


ORIGINAL ARTICLE

Efficacy of Probiotics in Prevention of Migraine Attacks in Children: A Randomized Clinical Trial Study

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Abstract

Objectives

Migraine is a chronic and joint disease in children. The results of previous studies on the effectiveness of probiotics in preventing migraine attacks in children have been controversial. This study aims to investigate the effect of probiotics on migraine prophylaxis in children.

Materials & Methods

In this clinical trial study, 41 children aged 5 to 15 with migraine enrolled the study in two control and intervention groups. Children in the intervention group (18 children) received propranolol at a dose of 1 mg per kilogram of body weight daily in two divided doses along with a 250 mg Yomogi capsule daily for three months, and children in the control group (23 children), received propranolol along with placebo for three months. The study compared the frequency and duration of headache days, PedMIDAS criteria, and parental satisfaction between the two groups before treatment, as well as one month and three months post-treatment.

Results

The number of headache days in both groups decreased over time, but in the intervention group, this decrease was more than the control group was statistically significant ($P=0.045$). The average PedMIDAS scale after treatment in the intervention group was 3.9 ± 3.8 ; in the control group, it was 8.4 ± 8.2 , which was statistically significant ($P=0.047$). Parents' satisfaction with the treatment was statistically significantly higher in the intervention group (94.4%) than in the control group (54.5%) ($P=0.011$). No significant drug complications were seen in any of the two groups.

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Conclusion

In children with migraine, adding probiotics to migraine treatment reduces the intensity and number of days of children's headaches and increases the Parents' satisfaction with the treatment.

Keywords: Migraine, Probiotics, Prevention, Children.

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Introduction

Headaches are one of the most vital symptoms of various diseases in pediatrics. Two to six percent of all emergency visits for children and adolescents are due to headaches. After tension headaches, migraine is the second most common headache in children, occurring in different forms and requiring timely diagnosis and treatment (1, 2).

The brain of migraine patients is more sensitive to neurochemical changes due to genetic reasons, reducing the threshold of neuronal inflammation and the excitability of the trigeminal nerve. Consequently, trigeminal nerve sensory stimuli stimulate the somatosensory and limbic cortex (2, 3). The prevalence of migraine in children aged three to seven years is 1% to 3%, increasing to 8% to 23% in 15-year-olds (4).

Migraine prophylaxis treatments include non-pharmacological and pharmacological treatments. Non-pharmacological treatments include sleep pattern modification, diet, stress management, physical activity, and avoidance of irritants. Pharmacological prophylaxis treatments that are used more in children include beta-blockers, calcium channel antagonists, antiepileptics, and antidepressants (5).

Despite the efforts that have been made to find

effective and safe preventive and therapeutic measures for migraine in children, existing drugs and non-pharmacological strategies are only partially useful (6, 7). Therefore, migraine control remains challenging.

Studies have indicated that the digestive and central nervous systems are interconnected, and one disturbance can impact the other. The term gut-brain axis refers to the mutual relationship between the central nervous and digestive system, involved in several diseases, including irritable bowel syndrome, helicobacter pylori infection, celiac disease, and headaches (8).

Glutamate, an excitatory neurotransmitter, is present in the intestinal nervous system and efferent nerves of the digestive system to the brain. It is effective in causing migraines through cortical spreading depression, central sensitization, and stimulating the trigeminovascular system. Previous research has shown that serotonin can alleviate migraine symptoms. Certain gut bacteria possess enzymes that boost the production of tryptophan metabolites, serving as building blocks for serotonin. Additionally, neurotransmitters like neuropeptide Y and calcitonin gene-related peptides are involved in the connection between the digestive system and brain disorders. (9).

On the other hand, probiotics are living and beneficial microorganisms play a significant role in improving the functioning of the digestive system. Most of the probiotics belong to the group of bifidobacteria or lactobacillus, which are part of the natural flora of the human intestine (10). The most crucial function of probiotics is the development, maturation, and regulation of the secretion-mucosal defense system. The first immunological effect of probiotics is probably to be located in the lymphatic tissue of the small intestine (11). In previous studies, the immune effects of probiotics have been shown. However, there is little direct evidence of the main mechanisms by which probiotics exert their effects (12). Probiotics improve migraine symptoms by affecting the immune system, and changing intestinal flora, and changing the vagus nerve signal and the level of some neurotransmitters. (13).

Many studies have been conducted on the effect of using probiotics in the prevention of chronic and episodic migraine. (11, 14, 15).

However, the findings could be more extensive and have mainly led to conflicting results. The majority of research has been carried out with adult participants, with only a limited number focusing on children. Considering the few studies conducted in children, as well as the limitations and contradictions in these studies, we decided to investigate the effect of probiotics on preventing migraine in children.

Materials & Methods

In this clinical trial study, forty-six children aged five to 15 with migraine who were referred to the pediatric neurology clinic of Besat Hospital in Hamadan, Iran, from 2021-2022 were studied. The inclusion criteria included diagnosis of

migraine by a pediatric neurologist based on the criteria of the International Headache Society and age between five and 15 years. Exclusion criteria included suffering from other types of headaches, including chronic or drug-related headaches, suffering from inflammatory bowel diseases, suffering from neurological disorders, using antibiotics within three months before the study, using probiotics within two weeks before the study, contraindications to the use of propranolol such as asthma or diabetes, not consenting to participate in the study.

The children who entered the study were randomly divided equally into intervention and control groups using a random number table. Three patients in the control group and two in the intervention group were unwilling to continue cooperation and were excluded. Children in the intervention group (18 children) were treated for three months with one capsule of Yomogi 250 mg (Yomogi Company) along with propanol (Tolid Darou Company) at a dose of 1 mg/kg, and children in the control group (23 children) were treated with propranolol at a dose of 1 mg/kg (Tolid Darou Company) along with placebo for three months. Then, the number of headache days, headache duration, PedMIDAS disability severity scale, and parents' satisfaction were compared between the two groups before, one month, and three months after treatment.

PedMIDAS and 3-point Likert questionnaire were used to collect data in addition to patient's the demographic and clinical information questionnaire.

In the PedMIDAS questionnaire, using six questions, the number of days per month that the child's performance was impaired at home, online classes, games, parties, and social activities due to headache was recorded, and based on the total

scores obtained, the severity of disability caused by migraine headache was determined (16). A 3-point Likert questionnaire (satisfied, unaffected, and dissatisfied) was used to evaluate parents' satisfaction with migraine treatment.

To determine the sample size according to the results of Martami et al.'s study (15), considering the alpha of 5% and the power of 80%, as well as the difference in the migraine intensity score between the two groups, with a standard deviation of 2 using G power software, at least 18 patients for each group was considered.

Data analysis was conducted using SPSS statistical software, version 2.

The significance level of the tests was considered less than 0.05.

This study was conducted with the approval of the Ethics Committee of the Hamadan University of Medical Sciences with the ethics code, the Deputy of Research and Technology ID IR.UMSHA.REC.1400.878, IRCT20160523028008N22.

Besides, informed consent was obtained from all the patients or their parents.

Results

In this study, forty-six children were enrolled in

two equal groups. Three patients in the control group and two in the intervention group were unwilling to continue cooperation and were excluded. Both study groups had no statistically significant differences in demographic and clinical variables (Table 1). After the treatment, 17 (94.4%) parents of the intervention group were satisfied with the treatment of their children, while this rate was 54.5% in the control group, a statistically significant difference (P=0.011). In both groups, the number of headache attacks per month decreased, and in the intervention group, this decrease was statistically significantly higher than in the control group (Table 2). The two study groups did not have a statistically significant difference before the intervention regarding disability using the PedMIDAS scale. After the intervention, the paired t-test showed that the amount of disability in both groups decreased statistically significantly, and this decrease in the intervention group was significantly higher than the control group (Table 3).

No significant drug side effects were seen in any of the two groups.

Table 1: Patient characteristics in intervention and control groups

Variable	control groups (n=23)	Intervention groups (n=18)	P-value
Gender(male)	10(43.5%)	11(61.1%)	0.262
age (years)	7.9±2.4	8.9±3.1	0.327
Age of headache onset (months)	38.7±3.4	38.6±1.2	0.638
History of previous illness	2(8.7%)	1(6.6%)	1.00
History of seizures	2(8.7%)	0	0.495

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Variable	control groups (n=23)	Intervention groups (n=18)	P-value
History of head injury	2(8.7%)	2(11.1%)	1.00
History of developmental problems	3(13%)	4(22.2%)	0.679
Family history of migraine	20(87%)	15(83.3%)	0.745
History of drug treatment	6(26.1%)	3(16.7%)	0.706
History of hospitalization	1(4.3%)	2(11.1%)	0.573
Change in sleep pattern	9(39.1%)	11(61.1%)	0.215
Decrease in patient performance	13(56.5)	11(61.1%)	1.00
Interference with academic activity	12(52.2%)	12(66.7%)	0.524
History of diagnostic imaging	14(60.9%)	9(50%)	0.539
Number of headache attacks in the month before treatment	8.8±7.7	10±5.3	0.585
Relationship with menstruation	3(13%)	3(16.7)	1.00
Common type of migraine	23(100%)	18(100%)	–
Headache intensity mild, moderate)	11(47.8%)	4(22.2%)	0.091

Table 2: Number of headache attacks in two study groups at the beginning, one and three months after treatment

Number of attacks per month	Control group		Intervention group		ANOVA	
	Mean ± SD	Mean ± SD	Time	Time with group	Group	Group
The beginning of the study	10±5.3	8.8±7.7	F=57.5	F= 1.3	F= 10.1	
One month after treatment	2.5±2.3	2±1.1	Sig=0.001	Sig=0.284	Sig=0.045	
Three months after treatment	2±1.7	0.6±0.8	ηp2= 0.59	ηp2= 0.032	ηp2= 0.35	

Table 3: PedMIDAS score before and after intervention in two groups

Variable	control groups (n=23)	Intervention groups (n=18)	P(t-test)
	Mean ± SD	Mean ± SD	
Before intervention	21.5±17.6	24.9±23.2	0.589
After intervention	8.4±8.2	3.9±3.8	0.047
P(Paired- t- test)	0.001	0.001	0.585

Discussion

Several studies have been conducted on the prophylactic effect of probiotics on patients with migraine, but no study was found on their effect on children with migraine.

This study’s findings showed that adding probiotics at a dose of 250 mg/day to propranolol treatment in children with migraine reduced the number of headache days, reduced the disability scale, and increased parental satisfaction with the treatment. Several mechanisms have been explained for the effect of probiotics in treating and preventing neurological diseases, including their effect on the immune system, changing the intestinal flora, changing the vagus nerve signal, and also changing the level of some neurotransmitters (13, 17). Several reasons have been suggested for improving migraine headaches following the use of probiotics, including improving gut integrity (18), reducing the entry of lipopolysaccharides from the lumen into the systemic circulation due to balancing the intestinal bacteria and reducing Gram-negative bacteria (19), increasing serotonin (20) and helping to increase the emptying rate of stomach contents due to neuroimmune interaction (21). Previous studies have shown that changes in the microbiome affect serotonin neurotransmission in both peripheral and central nervous systems. In

a meta-analysis study by Wallace et al. (22), which reviewed ten articles, probiotics were associated with increased serotonin and improved mood in patients. The study of Desbonnet et al. (23) showed that the consumption of probiotics increases the plasma level of the precursor of serotonin, i.e., tryptophan. According to the findings of Sajjadi et al.’s study (2021) conducted on an animal model, the consumption of probiotics can increase serotonin in mice (24).

The clinical trial study by Martami et al. (15) was conducted on thirty-nine episodic and forty chronic migraine patients. Two probiotic capsules containing 14 strains were prescribed to patients for ten weeks. The results of the study showed that the consumption of probiotics can improve migraine headaches in both chronic and episodic types. According to Arianfar et al.’s study (11) in 2022, consuming more low-fat dairy products may reduce migraine attacks in children and adolescents.

According to Straube et al.’s study (25) in 2018, an observational study with a large sample size, the consumption of probiotics for eight weeks reduced the headache score of patients from 1.5 to 1.2 and reduced migraine attacks from two times per week to 1.4 times per week. Similarly, other complications related to migraines decreased

significantly in these people. In 2010, a randomized controlled trial study on healthy volunteers showed that probiotics can improve the intestinal epithelial barrier by modulating the expression of tight junction proteins in the intestinal epithelium (12). Since probiotics can correct increased intestinal permeability and maintain intestinal barrier function, they may relieve migraine headaches by improving intestinal epithelial permeability. In another clinical study, forty patients with migraine headaches received several nutrients for three months, including vitamins, minerals, micronutrients, herbs, and probiotics. At the beginning of this trial, the participants had an average quality of life score of 38, which increased to 76 after treatment, and experienced a 60% reduction in headache attacks (26). In a clinical trial study of volunteers with migraine headaches, participants received two grams per day of multi-strain probiotic products for 12 weeks. The study's results showed that the number of migraine headache days decreased by 67%, and almost no severe side effect of medication was observed (27). However, the results of the study by Roos et al. in 2017 on 63 patients with migraine showed that, compared to placebo, probiotics cannot be effective in reducing the intensity and frequency of headaches (28). According to the opinion of Dai et al. in 2017, there is limited evidence of the positive effects of probiotics on migraine headaches and a need to conduct multiple clinical trial studies with a larger sample size (17).

According to the meta-analysis study by Naghibi et al. in 2019, which found only two studies eligible for review, there still needs to be a consensus regarding the use of probiotics in migraine headaches, and more studies are needed (13). In the meta-analysis study of Parohan et al., three clinical trial studies

were selected after the literature review. Out of 179 patients with migraine, ninety-four people had received probiotics, and the results showed that the consumption of probiotics has no significant effect on the frequency and intensity of headaches in patients. (14) The reason for the difference in the results of the studies may be due to the difference in the type of probiotic consumed, the studied populations, the duration of the intervention, and the methods used to evaluate the response to the treatment.

In Conclusion

The findings of this study showed that in children with migraine, adding probiotics to the treatment of migraine reduces the severity of headaches and the number of headache days and increases parental satisfaction with the treatment.

Probiotics are generally well-tolerated and have minimal side effects, suggesting they could be beneficial for children with migraines. However, further research is necessary before incorporating probiotics into their treatment regimen.

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Conflicts of Interest

The results of this study are not in conflict with the authors' interests.

References

1. El-Metwally A, Toivola P, AlAhmary K, Bahkali S, AlKhathaami A, Al Ammar SA, et al. The Epidemiology of Migraine Headache in Arab Countries: A Systematic Review. *ScientificWorldJournal*. 2020;2020:4790254.
2. Jain S, Yuan H, Spare N, Silberstein SD. Erenumab in the treatment of migraine. *Pain Manag*. 2018 Nov 01;8(6):415-426.
3. Al Khalili Y , Chopra P .Migraine Headache In Childhood. *StatPearls [Internet]*. StatPearls Publishing In: Treasure Island (FL); 2021 May 4.
4. Hoover L E. Migraines in Children: Recommendations for Acute and Preventive Treatment. *Am Fam Physician*. 2020 May 1;101(9):569-571.
5. Abbaskhanian A, Sadeghi HR, Erfani A, Rezaei MS. Effective dose of topiramate in pediatric migraine prophylaxis. *J Pediatr Neurosci*. 2012 Sep;7(3):171-4
6. Vikelis M, Spingos KC, Rapoport AM. A new era in headache treatment. *Neurol Sci*. 2018;39(Suppl 1):47-58.
7. Puledda F, Goadsby PJ. An Update on Non-Pharmacological Neuromodulation for the Acute and Preventive Treatment of Migraine. *Headache*. 2017;57(4):685-91.
8. Arzani M, Jahromi SR, Ghorbani Z, Vahabizad F, Martelletti P, Ghaemi A, et al. Gut-brain Axis and migraine headache: a comprehensive review. *J Headache Pain*. 2020;21(1):15.
9. Maqsood R, Stone TW. The gut-brain Axis, BDNF, NMDA and CNS Disorders *Neurochem Res*. 2016;41(11):2819–2835.
10. Greene K, Irwin SL, Gelfand AA. Pediatric Migraine: An Update. *Neurol Clin*. 2019;37(4):815-33.
11. Plaza-Diaz J, Ruiz-Ojeda FJ, Gil-Campos M, Gil A. Mechanisms of Action of Probiotics. *Adv Nutr*. 2020 Jul 1;11(4): 1054. PMID: 30721959; PMCID: PMC6363529
12. Karczewski J, Troost FJ, Konings I, Dekker J, Kleerebezem M, Brummer RJ, et al. Regulation of human epithelial tight junction proteins by *Lactobacillus plantarum* in vivo and protective effects on the epithelial barrier. *Am J Physiol Gastrointest Liver Physiol*. 2010;298(6):G851-9.
13. Naghibi MM , Day R , Stone S , Harper A. Probiotics for the Prophylaxis of Migraine A Systematic Review of Randomized Placebo Controlled Trials. *J. Clin. Med*. 2019, 8, 1441; doi:10.3390
14. Parohan M, Djalali M, Sarraf P, Yaghoubi S, Seraj A, Foroushani AR, et al. Effect of probiotic supplementation on migraine prophylaxis: a systematic review and meta-analysis of

- randomized controlled trials. *Nutr Neurosci.* 2022;25(3):511-8.
15. Martami, F.; Togha, M.; Seifishahpar, M.; Ghorbani, Z.; Ansari, H.; Karimi, T.; Jahromi, S.R. The Effects of a Multispecies Probiotic Supplement on Inflammatory Markers and Episodic and Chronic Migraine Characteristics: A Randomized Double-Blind Controlled Trial. *Cephalalgia* **2019**, 39, 841–853.
 16. Hershey AD, Powers SW, Vockell AL, LeCates S, Kabbouche MA, Maynard MK. PedMIDAS: development of a questionnaire to assess disability of migraines in children. *Neurology.* 2001;57(11):2034-9.
 17. 16. Dai YJ, Wang HY, Wang XJ, Kaye AD, Sun YH. Potential Beneficial Effects of Probiotics on Human Migraine Headache: A Literature Review. *Pain Physician.* 2017;20(2):E251-e5.
 18. van Hemert S, Breedveld AC, Rovers JM, Vermeiden JP, Witteman BJ, Smits MG, et al. Migraine associated with gastrointestinal disorders: review of the literature and clinical implications. *Front Neurol.* 2014;5:241.
 19. Yücel M, Kotan D, Gurol Çiftçi G, Çiftçi IH, Cikrikler HI. Serum levels of endocan, claudin-5 and cytokines in migraine. *Eur Rev Med Pharmacol Sci.* 2016;20(5):930-6.
 20. Drummond PD. Tryptophan depletion increases nausea, headache and photophobia in migraine sufferers. *Cephalalgia.* 2006;26(10):1225-33.
 21. Indrio F, Riezzo G, Raimondi F, Bisceglia M, Filannino A, Cavallo L, et al. *Lactobacillus reuteri* accelerates gastric emptying and improves regurgitation in infants. *Eur J Clin Invest.* 2011;41(4):417-22.
 22. Wallace CJK, Milev R. The effects of probiotics on depressive symptoms in humans: a systematic review. *Annals of General Psychiatry.* 2017;16(1):14.
 23. Desbonnet L, Garrett L, Clarke G, Bienenstock J, Dinan TG. The probiotic *Bifidobacteria infantis*: An assessment of potential antidepressant properties in the rat. *J Psychiatr Res.* 2008;43(2):164-74.
 24. Sajedi D, Shabani R, Elmieh A. Changes in leptin, serotonin, and cortisol after eight weeks of aerobic exercise with probiotic intake in a cuprizone-induced demyelination mouse model of multiple sclerosis. *Cytokine.* 2021;144:155590.
 25. Straube A, Müller H, Stiegelbauer V, Frauwallner A. [Migraine prophylaxis with a probiotic. Results of an uncontrolled observational study with 1,020 patients]. *MMW Fortschr Med.* 2018;160(Suppl 5):16-21.
 26. Sensenig J, Johnson M, Staverosky T. Treatment of migraine with targeted nutrition focused on improved assimilation and elimination. *Altern Med Rev.* 2001;6(5):488-94.
 27. de Roos NM, Giezenaar CG, Rovers JM, Witteman BJ, Smits MG, van Hemert S. The effects of the multispecies probiotic mixture *Ecologic®Barrier* on migraine: results of an open-label pilot study. *Benef Microbes.* 2015;6(5):641-6.
 28. de Roos NM, van Hemert S, Rovers JMP, Smits MG, Witteman BJM. The effects of a multispecies probiotic on migraine and markers of intestinal permeability-results of a randomized placebo-controlled study. *Eur J Clin Nutr.* 2017;71(12):1455-62.

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