ORIGINAL ARTICLE

The Effect of Probiotics on Headaches in Children with Migraine Treated with Sodium Valproate
A Randomized Controlled Clinical Trial

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Abstract

Objective

Migraine is one of the most common complaints in children. This study aimed to determine the effect of probiotics (KidiLact) on headaches in children aged six to 15 years with migraine treated with sodium valproate.

Materials & Methods

This double-blind, randomized controlled clinical trial was performed on eighty children with migraine treated with sodium valproate. Patients were divided into two groups. All patients in the intervention and control groups received two sachets of probiotics and a placebo daily for four months, respectively. They were compared in terms of frequency and severity of headaches and painkiller consumption before and two and four months after initiating probiotics.

Results

The mean number of headaches in the second and third visits in the probiotic group was 1.27 and 1.18, and 2 and 1.50 per month in the placebo group, respectively. The authors observed a significant difference between the two groups in the second (P = 0.010) and the third visit (P = 0.019). Moreover, the mean severity of headache in the second and third visits in the probiotic group was 1.38 and 1.23, and 1.60 and 1.53 in the placebo group, respectively. The authors demonstrated that the daily consumption of painkillers in the probiotic group was significantly reduced compared to the placebo group (P = 0.007).

Conclusion

Using probiotic supplements seems to significantly affect the severity and frequency of migraine headaches compared to the placebo, and daily consumption of painkillers was significantly reduced in the probiotic group compared to the placebo group.

Keywords: Probiotic; Headache; Migraine; Sodium Valproate

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Introduction

Headache is one of the crucial symptoms of various diseases in pediatrics, which accounts for 2 to 6% of all emergency visits of children and teenagers. Among diverse types of headaches, migraine after tension headache is the most common type of headache that occurs in children in different forms and requires early diagnosis and treatment (1). According to the International Headache Society criteria, migraine is defined as recurrent headaches with or without aura lasting one to seventy-two hours. These headaches are one-sided, pulsating with moderate to severe intensity, aggravated by daily activities, and accompanied by nausea, vomiting, anorexia, and photophobia (2). Compared to adults, migraine in children is often without aura and is bilateral, and the duration of headaches in children is shorter than in adults (3). Previous studies showed that symptoms appeared in 20% of adults with migraines before the age of ten (4).

Recent advances in understanding the gut microbiome have revealed the role of gut microorganisms in disease outcomes, but research on this issue is limited (5).

Probiotics are living organisms, such as Lactobacillus and Bifidobacteria, that can increase the cohesion of the intestinal epithelial barrier. They are used for many problems, such as preventing necrotizing enterocolitis and diarrhea caused by antibiotics (6). Probiotics can regulate intestinal permeability and maintain intestinal barrier function. Previous studies on adults with migraines have shown the positive effect of probiotics in improving headache symptoms (7-8).

Considering the high prevalence of migraine headaches in children and the shortage of evidence on the effect of probiotics on children, this study aimed to assess the effect of probiotics on the symptoms of children with migraine.

Materials & Methods

This randomized, double-blind controlled clinical trial was conducted on children with migraine treated with sodium valproate aged six to 15 years who were referred to 17 Shahrivar Hospital in Rasht in 2020. The inclusion criteria were the age of 6-15 years, treatment only with sodium valproate, and migraine diagnosis based on the International Classification of Headache Disorders (ICHD) criteria. Participants were enrolled if they had a history of at least five attacks with the following features: headache attacks lasting for 4-72 hours, having at least two of the following four criteria (one-sidedness, pulsating nature, moderate to severe pain, and worsening with physical activity), having at least one of the following symptoms: nausea or vomiting, or fear of light and sound

during the headache, and those who had no other pathology. Patients with intestinal anatomical disorders, underlying problems such as Fanconi syndrome, malabsorption, metabolic diseases, sodium valproate intolerance, gastrointestinal disorders, and using probiotics or drugs with probiotic effect in less than two months were excluded. Exclusion criteria were sodium valproate complications, unwillingness to participate, taking probiotics, gastrointestinal bleeding, and use of antibiotics.

Children with consecutive sampling were randomly assigned to two groups, "probiotic" and "placebo." The random allocation of patients was determined according to the determined sample size through random allocation software. Patients were treated with an initial dose of sodium valproate 20 mg/Kg/24hr and a maintenance dose of 5 mg/Kg/24hr, which was the standard treatment for migraine without aura. The probiotic group was treated with a 1g probiotic sachet (KidiLact) prepared and distributed by Zist-Takhammir Company (Iran). The control group received a placebo similar in shape and color for four months.

KidiLact contains 10 units of probiotics. One sachet of 1g probiotic contains the following bacteria [in the colony-forming unit (CFU)]: Lactobacillus acidophilus (2.5×10^{10}), Lactobacillus rhamnosus (3.5×10^{10}), Lactobacillus bulgaricus (2×10^{9}), Bifidobacterium infantis (5×10^{10}), Lactobacillus casei (3×10^{10}), Bifidobacterium breve (2.5×10^{10}), and Streptococcus thermophilus (2×10^{9}). Furthermore, it comprises fructooligosaccharides, lactose, magnesium stearate, talc, cantaloupe flavor, sucralose, and silicon dioxide.

On the first visit, the patient's demographic characteristics, including sex, age, the severity of headache, frequency of migraine attacks, and the presence or absence of aura, were gathered. The severity of migraine headaches was evaluated based on the Migraine Disability Assessment (MIDAS) (9). Two and four months later, the variables were assessed, including the severity of the headache, frequency of migraine attacks, painkiller consumption, and the aura. The severity and number of attacks were indicated as primary outcomes, and painkiller consumption was the secondary outcome.

Sample size

The sample size required to compare probiotics' effect on migraine headaches' frequency compared to the routine treatment method was indicated based on the results of De Roos et al. (10). Forty children were indicated in each group with a 95% confidence interval and 80% power.

$$1-\alpha = 95\% \Rightarrow Z_{1-\frac{\alpha}{2}} = Z_{\%975} = 1.96$$

$$1-\beta = 80\% \rightarrow z_{1-\beta} = z_{0.8} = 0.84$$

$$SD^2_{Diff} = 2 \times 2.4^2 \times (1\text{-}0.5) = 5.76$$

$$n = \frac{\left(z_{1-\frac{\alpha}{2}} + z_{1-\beta}\right)^2 SD^2_{diff}}{d^2} = \frac{(1.96+0.84)^2(5.76)}{1.5^2} = 40$$

Statistical Analysis

IBM SPSS Statistics analyzed data for Windows, Version 21.0. (Armonk, NY: IBM Corp). Data were reported by frequency, percent, mean, standard deviation, and median. The Kolmogorov-Smirnov test checked the normality of quantitative variables. Chi-square analyzed data, Fischer's Exact, independent T, Mann-Whitney U tests, and repeated measure analysis of variance (ANOVA). The significance level of the tests in this study was considered as $P<0.05$.

Ethical considerations

Informed consent was obtained from the parents or legal guardians of minors. The Vice-Chancellor of Research at Guilan University of Medical Sciences approved this study (Code: IR.GUMS.REC.1399.369, Date: 2020-11-09). The study was registered in the Iranian Registry of Clinical Trials (Code: IRCT20200608047689N1, Date: 2020-11-28).

Results

The present study was performed on eighty patients with a mean age of 10.9 ± 2.8 years, with forty patients in each group consisting of 56.3% boys and 43.7% girls (Table 1).

A significant difference in the frequency and severity of headaches before and after initiating probiotics (P=0.001 for both parameters) and placebo (P=0.001 for both parameters) was observed. The mean frequency of headaches in the second and third visits in the probiotic group was 1.27 and 1.18. In the placebo group, it was 2 and 1.50 per month, respectively, with a significant difference in the second (P = 0.010) and the third visit (P = 0.019) between the two groups. The severity of headache in the probiotic group was significantly less than in the placebo group at two (P=0.045) and four months (P=0.024). Comparing the groups in terms of the aura showed no significant difference in these periods (Table 2).

Results of the generalized linear model (GLM) and generalized estimating equations (GEE), with control of the effects of age, sex, and aura, demonstrated that the daily consumption of painkillers in the probiotic group was significantly reduced compared to the placebo group (P = 0.007, β = - 0.579). Probiotics significantly decreased the severity of headaches (P = 0.005, β = ± 0.267).

Table 1. Comparing the demographic characteristics in the two groups.

		Probiotic	Placebo	Total	P-Value
Sex	Girl	16	19	35	0.499
	Boy	24	21	45	
	Total	40	40	80	
Age groups (years)	6-9	12	12	24	0.369
	9-12	7	12	19	
	12-15	21	16	37	
	Total	40	40	80	
Mean age ± standard deviation		11.0 ±1.3	10.7 ± 2.6	10.9 ± 2.8	0.512

Table 2. Comparing groups regarding features of headache

headache	Visit		Groups		P-Value
			Probiotic	Placebo	
Frequency	first	Mean ± SD*	11.20 ± 8.97	12.80 ± 7.83	0.231
	After 2 months	Mean ± SD*	1.27 ± 1.28	2.00 ± 1.30	**0.010**
	After 4 months	Mean ± SD*	1.18 ± 0.71	1.50 ± 0.64	**0.019**
Severity	first	Mean ± SD*	3.00 ± 0.78	2.93 ± 0.76	0.666
	After 2 months	Mean ± SD*	1.38 ± 0.49	1.60 ± 0.50	**0.045**
	After 4 months	Mean ± SD*	1.23 ± 0.42	1.53 ± 0.64	**0.024**
Aura	first	negative	29 (72.5%)	28 (72.0%)	0.805
		positive	11 (27.5%)	12 (30.0%)	
	After 2 months	negative	34 (85%)	34 (85%)	0.580
		No change	0	1 (2.5%)	
		positive	6 (15.0%)	5 (12.5%)	
	After 4 months	negative	37 (92.5)	38 (95.0%)	0.630
		No change	1 (2.5%)	0	
		positive	2 (5.0%)	2 (5.0%)	

* SD = Standard deviation

Discussion

The present double-blind clinical trial investigated the effects of probiotics in improving the severity and frequency of migraine in children compared to a placebo. Although a significant difference in the frequency and severity of headaches before and after initiating probiotics (P=0.001 for both parameters) and placebo (P=0.001 for both parameters, probably due to the placebo effect) was observed, the present study showed a significant difference in the frequency of headaches between the probiotics compared to the placebo group.

A study by Martami et al. on adults showed that the frequency of headache attacks in the group receiving probiotics decreased significantly compared to placebo (P=0.001) (11), which was consistent with this study's results. Similarly, Sensenig et al.' study revealed that probiotic supplements provided almost complete relief in 60% of migraine patients after 12 weeks. They pointed out that the beneficial effects of probiotics on migraine may be related to their role in improving intestinal integrity (12).

Although in the study of De Roos et al., the mean number of days with headache in the month decreased, this decrease was not statistically significant (9). A meta-analysis study by Parohan et al. was conducted to evaluate the effect of probiotic supplementation on the frequency and severity of migraine attacks and showed that probiotic supplementation did not significantly affect the

frequency of migraine attacks per month (13), which was inconsistent with the current results.

The study by Martami et al. demonstrated that the severity of headache attacks in the probiotic group was significantly decreased compared to the placebo group (P=0.007) (11). In the study by Ghavami et al., which was conducted to investigate the effect of symbiotics in women with migraine, no significant difference was observed in the severity of migraine between the placebo and symbiotic groups (14), which was in contrast with this study and can be due to the difference in the type of prescribed supplement. Consistent with this study, De Roos et al. revealed that the severity of migraine headaches was significantly decreased in patients receiving probiotic consumption (9).

The current study indicated that probiotics reduced painkiller consumption compared to placebo. Patients who did not have aura symptoms had less painkiller consumption than patients with aura. Moreover, the results showed that the only variable related to the number of headaches was the amount of painkiller consumption. Martami et al. showed that the daily consumption of painkillers in the intervention group significantly decreased compared to the placebo (P=0.007). They mentioned that taking probiotic supplements for ten weeks can reduce the need for painkillers (11), which was in line with the results of the present study. In a study conducted by Ghavami et al., results showed that using symbiotics reduced the number of painkillers, which was consistent with the results of the present study (14).

In Conclusion

Seemingly, the use of probiotic supplements significantly affected the severity and frequency of migraine headaches compared to the placebo. Furthermore, daily consumption of painkillers were significantly reduced in the probiotic group compared to the placebo group.

Considering the limitations of the studies conducted in children, more detailed research is needed to determine the effectiveness of probiotics in migraine treatment and find the primary mechanism of probiotic effect in this age group. Additionally, in future studies, inflammatory markers involved in migraine pathology can be compared between the probiotic and the placebo group. Conducting studies with a larger sample size and a more extended follow-up period to investigate the effect of probiotics on migraine parameters is suggested.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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