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Using Probiotics in Infants with Cow's Milk Allergy: A Randomized Clinical Trial

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Abstract

Background: One of the most common food allergies in infants is cow's milk allergy (CMA). There is no available effective therapeutic strategy for this issue. It's important to develop effective approaches to reduce the risk of cow's milk allergy. The purpose of this study was to investigate the effect of probiotics on the infants with cow's milk protein intolerance.

Methods: This study was a randomized clinical trial in full-term infants with CMA diagnosis. These patients were divided into case and control groups (receiving placebo and probiotics). Clinical symptoms such as diarrhea, abdominal pain, etc. were evaluated in 2, 4, 8, 12 and 16 weeks after receiving probiotics.

Results: During the 16 weeks of the study, a significant decrease was observed in the clinical and paraclinical findings in both groups. There was a statistically significant decrease in times of mucosal, bloody and daily defecation of the patients on the 4th, 8th and 12th weeks. Also, a significant difference was found between the groups in diarrhea and abdominal cramps from the 4th week.

Conclusion: The consumption of probiotics for a short time in infants with CMA significantly decreased the clinical and paraclinical symptoms.

Key Words: Cow's milk allergy, Diarrhea, Infant, Probiotics.

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1- INTRODUCTION

Breastfeeding is the first choice for infants (1) and Cow's Milk Allergy (CMA) is one of the most common causes of food allergies among infants, caused by either breast milk or cow's milk. CMA is an immune response that occurs reproducibly on exposure to a protein present in cow's milk (3). The risk to develop the allergic disease is multifactorial including the intestinal microbiome, genetic background for allergy and early feeding with cow's milk (4). Both IgE and non-IgE mediated immune responses in CMA exist (5).

Cow's milk protein can transfer directly (infants who drink cow's milk) or indirectly (via cow's milk products consumed by the mother of the infant) to sensitive infants (6). Four casein fractions (αS 1, αS 2, β, and κ-casein) and two whey proteins (α-lactalbumin and β-lactoglobulin) are considered the most important allergenic proteins contained in cow's milk (7).

GastroEsophageal Reflux Disease (GERD) commonly occurs in infants fed with cow's milk. Also, the association between GERD and cow's milk allergy has been described in infants and toddlers (8).

The most frequent clinical manifestation of cow's milk allergy is blood in the stool (9). Other symptoms include failure to thrive, anemia, constipation, and rhinorrhea, wheezing and vomiting (10). Although the prevalence of Cow's Milk Protein Allergy (CMPA) is relatively high, its management is different and depends on several modified guidelines by physicians, including neonatologists, pediatricians, pediatric allergists and pediatric gastroenterologists (5).

Some physicians recommend antihistamines (e.g. loratadine, cetirizine) for treatment of mild cutaneous or digestive reactions and administer prebiotics which help by altering bowel flora and have a potential role in primary allergy prevention during infancy (3). Some studies suggest Probiotics as live organisms that could potentially restore intestinal homeostasis, provide benefits to the host if given in adequate amounts and prevent allergy through interaction with the intestinal immune cells especially in early life (11). Gut microbiota play an important role in the development of immune response (12). The pathways for benefits of probiotics could include enhancement of gut mucosal barrier function, competitive inhibition of pathogenic bacteria, modulation of the immune response towards non-allergy, and degradation of protein antigen (13). The effects of probiotics are strain-dependent; and the appropriate selection of the probiotic causes a better therapeutic response. Type of the probiotics and the primary outcomes varies among trials; and most of the studies have used Lactobacillus GG (11-15) which has been shown to have potential effects on immune reactions, prevention and treatment of allergic inflammation (11). It is shown that administration of *Bifidobacterium* and *Streptococcus thermophilus* improves gastrointestinal symptoms in infants with cow's milk allergy (16). Prophylactic and therapeutic effects of LGG have been demonstrated in infants with atopic diseases especially cow's milk protein-susceptible atopic dermatitis (11).

Despite the effect of probiotics in the management of dysbiosis defined as a reduction in microbial diversity, beneficial effects of probiotics are still controversial, many researchers have reported a decrease in inflammation and faster tolerance of cow's milk with probiotics administration in these patients (17, 18). And several studies have shown the efficacy of probiotics on the improvement of allergic symptoms in infants with cow's milk protein allergy (12, 19-21).

Despite multiple complications such as blood and mucus in the stool which sometimes last for a few months and may have a financial burden and psychological stress for parents and society, there is still a lack of studies on complications and the effective treatment of CMA in Iran. In this study, we evaluated the therapeutic effect of probiotics according to the clinical and paraclinical findings in CMA infants.

2- MATERIALS AND METHODS

In this single-blind randomized clinical trial study, full-term infants younger than one year with an allergy to cow's milk protein referring to Buali hospital of Sari, Iran from March 2016 to March 2017 were enrolled. Excluding criteria were receiving probiotics and prebiotics in the last 2 months, receiving antibiotics over the past 2 weeks, any evidence of systemic infection in clinical examination, positive stool culture with pathogens, febrile patients, Hirschsprung's disease, coagulopathy, systemic disease diagnosed and formula-fed infants. The ethics committee of Mazandaran University of Medical Sciences approved the study protocol (Ethics committee reference number: IR.MAZUMS.REC.96.2123) and it was registered in the Iranian registry of clinical trials with the registration number of IRCT2017043033595N2.

Laboratory findings included WBC>5 and positive fecal calprotectin in the stool or positive OB (occult blood) and symptoms following casein based formula feeding or breastfeeding and CMA diagnosis was confirmed by a Pediatric Gastroenterologist. WBC and RBC in stool (≥5) were considered as a positive response. Allocation in groups was performed randomly.

After obtaining informed consent from the parents of the patients, they were randomly divided into two intervention and control groups with the table of random numbers. Limitation of dairy products consumption was applied for the mothers and infants. For the intervention group, in addition to diet protocol, one sachet Protexin probiotic that was the most available and popular probiotic for infants in Iran covering all three different categories of the beneficial probiotic genus with the most potent strains (consisting of *Lactobacillus rhamnosus*, *Streptococcus thermophilus*, *Bifidobacterium breve*, *Lactobacillus acidophilus*, *Bifidobacterium infantis*, *Lactobacillus bulgaricus* and FOS- the form of freeze dried powder) made by protexin Healthcare co. was administered daily for 4 weeks. The control group received the same package containing starch powder one sachet per day for 4 weeks.

At the beginning of the study, stool culture was performed and the patient's data including clinical symptoms (Diarrhea, abdominal pain, and the times of daily defecation, bloody and mucosal stool) were recorded. Also, fecal calprotectin, WBC, RBC and occult blood (OB) in stool were measured and recorded for all patients. Then, at second, 4th, 8th, 12th and 16th weeks following the treatment, WBC, RBC, occult blood and fecal calprotectin (FC) were measured. Based on fecal calprotectin test results, 3 categories of negative (FC <50 µg/g), intermediate (50-200 µg/g) and positive (200 µg/g <FC) calprotectin existed.

At the 4th and 16th weeks following the treatment, stool exam and culture were performed to determine the ova, parasite and occult blood in the stool. During the first 16 weeks of the treatment, nausea, dysphagia, diarrhea, constipation, hematochezia, frequency of defecation, mucoid and bloody stool per week, and also the frequency of abdominal pain/cramp in the week were recorded and compared between the two groups.

Statistical analyses were performed by SPSS software version 20.0. In addition,

data was analyzed by Mann-Whitney, chi-square, and Kolmogorov–Smirnov tests.

3- RESULTS

Totally, 132 children, 50 boys (37.9%) and 82 girls (62.1%), with the mean age of 16.19±5.8 weeks enrolled in the study (Control group: 16.19±5.8 years and intervention group: 15.35±5.4 years; p>0.05). One hundred and six infants (80.3%) were breastfed (86% in control and 75% in the intervention group, p>0.05). Demographic data and characteristics of the patients are shown in **table 1**.

Table-1: Demographic data and Characteristics of the patients with cow's milk allergic

		Case	Control	P value
Age		17.11± 6.0	15.35± 5.8	P> 0.05
Sex	Female	40	42	P> 0.05
	Male	23	27	P>0.05
Breast feeding		75%	86%	P> 0.05
Family history of allergic disease		52%	35%	P>0.05

Follow-up of the patients was performed for 16 weeks by filling the questionnaire at 0, 2, 4, 8, 12 and 16 weeks. Statistically significant differences were found in times of daily defecation between the groups, from the 12th week of the follow-up (**Table 2**). Comparing the frequencies of the daily bloody stool, significant differences were initially found between the 2 groups, in different weeks of the follow-up (**Table 2**).

Table-2: The average rating of daily defecation and bloody stool in both groups

Variables	Time	Average rating		P value
		Control (n=69)	Intervention (n=63)	
Defecation	Before treatment	70.70	61.90	0.159
	2 weeks after treatment	64.10	69.13	0.436
	4 weeks after treatment	69.70	62.99	0.296
	8 weeks after treatment	70.12	62.53	0.24
	12 weeks after treatment	75.64	56.42	0.003
	16 weeks after treatment	72.57	59.86	0.05
Bloody stool	Before treatment	68.66	64.13	0.49
	2 weeks after treatment	71.91	60.57	0.08
	4 weeks after treatment	80.38	51.30	0.0
	8 weeks after treatment	83.01	48.42	0.0
	12 weeks after treatment	85.04	46.20	0.0
	16 weeks after treatment	86.65	44.43	0.0

However, since the times of daily mucoid stool between the two groups were not equal at the start of the study, according to covariance analysis, the decreasing frequency of defecation in the treatment group was proved to be significantly different from that of the control group, only from the 8th week.

After matching the two groups, diarrhea and abdominal cramps were proved to have a significant decrease in the treatment group as compared to that of the control group, from the 4th week of the intervention. At the beginning of the study, 91.2% of the patients suffered from diarrhea and abdominal cramps and it decreased to 27.3% and 30.5% after 4 weeks, whereas there was no significant decrease in diarrhea and abdominal cramps from the 4th week (**Table 3**).

Table-3: The qualitative variables studied between both case and control groups

Variable	Time	P value	Odds ratio	95% CI
Diarrhea	Before treatment	1.0	0.912	0.06-14.9
	2 weeks after treatment	1.0	0.912	0.06-14.9
	4 weeks after treatment	0.014	0.273	0.09-0.81
	8 weeks after treatment	0.0	0.162	0.07-0.36
	12 weeks after treatment	0.0	0.176	0.08-0.37
	16 weeks after treatment	0.0	0.152	0.07-0.33
Abdominal cramps	Before treatment	1.0	0.912	0.06-14.9
	2 weeks after treatment	1.0	0.912	0.06-14.9
	4 weeks after treatment	0.018	0.305	0.11-0.84
	8 weeks after treatment	0.002	0.328	0.16-0.67
	12 weeks after treatment	0.001	0.308	0.15-0.63
	16 weeks after treatment	-	-	-

In the paraclinical study of the stool, RBC, WBC, fecal calprotectin (FC) and occult blood (OB) were evaluated during 16 weeks in both groups and a significant change was found in OB from the 4th week (p=0.000). RBC, WBC and FC changes in stool in the 4^{th} and 8^{th} weeks were significant in both groups (p=0.000).

4- DISCUSSION

Cow's milk protein allergy is the most frequent food allergy during early childhood with an estimated prevalence between 1.9% and 4.9% in the first year of life (11, 15). This study was designed to investigate the efficacy of probiotics on diarrhea, abdominal cramps and laboratory findings of infants with sensitivity to cow's milk protein during 16 weeks.

In this study, after probiotic consumption, diarrhea and abdominal cramps decreased in both groups in the 4^{th} week. In Basturk *et al*.'s study, after 4 weeks, significant improvements were seen in bloody and mucoid stool, diarrhea, restiveness, vomiting and abdominal distention in probiotic group but statistically significant improvements were not seen in abdominal pain and constipation in probiotic group (11). A meta-analysis by Tan-Lim *et al.* showed that probiotics can relieve and reduce symptoms of children with cow's milk allergy. They also claimed that there were some doubts about the effect of probiotics in induction of tolerance in children with CMA and consumption of *Lactobacillus rhamnosus* GG leading to tolerance induction among infants suspected to have CMA (22). Based on two systematic reviews, more studies must be done for fully understanding the association between factors such as consumption of probiotics with food allergies or autoimmune disease (23, 24). Furthermore, maternal probiotics may reduce the risk of eczema and food allergy (25). Muraro *et al.* reported that after 4 weeks of receiving diet with LGG,

significant improvement had been demonstrated in the symptoms of allergic colitis and stool consistency in comparison to the placebo (18). In Ivakhnenko *et al.*'s study, infants with CMA received the probiotics complex treatment including *Bifidobacterium lactis* BB-12 (1×10^9 CFU) and *Streptococcus thermophilus* TH-4 (1×10^8 CFU) in four weeks and they found a significant impact on reducing the frequency of diarrhea in the 8th week (20). The reason behind the difference and faster effects in our study can be the type of the probiotics administered. Contrary to our findings, in Ahanchian *et al.*'s study evaluating the effect of synbiotic in breastfed infants with CMA, the treatment group had not shown a significant decrease in diarrhea (16). Our sample size was larger and the difference may be due to probiotic consumption in our study. Also, in Ahanchian *et al.*'s study, abdominal cramps improved after 72 hours and the result of their study is not similar to ours, which can be due to a higher rate of abdominal cramp at baseline (26). Contrary to our results, Schnadower *et al.*reported that the children with acute gastroenteritis who received placebo had better outcomes than those receiving *Lactobacillus rhamnosus* GG (27).

Our study demonstrated that consumption of probiotics in CMA infants did not affect the frequency of daily defecation and mucoid stool. Harvey *et al.* investigated the effect of amino acid and synbiotic based formula on allergic symptoms in infants with CMA for 16 weeks (28). Their results demonstrated a significant difference in the appearance of stool but only 10% of infants with CMA showed hypoallergenic interactions.

The result of our study demonstrated a significant reduction in the rate of bloody stool in both groups from the 4th week. Baldassarre et al. investigated the effect of Lactobacillus GG (LGG) in comparison to the consumption of Extensively Hydrolyzed Casein Formulation (EHCF) on bloody stool and possible allergic colitis in infants with CMA during 4 weeks (26). No RBC was found in the stool of infants receiving EHCF+LGG but in the EHCF-LGG group, 5 of the14 cases were confirmed to have blood in the stool, which is in accordance with our results. Also, the double-blind placebo-controlled study of Basturk et al. revealed beneficial effects of LGG on bloody stool in infants with CMA in both groups (11). (17)In another study, Szajewska et al. investigated infants with infantile colic. In contrast to our results, they found that the usage of L.reuteri was effective in decreasing colic compared to placebo (29).

In our study, there was no significant difference in the amount of OB in stool between 2 groups from 0 to 2nd weeks but this amount was significant from the 4th week. In a similar study, Baldassarre *et al.*, showed a significant stool OB decrease in both of the intervention and control groups in the 4th week (26). Then cautious should be made in applying these findings, since maintaining a positive stool OB, even after a 4-week cow's milk restriction, may indicate the effect of other antigens other than cow's milk on stool production.

There was a significant decrease in fecal calprotectin in both groups after 8 and 12 weeks of probiotic consumption in this study. In Baldassarre *et al.*'s study (13) FC reached to the 50% of the baseline in the intervention group after 4 weeks and the decrease in FC was higher in the intervention group, but it was still higher than that in the control group. Contrary to Baldassarre *et al.*'s study, the cause of this difference can be attributed to applying single or multiple strains of probiotic and the kind of strains in it, dosage, and treatment duration and study population.

5- CONCLUSION

According to the results of this study, the addition of probiotics to CMA infants'

feeding might have an impact on improving the recovery of symptoms such as abdominal cramp, diarrhea, mucosal and bloody stool, duration of daily defecation, and the decrease of WBC, RBC, FC and OB in stool. Although the mechanism of probiotic function in this positive trend is not clear, but it can be due to its effect on increasing the capacity of the intestinal mucous membrane, participation in the destruction of protein antigens, competition with pathogenic bacteria and progression of the basic immune system maturation to non-allergic immune system. In sum, powered randomized clinical trials with long-term follow-ups are needed to assess the potential of probiotics as an intervention for children with CMPA.

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