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Original Article PEDIATRICS

Efficacy and safety of magnesium prophylaxis in children with migraine without aura

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ABSTRACT

OBJECTIVE: Migraine is one of the prevalent types of primary headache disorders in children and significantly affects their quality of life. Although pharmacological prophylaxis is often necessary, conventional treatments are frequently limited by adverse effects and modest efficacy. Magnesium, a vital intracellular cation involved in numerous neuronal and vascular functions, has been proposed as a safer alternative. However, data on its use in pediatric migraine remain limited. To investigate the effectiveness and safety profile of magnesium oxide prophylaxis in children diagnosed with migraine without aura.

METHODS: This retrospective study included pediatric patients aged 7–18 years with a diagnosis of migraine without aura, treated exclusively with magnesium oxide at a dosage of 6–9 mg/kg/day or a fixed dose of 365 mg/day for four months. Headache frequency, migraine-related disability (assessed by PedMIDAS), and quality of life (measured by HIT-6) were evaluated before and after four months of prophylaxis.

RESULTS: Following magnesium prophylaxis, a statistically significant reduction was observed in headache frequency, PedMIDAS scores, and HIT-6 scores ($p<0.001$ for all). Additionally, disability levels according to PedMIDAS grading improved significantly. No participants reported side effects during the study.

CONCLUSION: Magnesium oxide appears to be a well-tolerated, safe, and potentially effective prophylactic option for children with migraine without aura. It was associated with a significant reduction in attack frequency, disability scores, and improved quality of life. Despite promising results, the absence of a control group and serum magnesium data are notable limitations. Further prospective, randomized controlled studies are required to confirm these findings and establish the most effective dosage, duration, and formulation of magnesium for pediatric use.

Keywords: Children; magnesium; migraine; nutraceuticals; prophylaxis.

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Migraine is the most frequent primary headache in children, with a reported prevalence of approximately 10% [1]. It typically presents with recurrent episodes of headache accompanied by symptoms such as nausea, vomiting, photophobia, and/or phonophobia. It is one of the most important disease-causing conditions associated with disability and has a negative impact on the child's quality of life. Therefore, effective management is critical. The treatment of pediatric migraine consists of the acute treatment of attacks and prophylactic therapy.

It is estimated that about 30% of children with migraine require prophylactic treatment [2]. The primary

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aim of prophylaxis is to decrease the frequency, severity, and duration of migraine attacks, thereby minimizing their disruptive effects on the child's life. Prophylactic treatment includes antidepressants, antiseizure medications, antihistamine drugs, beta-blockers, and calcium channel antagonists. Some studies have demonstrated limited efficacy of these agents in children, with a relatively high incidence of adverse effects [3]. In recent years, this has led to growing interest in alternative treatment modalities—particularly nutraceuticals—among clinicians, patients, and their families, due to their perceived safety and tolerability. Nutraceutical approaches include vitamins (e.g., riboflavin), trace elements such as magnesium, coenzyme Q10, and various herbal compounds [4]. Although several studies support the use of these agents in adults, evidence in the pediatric population remains limited [5–7].

Among these options, magnesium has garnered particular attention. It is the second most common cation inside the cell and is involved in many enzymatic reactions. Magnesium plays a key role in neuronal excitability, neurotransmitter release, and vascular tone regulation—all processes involved in migraine pathophysiology [8, 9]. Magnesium deficiency is hypothesized to contribute to migraine through multiple mechanisms, including promoting cortical spreading depression, enhancing platelet aggregation, modulating serotonin receptor function, and altering the synthesis and release of neurotransmitters such as nitric oxide. It has been proposed that magnesium may be a key factor in determining individual susceptibility to migraine attacks. Its potential effects include neuroinflammation suppression, calcium channel antagonism, N-methyl-D-aspartate (NMDA) receptor inhibition, and regulation of hormonal and serotonergic systems. Additionally, magnesium deficiency may facilitate neurogenic inflammation, partly mediated by substance P, further implicating its role in migraine pathogenesis [8, 9].

Given the limited evidence available in children, the present study was conducted to assess the safety and effectiveness of magnesium prophylaxis in pediatric patients diagnosed with migraine without aura.

MATERIALS AND METHODS

This retrospective study evaluated the medical records of children diagnosed with migraine without aura who received magnesium prophylaxis and were followed at the Pediatric Neurology Outpatient Clinic of Istanbul Medeniyet University Goztepe Prof. Dr. Suleyman Yalcin State Hospital between January 2022 and July 2023.

Highlight key points

- Magnesium prophylaxis significantly reduced headache frequency in children with migraine without aura.
- Prophylaxis with magnesium also improved quality of life and reduced migraine-related disability, as assessed by HIT-6 and PedMIDAS scores.
- No serious side effects were documented, supporting the safety and tolerability of magnesium in the pediatric population.

Data collected included demographic information (age, sex), family history of migraine, duration of migraine, and the frequency of attacks before and after magnesium prophylaxis.

Inclusion Criteria were as Follows

- Age between 7 and 18 years,
- Diagnosis of migraine without aura according to the International Classification of Headache Disorders, 3rd edition (ICHD-3) [10],
- Not receiving any other prophylactic treatment for migraine aside from magnesium.

Exclusion Criteria Included

- Presence of a chronic systemic illness or psychiatric disorder,
- Discontinuation of magnesium treatment before study completion,
- Headaches not fulfilling diagnostic criteria for migraine,
- Non-compliance with follow-up visits,
- Concurrent use of other migraine prophylactic medications or vitamin/mineral supplements.

Magnesium prophylaxis was initiated in patients experiencing frequent migraine attacks (defined as ≥4 attacks per month) or significant impairment in quality of life. All participants received oral magnesium oxide at a dosage of 6–9 mg/kg/day or a fixed dose of 365 mg/day, administered for a period of four months [5–7].

Patients were evaluated at baseline, after one month, and at the end of the fourth month. At each visit, data were collected on headache frequency and severity, functional disability due to migraine, and any reported side effects.

Table 1. Characteristics of headache before and after treatment (n=50)

	Before treatment (Mean±SD)	After treatment (Mean±SD)	p
Headache frequency (day/month)	11.3±8.3 (2–30)	5.6±7 (0–30)	<0.001
HIT-6 scores	65.4±6.6 (50–78)	59±10 (31–76)	<0.001
PedMIDAS scores	28.9±24.2 (4–130)	16.1±21.5 (0–120)	<0.001

HIT-6: Headache Impact Test; PedMIDAS: Pediatric migraine disability assessment tool; SD: standard deviation.

Migraine-related disability was measured using the Pediatric Migraine Disability Assessment (PedMIDAS) tool [11]. PedMIDAS scores were categorized into four grades: Grade 1, 0–10 (little to no disability); Grade 2, 11–30 (mild disability); Grade 3, 31–50 (moderate disability); and Grade 4, >50 (severe disability) [12].

Quality of life was assessed using the Headache Impact Test (HIT-6), a validated six-item self-report questionnaire widely used in headache research and clinical practice [13].

Both the PedMIDAS and HIT-6 assessments were administered before treatment (baseline) and at the fourth month of magnesium prophylaxis. The primary outcomes were changes in headache frequency (average days of headache per month), PedMIDAS scores, and HIT-6 scores before and after prophylaxis.

The study protocol was approved by the Istanbul Medeniyet University Ethics Committee under decision number 2023/0627 and was conducted in accordance with the Helsinki Declaration.

Statistical Analysis

All statistical analyses were performed using SPSS for Windows, version 15.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were presented as mean±standard deviation. Student's t-test was employed for comparisons between two groups, while the chi-square test was used to analyze categorical variables. The Wilcoxon signed-rank test was used to assess differences in PedMIDAS disability grades before and after treatment. A p-value<0.05 was considered statistically significant.

RESULTS

The study consisted of 50 children (16 males, 34 females; mean age: 13.4±2.75 years) diagnosed with migraine without aura. A positive family history of migraine was present in 19 patients (38%). The average duration of migraine symptoms was 36±12 months.

Table 2. Comparison of migraine-related disability based on the PedMIDAS grading system before and after treatment (n=50)

Disability grade	Before treatment (%)	After treatment (%)
Grade 1 (little/none)	14	60
Grade 2 (mild)	52	26
Grade 3 (moderate)	22	8
Grade 4 (severe)	12	6

PedMIDAS: Pediatric migraine disability assessment tool.

Characteristics of headache before and after treatment are presented in Table 1. After magnesium prophylaxis, there was a statistically significant decrease in headache frequency, PedMIDAS scores, and HIT-6 scores (p<0.001) (Table 1). None of the children reported any side effects related to magnesium prophylaxis.

Furthermore, analysis of migraine-related disability using the PedMIDAS grading system revealed a significant improvement in disability levels after treatment compared to baseline (p<0.001) (Table 2).

DISCUSSION

In this study, we evaluated the effect of magnesium oxide prophylaxis on the frequency and disability of migraine in children without aura. Our findings demonstrated that a 4-month magnesium prophylaxis significantly reduced both headache frequency and associated disability, while also improving the quality of life in affected children.

Pediatric migraine management often presents unique challenges. Conventional prophylactic medications such as amitriptyline and topiramate have shown limited benefit in children and are frequently associated with adverse effects [3]. Additionally, the high placebo response observed in pediatric trials complicates clinical decision-making [14]. These factors have led to increased interest in nutraceuticals, including magnesium, as safer and more acceptable alternatives for children [15].

Magnesium is an important intracellular cation involved in many enzymatic and physiological reactions, including neurotransmitter release, vasomotor tone regulation, and energy metabolism [8, 9]. It also acts as a natural NMDA receptor antagonist, a mechanism believed to play a role in migraine pathogenesis. Some studies have reported lower magnesium levels in serum, intracellular compartments, blood cells, saliva, and brain tissue of patients with migraine, indicating a potential link between magnesium deficiency and migraine development [16–19].

While the American Academy of Neurology and the American Headache Society support magnesium use for adult migraine prophylaxis according to evidence classified as Level B [20], its effectiveness in children remains controversial and not yet well established. The current literature on this topic is sparse, with a limited number of studies evaluating magnesium's role in pediatric migraine prophylaxis [5–7, 21, 22].

In a double-blind, randomized, placebo-controlled study, Wang and colleagues administered magnesium oxide at a dosage of 9 mg/kg/day for a duration of 12–16 weeks to a group of 42 pediatric migraine patients. The study observed a notable reduction in the severity of headaches among those receiving magnesium. However, the impact on headache frequency was less definitive. While there was a decrease in the number of headache days within the magnesium group, the difference in the rate of reduction between the magnesium and placebo groups was not statistically significant [5]. Gastrointestinal symptoms, such as diarrhea and soft stools, were reported more frequently in the magnesium group, though no other major adverse events were noted. Overall, the findings suggested that magnesium oxide, at doses up to 9 mg/kg/day, is well tolerated in children [5].

In a cohort study including 34 children who were given either magnesium oxide or magnesium glycinate at a dosage of 4–6 mg/kg/day for six months, the authors reported a decrease in the frequency of migraine attacks, as well as improvements in quality of life and anxiety and depressive symptoms. Additionally, migraine-related disability, assessed using PedMIDAS scores, decreased after three months of magnesium prophylaxis, with the most significant improvement observed at six months. No adverse effects were reported [7].

Gallelli et al. [6] used magnesium at a dosage of 400 mg/day for 18 months in 160 children with migraine without aura. The children were divided into four treatment groups based on whether they received paracetamol or ibuprofen for acute attacks, with or without magnesium as prophylactic treatment. The authors found that magnesium prophylaxis reduced both the intensity and frequency of headache attacks. In addition, no side effects related to the treatment were reported.

Castelli et al. [21] studied 41 children with periodic syndromes, 25 of whom were diagnosed with migraine and received magnesium pidolate at a dosage of 1.5–4.5 g/day (corresponding to 122–366 mg of elemental magnesium). They reported a decrease in headache frequency in 72.5% of the patients.

In our study, consistent with the existing literature, magnesium prophylaxis was found to decrease the frequency of migraine attacks [5–7, 21].

A significant reduction was observed in migraine-related disability, as assessed by PedMIDAS scores, and in quality of life scores, as measured by HIT-6, following magnesium treatment. Furthermore, when patients were classified according to the PedMIDAS grading system, a marked improvement in disability grades was noted after treatment. To date, only one study in the literature has addressed this issue: Kovacevic et al. [7] reported a decrease in migraine-related disability, assessed by PedMIDAS, and an improvement in quality of life, assessed by the KIDSCREEN-27 questionnaire, following magnesium prophylaxis.

The optimal dosage, duration of treatment, and most effective formulation of magnesium vary between studies. Wang et al. [5] administered magnesium oxide at a dosage of 9 mg/kg/day for 12–16 weeks. Kovacevic et al. [7] used both magnesium oxide and magnesium glycinate at doses of 4–6 mg/kg/day for 3–6 months. Gallelli et al. [6] administered 400 mg/day of magnesium for 18 months, although the specific formulation was not reported. Castelli et al. [21] used magnesium pidolate at a dosage of 1.5–4.5 g/day (equivalent to 122–366 mg of elemental magnesium) for 1–2 months. In our study, magnesium oxide was used at a dosage of 6–9 mg/kg/

day or 365 mg/day for a duration of four months. Consistent with previous studies, no serious side effects were observed in our cohort. Although the ideal dosage and duration of magnesium prophylaxis in pediatric patients have yet to be clarified, existing data indicate that daily doses up to 9 mg/kg and treatment periods of 3–6 months are both safe and tolerable.

One of the major limitations in evaluating the effectiveness of magnesium in pediatric migraine is the high placebo response rate reported in this population [3, 14]. This raises uncertainty as to whether the observed improvement is due to the pharmacological effect of magnesium itself or to a placebo effect. In our study, the absence of a control group and the lack of comparison with a placebo arm prevent definitive conclusions regarding the specific efficacy of magnesium. Additionally, serum magnesium levels could not be assessed, as this was a retrospective study and such data were not available in the medical records. However, it is important to emphasize that previous studies have reported that only about 2% of total body magnesium is present in the extracellular compartment [8]. Therefore, routine serum magnesium measurements do not accurately reflect total body magnesium status.

Conclusion

Despite the impact of migraine on children's daily quality of life and disability, the majority of children with migraine who present to healthcare providers do not receive prophylactic treatment. Magnesium appears to be a cost-effective, accessible, and safe supplement that may help reduce attack frequency and improve both disability and quality of life in the pediatric population. Further prospective, randomized controlled studies are warranted to validate the effectiveness of magnesium prophylaxis, determine the most appropriate dosage and formulation, and establish standardized treatment protocols for children with migraine.

Ethics Committee Approval: The Istanbul Medeniyet University Clinical Research Ethics Committee granted approval for this study (date: 27.09.2023, number: 2023/0627).

Informed Consent: Written informed consents were obtained from patients who participated in this study.

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