**). On the other hand, nasal sumatriptan was demonstrated to be effective and well tolerated, although more research is required to establish its safety in this age group.

Zolmitriptan

Nasal therapy was used as the treatment method in all three zolmitriptan studies. Two of these studies involved patients aged 12-17 years,[20,22] while one study focused on patients aged 6-11 years.[21]

In the study conducted by Winner et al. zolmitriptan nasal therapy proved to be more effective than placebo in achieving a headache response at 2 hours after treatment ($p < 0.001$, OR:2.18; 95% CI 1.40, 3.39). The efficacy was sustained even 3 and 4 h after treatment ($p < 0.001$).

Yonker et al. compared zolmitriptan nasal spray with a placebo in 300 patients. Although the difference in response after 2 hours was not statistically significant ($p = 0.0777$), there was still a trend towards a higher response with zolmitriptan (OR: 1.51; 95% CI: 0.96, 2.38).

In the study conducted by Lewis et al. on the acute treatment of adolescent migraine, zolmitriptan nasal spray was well tolerated and provided rapid relief from migraine symptoms ($p < 0.01$).

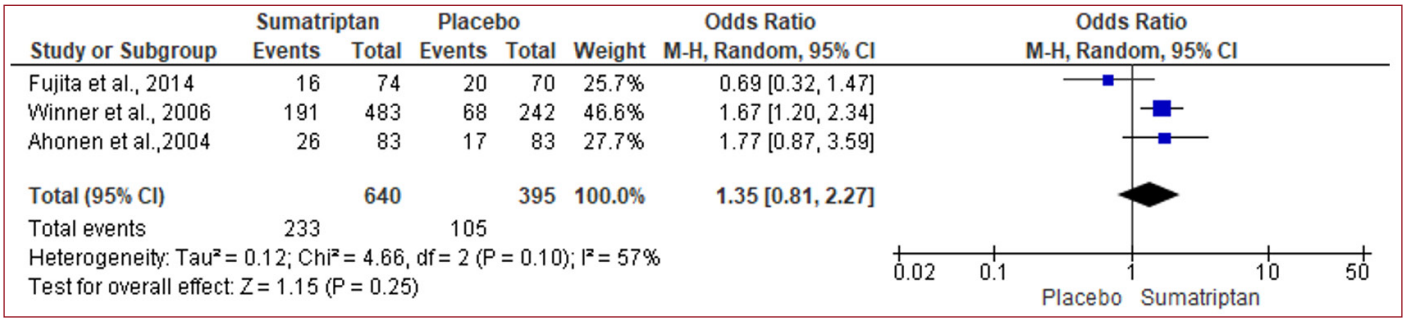

Figure 5. Forest plot of comparison: Sumatriptan vs placebo

Based on the three studies, zolmitriptan nasal therapy demonstrated efficacy in providing effective relief from migraine symptoms in adolescents and was generally well tolerated (OR: 2.18; 95% CI 1.45,3.28) (**Figure 6**).

Ibuprofen

Two RCTs were considered eligible for comparison between ibuprofen and placebo in the acute treatment of pediatric migraine. Alongside the three-way crossover study involving acetaminophen, ibuprofen, and placebo, there was also a smaller RCT that assessed ibuprofen (7.5 mg/kg liquid suspension) versus placebo in children aged 6–12 years, evaluated in a hospital setting.

The summarized data indicated that ibuprofen provided significantly more effective pain-free after 2 hours of migraine treatment compared to placebo, with a OR of 2.54 (95% CI 1.20, 5.37) (**Figure 7**).

DISCUSSION

The acute treatment of pediatric migraine with ibuprofen, triptans (sumatriptan, zolmitriptan, and rizatriptan), and placebo was compared in 12 RCTs. The main outcome was a pain-free status at 2 h post-treatment. The results showed that ibuprofen, rizatriptan, and zolmitriptan were significantly more effective than placebo in achieving this outcome.

Sumatriptan did not differ from placebo in terms of pain-free status at 2 h post-treatment, despite some individual studies showing positive effects. Rizatriptan had inconsistent results across different age groups, with no significant difference compared to placebo in adolescents aged 12-17 years. Zolmitriptan had a dose-dependent effect, with higher doses being more effective than lower ones. Ibuprofen was the only non-triptan medication that showed efficacy in a pain-free status at 2 h post-treatment, and it had a favorable safety profile.

All triptans were generally well tolerated, but some studies were funded by the same company that produced them, which may raise some concerns about bias.

Limitations: This review had some limitations that should be acknowledged. We excluded several studies from the meta-analysis owing to methodological limitations. We also discarded clinical trials that were not available in the full text or that could not be accessed. The final 12 RCTs had heterogeneous population characteristics such as age and sex. Many of the trials had small sample sizes. We pooled the data based on time and an intention-to-treat analysis, which may have increased the strength of the evidence but also introduced some heterogeneity.

CONCLUSION

According to this review, ibuprofen, zolmitriptan, and rizatriptan can help children with migraine relieve their pain quickly. However, ibuprofen may be more convenient and cost-effective than triptans, as it requires fewer doses to achieve the same effect. More research is needed to confirm these findings and explore other aspects of migraine in children, such as how often it comes back, how it affects their daily activities, and how it impacts their well-being. These studies should use larger and more diverse samples of children and adolescents and compare different treatments in a fair and rigorous manner.

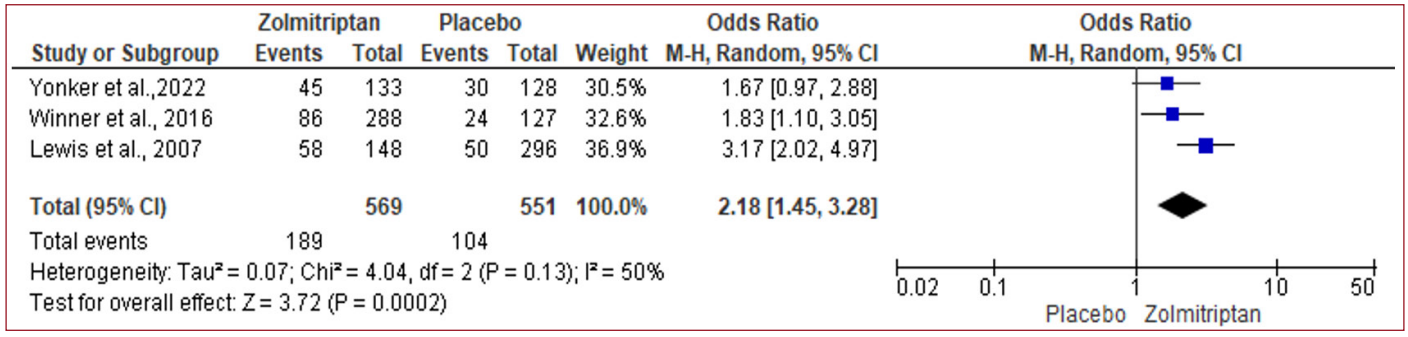

Figure 6. Forest plot of comparison: Zolmitriptan vs placebo

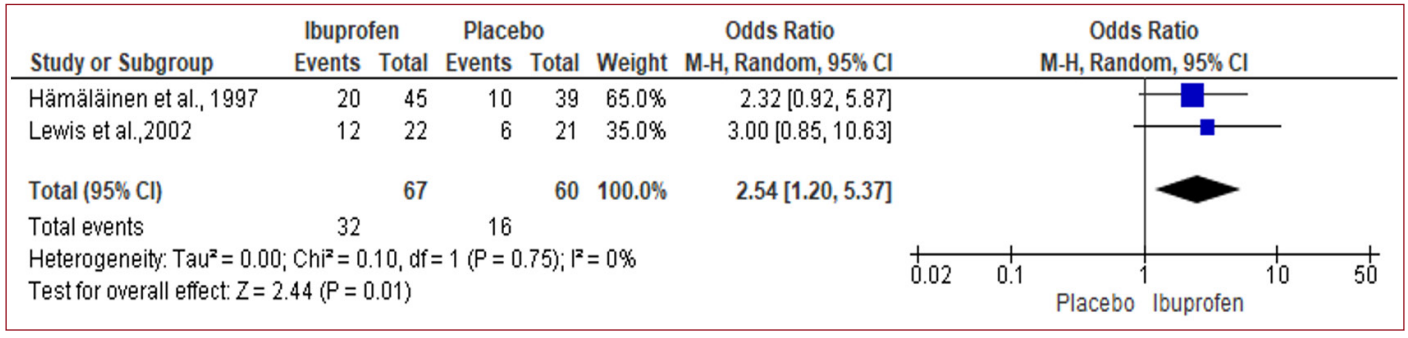

Figure 7. Forest plot of comparison: Ibuprofen vs placebo

Highlights

- Sumatriptan did not show a significant difference from placebo in achieving a pain-free status at 2 hours post-treatment, despite some positive effects observed in individual studies.
- Rizatriptan yielded inconsistent results across different age groups. In adolescents aged 12-17 years, there was no significant difference compared to placebo in terms of effectiveness.
- Zolmitriptan displayed a dose-dependent effect, where higher doses demonstrated greater efficacy in achieving the desired outcome compared to lower doses.
- Among non-triptan medications, only ibuprofen exhibited efficacy in achieving a pain-free status at 2 hours post-treatment. Additionally, ibuprofen demonstrated a favorable safety profile.

Abbreviations

CI: Confidence Interval, ICHD: International Classification of Headache Disorders, OR: Odds Ratio, PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses, RCT: Randomized Controlled Trials

ETHICAL DECLARATIONS

Ethics Committee Approval: We conducted this meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines. Ethics committee approval was not obtained as this is a meta-analysis.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Victor TW, Hu X, Campbell JC, Buse DC, Lipton RB. Migraine prevalence by age and sex in the United States: a life-span study. Cephalalgia. 2010;30(9):1065-72.
2. Linet MS, Stewart WF, Celentano DD, Ziegler D, Sprecher M. An epidemiologic study of headache among adolescents and young adults. JAMA. 1989;261(15):2211-6.
3. Szperka C. Headache in Children and Adolescents. Continuum (Minneap Minn). 2021;27(3):703-31.
4. Ayatollahi SM, Moradi F, Ayatollahi SA. Prevalences of migraine and tension-type headache in adolescent girls of Shiraz (southern Iran). Headache. 2002;42(4):287-90.
5. Abu-Arafeh I, Razak S, Sivaraman B, Graham C. Prevalence of headache and migraine in children and adolescents: a systematic review of population-based studies. Dev Med Child Neurol. 2010;52(12):1088-97.
6. Bille B. A 40-year follow-up of school children with migraine. Cephalalgia. 1997;17(4):488-91.
7. O'Brien HL, Kabbouche MA, Kacperski J, Hershey AD. Treatment of pediatric migraine. Curr Treat Options Neurol. 2015;17(1):326.
8. Hämäläinen M, Jones M, Loftus J, Saiers J. Sumatriptan nasal spray for migraine: a review of studies in patients aged 17 years and younger. Int J Clin Pract. 2002;56(9):704-9.
9. Moher D, Liberati A, Tetzlaff J, Altman DG. PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009;151(4):264-9, W64.
10. Higgins JP, Altman DG. Assessing risk of bias in included studies. Cochrane handbook for systematic reviews of interventions: Cochrane book series. 2008:187-241.
11. Hämäläinen ML, Hoppu K, Valkeila E, Santavuori P. Ibuprofen or acetaminophen for the acute treatment of migraine in children: a double-blind, randomized, placebo-controlled, crossover study. Neurology. 1997;48(1):103-7.
12. Lewis DW, Kellstein D, Dahl G, et al. Children's ibuprofen suspension for the acute treatment of pediatric migraine. Headache. 2002;42(8):780-6.
13. Ahonen K, Hämäläinen ML, Eerola M, Hoppu K. A randomized trial of rizatriptan in migraine attacks in children. Neurology. 2006;67(7):1135-40.
14. Ho TW, Pearlman E, Lewis D, et al. Rizatriptan Protocol 082 Pediatric Migraine Study Group. Efficacy and tolerability of rizatriptan in pediatric migraineurs: results from a randomized, double-blind, placebo-controlled trial using a novel adaptive enrichment design. Cephalalgia. 2012;32(10):750-65.
15. Visser WH, Winner P, Strohmaier K, et al. Rizatriptan Protocol 059 and 061 Study Groups. Rizatriptan 5 mg for the acute treatment of migraine in adolescents: results from a double-blind, single-attack study and two open-label, multiple-attack studies. Headache. 2004;44(9):891-9.
16. Winner P, Lewis D, Visser WH, Jiang K, Ahrens S, Evans JK. Rizatriptan Adolescent Study Group. Rizatriptan 5 mg for the acute treatment of migraine in adolescents: a randomized, double-blind, placebo-controlled study. Headache. 2002;42(1):49-55.
17. Ahonen K, Hämäläinen ML, Rantala H, Hoppu K. Nasal sumatriptan is effective in treatment of migraine attacks in children: a randomized trial. Neurology. 2004;62(6):883-7.
18. Fujita M, Sato K, Nishioka H, Sakai F. Oral sumatriptan for migraine in children and adolescents: a randomized, multicenter, placebo-controlled, parallel group study. Cephalalgia. 2014;34(5):365-75.
19. Winner P, Rothner AD, Wooten JD, Webster C, Ames M. Sumatriptan nasal spray in adolescent migraineurs: a randomized, double-blind, placebo-controlled, acute study. Headache. 2006;46(2):212-22.
20. Winner P, Farkas V, Štillová H, et al. TEENZ Study Group. Efficacy and tolerability of zolmitriptan nasal spray for the treatment of acute migraine in adolescents: Results of a randomized, double-blind, multicenter, parallel-group study (TEENZ). Headache. 2016;56(7):1107-19.
21. Yonker ME, McVige J, Zeitlin L, Visser H. A multicenter, randomized, double-blind, placebo-controlled, crossover trial to evaluate the efficacy and safety of zolmitriptan nasal spray for the acute treatment of migraine in patients aged 6 to 11 years, with an open-label extension. Headache. 2022;62(9):1207-17.
22. Lewis DW, Winner P, Hershey AD, Wasiewski WW. Adolescent Migraine Steering Committee. Efficacy of zolmitriptan nasal spray in adolescent migraine. Pediatrics. 2007;120(2):390-6.