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Original article

Synbiotic therapy in infantile colic resistant to conservative therapy: a clinical trial

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Abstract

Background: Infantile colic is a disturbing problem for parents. The Rome IV criteria are the last modality for the diagnosis of colic. Available medications have variable effects on the treatment of colic. However, no definite treatment has been identified yet.

Aims: To our knowledge, few clinical trials have compared the efficacy of synbiotics in infantile colic, so the present study was conducted.

Material and methods: This study was performed on 120 infants (51.66% boys; mean age: 42.09 ± 21.14 days; mean birth weight: 3,155 ± 420 g) with the diagnosis of infantile colic resistant to conservative therapy. The infants were randomly divided into groups A and B. A synbiotic containing *B. infantis*, *L. reuteri*, *L. rhamnosus*, and fructooligosaccharides (FOS) (PediLact® [Zist-Takhmir Co., Tehran, Iran] drop) was administered to group A, while group B received a synbiotic containing *B. lactis* and FOS (BBCare® [Zist-Takhmir Co., Tehran, Iran] drop). The primary outcome was the response rate to each synbiotic, and the secondary outcome was the complications of each synbiotic.

Results: The response rate to both synbiotics was significant after 1 week of intervention (1.97 ± 0.91 [44.95%] versus 1.64 ± 0.77 [54.23%], p = 0.000). Both groups showed a significant response rate to each synbiotic after 1 month of intervention too (1.19 ± 0.84 [63.48%] versus 0.70 ± 0.48 [79.65%], p = 0.000). The response rate was significantly higher in group B compared to group A after 1 week (54.23% versus 44.95%) and after 1 month (79.65% versus 63.48%) of intervention. Neither synbiotic was associated with adverse effects.

Conclusion: The present study showed that both synbiotics were effective in the treatment of infantile colic. However, the synbiotic containing *B. lactis* was significantly more effective than the synbiotic containing *B. infantis*, *L. reuteri*, and *L. rhamnosus* in infantile colic.

Keywords

Synbiotic therapy, infantile colic, *B. lactis*, *B. infantis*, *L. reuteri*, *L. rhamnosus.*

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Introduction

Wessel et al. defined infantile colic as crying that lasted more than 3 hours a day for at least 3 days a week for 3 weeks or longer for the first time in 1954 [1, 2]. According to the new Rome IV criteria, any healthy infant under 5 months of age with recurrent and prolonged periods of fussing, irritability and crying with no obvious cause that cannot be prevented or resolved by caregivers is diagnosed as colic [2]. The prevalence of colic ranges from 2% to 73%, with a median of 17.7% [3]. It typically presents between 2 and 3 weeks of life and recovers at 4 months of age [4].

Etiology

The etiology of colic is multifactorial and can be classified into two basic categories [5]: non-gastrointestinal factors and gastrointestinal factors.

Non-gastrointestinal factors

This category includes maternal, environmental, and infantile factors. Maternal factors include maternal age, education level, positive history of smoking or alcohol consumption, perinatal stress or anxiety, and improper feeding. Environmental factors include insufficient caregiver's response to the infant's troublesome cries that causes dissatisfaction in the infant and induces a defective behavioral interaction between them [6]. Infantile factors include improper adaptation to environmental changes and immaturity of the central nervous system. A new theory suggests that colic may be a clinical presentation of migraine [7].

Gastrointestinal factors

Air swallowing can induce colic. Gastrointestinal motility disorders, gut hormones, abnormal intestinal microflora [8], increased serum hormones (especially motilin and ghrelin) [9], and increased motilin receptors induce increased intestinal peristalsis and pain. Intestinal mucosal immaturity results in incomplete gut integrity and passage of large molecules into the blood and colic [10].

Liver function immaturity, low levels of bile acids in the gut, and partial absorption of bile acids in the ileum result in malabsorption of fat and other nutrients, that in turn lead to abnormal microbial flora, increased nutrient fermentation, gas production, and reduced levels of dehydroxylated bile acids in the colon [4, 11].

de Weerth et al. found that *Bifidobacteria* and *Lactobacilli* decreased significantly while *Proteobacteria*, including species producing gas and inflammation, increased significantly in colicky infants [12]. The microorganism most recently reported to be associated with infantile colic is *H. pylori* [13].

Lactose intolerance and lactase deficiency cause lactose malabsorption and fermentation, increased gas production, and colic [11]. Cow's milk protein allergy may induce colic, too [5].

Interventions

In the past few decades, various treatments have been suggested for colic, including non-pharmacological and pharmacological treatments [14-16].

Non-pharmacological interventions

Non-pharmacological treatments include limiting air swallow, dietary modifications, behavioral

interventions and alternative treatment. In order to limit air swallow, mothers should be trained about feeding techniques. Dietary modifications including microbiological intervention like administration of probiotics, prebiotics, tyndallized probiotics, and synbiotics [17-23], lactase supplementation, hydrolyzed infant formula (in infants with cow's milk allergy) are among effective therapeutic strategies [5, 15]. Behavioral modifications include managing the improper parent-infant interactions resulting in colic. Studies have shown higher responsiveness to parental counseling compared to dietary changes [5]. Non-pharmacological alternative treatments include spinal manipulation, abdominal massage, and acupuncture. However, there are controversies in this regard, and small trials have evaluated the usefulness and side effects of alternative medicine; therefore, they should be practiced with caution [5, 15].

Pharmacological interventions

Pharmacological interventions include the use of chemical and non-chemical (herbal) agents. Chemical agents include the use of oral sucrose or hypertonic glucose solutions, anti-bloating drugs (simethicone and dimethazone), and antispasmodic drugs (dicyclomine and cimetropium) [24]. Non-chemical interventions include herbal agents and homeopathic remedies [5, 15].

Effective treatment

Generally, according to recent studies, effective treatment of infantile colic includes parental reassurance, managing cow's milk protein allergy and administering sucrose or hypertonic glucose solutions, lactase, probiotics, prebiotics, and synbiotics [5, 14-16, 25]. There has been a particular focus on the composition and role of probiotics, prebiotics, and synbiotics in the treatment of infantile colic in the past few decades. A few studies have investigated synbiotics. This study was conducted to evaluate the efficacy of synbiotics in the management of infantile colic 1 week and 1 month after supplementation.

Methods

This triple-blind, randomized, clinical trial was conducted in Bahrami Hospital, Tehran, Iran, from June 2017 to January 2019. One hundred and twenty infants aged below 4 months with a diagnosis of infantile colic according to the Rome IV criteria (including: 1. crying or fussing for ≥ 3 hours per day for ≥ 3 days in a week in telephone or face-to-face reports of the caregiver; and 2. total 24-hour crying and fussing of 3 hours or more measured by a 24-hour behavior diary) were recruited in the study.

Male and female infants (58 girls, 62 boys) who did not respond (< 50% recovery rate) to conventional therapies (anti-bloating drugs, herbal products, etc.) were included in this study. Informed consent was obtained from the parents after explaining the purpose of the study. All infants with acute or chronic diseases, gastrointestinal problems, or using antibiotics or probiotics for 1 week before the study were excluded. The treatment period was 1 month. The participants were randomly allocated to group A and B. The infants in group A received a synbiotic containing *B. infantis*, *L. reuteri*, *L. rhamnosus* (1×10^9 CFU per ml) and fructooligosaccharides (FOS) (PediLact® [Zist-Takhmir Co., Tehran, Iran] drop), while group B received a synbiotic containing *B. lactis* (1×10^9 CFU per ml) and FOS (BBCare® [Zist-Takhmir Co., Tehran, Iran] drop). The bottles of both drops were identical and were coded by different color labels. The caregivers who administered the drugs, the researcher who completed the questionnaires and collected the data, and the statistician who analyzed the data were blinded throughout the study.

The primary outcome was the response rate to each synbiotic, and the secondary outcome was the complications of each synbiotic.

Study protocol

Before the intervention, each participant underwent a complete examination, and the following data were collected: gestational age, birth weight, anthropometric data on admission, family history of atopy, and maternal stress.

After breastfeeding, the caregiver administered 5 drops of the drug orally 4 times a day for 30 days. The researcher completed the questionnaires on days 1, 7, and 30 after the intervention. She recorded the time and duration of crying and fussing in a day, number of days with crying and fussing in a week, number of weeks with crying and fussing in a month, and any adverse events of the drops such as constipation, vomiting, and skin reactions after the intervention. A scoring system of 0-4 scores was used for each of the above findings (Score 4 for crying and fussing > 3

hours per day or > 3 days per week or > 3 weeks per month; Score 3 for crying and fussing 2-3 hours per day or 2-3 days per week or 2-3 weeks per month; Score 2 for crying and fussing 1-2 hours per day or 1-2 days per week or 1-2 weeks per month; Score 1 for crying and fussing 0-1 hour per day or 0-1 day per week or 0-1 week per month). According to a study by Kianifar et al. [22], a total sample size of 64 infants was estimated using $\alpha = 0.05$, $\beta = 20\%$, confidence level = 95%, power = 80%, and d = 0.2. In order to increase the power of the study, the sample size was increased to 120 patients.

Statistical analysis

The statistical analysis was performed using the SPSS® software version 24 (SPSS Inc., Chicago, IL, USA). Normally distributed quantitative variables were compared using the Student's t-test. Non-normally distributed variables were compared using the Mann-Whitney U test and the Wilcoxon test. X^2 test was used for qualitative variables such as sex and history of allergy and stress. All statistical tests were two-tailed. P-values less than 0.05 were considered significant.

Results

In this triple-blind, randomized, controlled trial, 146 colicky infants were assessed for eligibility to participate in the study. Sixteen infants were excluded from the study because of not meeting the inclusion criteria, unwillingness to participate in the study, etc. One hundred and thirty infants were eligible and were randomly assigned to two intervention groups. Five patients in each group were excluded from the analysis because they did not respond to intervention, or due to loss to follow-up or withdrawal from the intervention. One hundred and twenty infants completed the study, and their data were analyzed (**Fig. 1**).

The mean (range) gestational age of the 120 eligible breastfed infants with colic was 38 (37-41) weeks, and their mean (range) birth weight

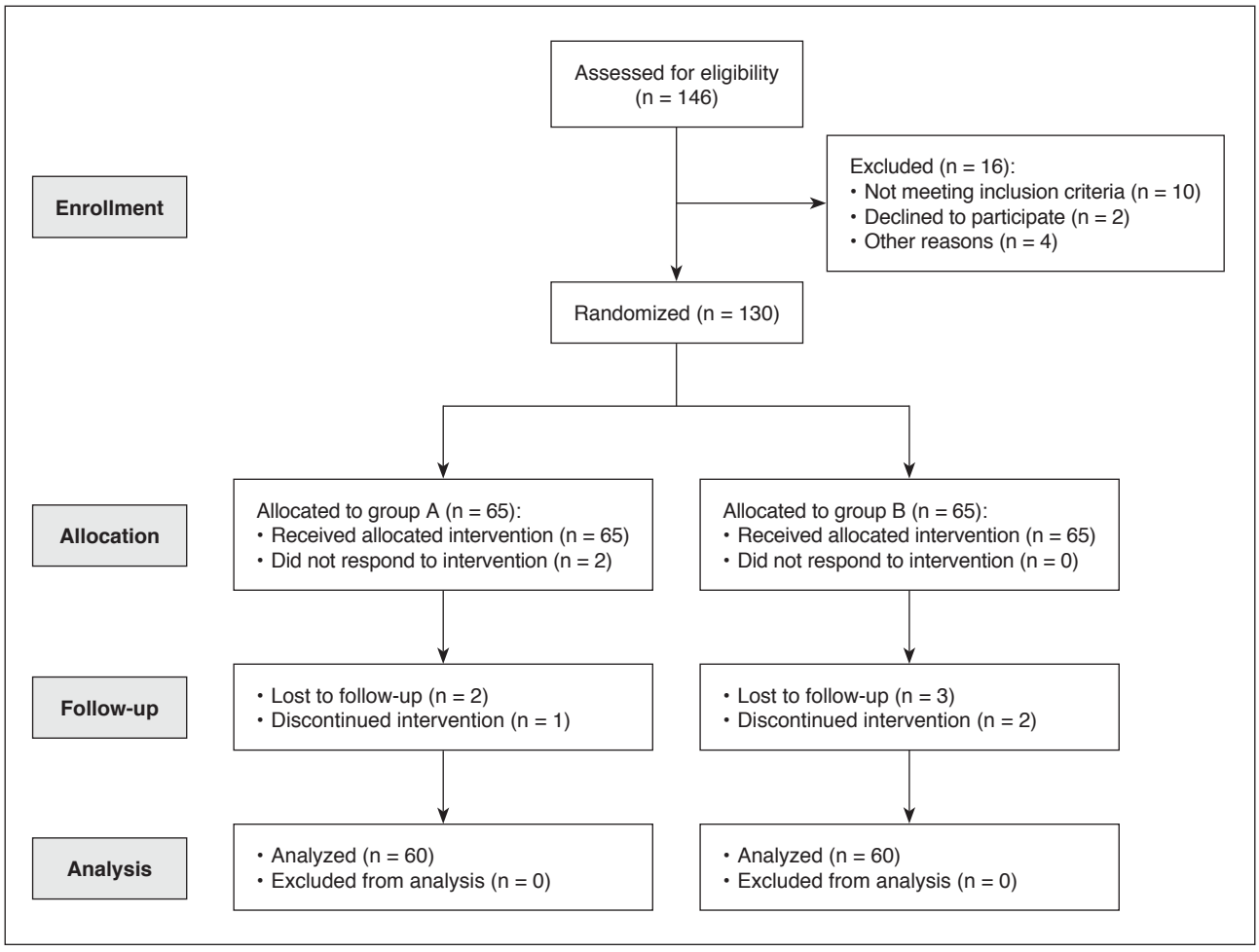

Figure 1. Flow diagram of the patients' progression throughout the study.
Group A received PediLact® drop; group B received BBCare® drop.

was 3,155 ± 420 g (2,300-4,590 g). No significant difference was seen in demographic characteristics between the two study groups (**Tab. 1**).

The response rate to both synbiotics was significant after 1 week and after 1 month of intervention (**Tab. 2** and **Tab. 3**).

The response rate was significantly higher in group B (54.23%) compared to group A (44.95%) (inter-group p-value = 0.000) after 1 week (**Tab. 2**). Although the total response rate in each group was more than 60% after 1 month, the results showed that the response rate was significantly higher in group B (79.65%) compared to group A (63.48%) (inter-group p-value = 0.000) (**Tab. 3**). Neither synbiotic was associated with adverse effects.

Table 1. Demographic characteristics of study groups.

Demographic characteristics		Group A (n = 60)	Group B (n = 60)	p-value
Sex [a]	Female, n (%)	31 (51.7%)	27 (45%)	0.465
	Male, n (%)	29 (48.3%)	33 (55%)	
Gestational age, weeks, mean ± SD [b]		38.50 ± 0.98	38.45 ± 0.93	0.969
Age at intervention, days, mean ± SD [b]		41.80 ± 24.26	42.38 ± 18.03	0.921
Birth weight, grams, mean ± SD [b]		3,104.83 ± 410.69	3,204.42 ± 429.51	0.122
Weight at the time of intervention, grams, mean ± SD [b]		4,214.42 ± 1,140.41	4,220.08 ± 858.55	0.432
Weight 1 week after intervention, grams, mean ± SD [b]		4,572.00 ± 1,172.50	4,612.58 ± 926.53	0.605
Weight 1 month after intervention, grams, mean ± SD [b]		5,390.58 ± 1,200.87	5,455.67 ± 1,004.91	0.526
Maternal stress [a]	Yes	52 (86.7%)	54 (90%)	0.571
	No	8 (13.3%)	6 (10%)	
Allergic family history [a]	Yes	56 (93.3%)	55 (91.7%)	0.730
	No	4 (6.7%)	5 (8.3%)	
Mean percentage of clinical manifestations before intervention [b]		68.43 ± 14.48	66.18 ± 13.40	0.236

[a] X^2 test; [b] Mann-Whitney test.
Group A received PediLact® drop; group B received BBCare® drop.

Table 2. Colic-related crying or fussing and crying plus fussing scoring, before intervention and 1 week after intervention.

Clinical manifestations		Group A (n = 60)	Group B (n = 60)	Inter-group p-value
Crying or fussing (hour/day), scoring	Pre-intervention, mean ± SD	3.86 ± 0.54	3.52 ± 0.96	0.000
	1 week after intervention, mean ± SD	2.4 ± 1.38	1.5 ± 1.01	
	Response rate, %	37.82%	57.38%	
	Intra-group p-value	0.000	0.000	
Crying or fussing (day/week), scoring	Pre-intervention, mean ± SD	3.85 ± 0.40	3.90 ± 0.30	0.001
	1 week after intervention, mean ± SD	2.33 ± 0.63	2.07 ± 0.65	
	Response rate, %	39.48%	46.92%	
	Intra-group p-value	0.000	0.000	
Crying or fussing (week/month), scoring	Pre-intervention, mean ± SD	2.78 ± 1.19	3.22 ± 1.17	0.000
	1 week after intervention, mean ± SD	1.18 ± 0.43	1.34 ± 0.59	
	Response rate, %	57.55%	58.38%	
	Intra-group p-value	0.000	0.000	
Total 24-hr crying plus fussing measured by at least 1 prospectively kept, 24-hr behavior diary (hour/day), scoring	Pre-intervention, mean ± SD	2.17 ± 1.06	3.47 ± 0.50	0.017
	1 week after intervention, mean ± SD	1.33 ± 0.85	0.98 ± 0.70	
	Response rate, %	38.7%	71.75%	
	Intra-group p-value	0.000	0.000	
Overall response rate 1 week after intervention, mean ± SD (%)		1.97 ± 0.91 (44.95%)	1.64 ± 0.77 (54.23%)	0.000

Group A received PediLact® drop; group B received BBCare® drop.

Table 3. Colic-related crying or fussing and crying plus fussing scoring, before intervention and 1 month after intervention.

Clinical manifestations		Group A (n = 60)	Group B (n = 60)	Inter-group p-value
Crying or fussing (hour/day), scoring	Pre-intervention, mean ± SD	3.86 ± 0.54	3.52 ± 0.96	0.000
	1 month after intervention, mean ± SD	1.4 ± 1.16	0.61 ± 0.52	
	Response rate, %	63.73%	82.67%	
	Intra-group p-value	0.000	0.000	
Crying or fussing (day/week), scoring	Pre-intervention, mean ± SD	3.85 ± 0.40	3.90 ± 0.30	0.000
	1 month after intervention, mean ± SD	1.47 ± 0.81	1.13 ± 0.03	
	Response rate, %	61.81%	71.05%	
	Intra-group p-value	0.000	0.000	
Crying or fussing (week/month), scoring	Pre-intervention, mean ± SD	3.22 ± 1.18	2.78 ± 1.19	0.000
	1 month after intervention, mean ± SD	1.00 ± 0.43	0.64 ± 0.52	
	Response rate, %	68.94%	76.97%	
	Intra-group p-value	0.000	0.000	
Total 24-hr crying plus fussing measured by at least 1 prospectively kept, 24-hr behavior diary (hour/day), scoring	Pre-intervention, mean ± SD	2.17 ± 1.06	3.47 ± 0.50	0.001
	1 month after intervention, mean ± SD	0.88 ± 0.78	0.42 ± 0.62	
	Response rate, %	59.45%	87.89%	
	Intra-group p-value	0.000	0.000	
Overall response rate 1 month after intervention, mean ± SD (%)		1.19 ± 0.84 (63.48%)	0.70 ± 0.48 (79.65%)	0.000

Group A received PediLact® drop; group B received BBCare® drop.

Discussion

The present randomized clinical trial study was conducted to compare the effectiveness of a synbiotic containing *B. infantis*, *L. reuteri*, and *L. rhamnosus* with a synbiotic containing *B. lactis* in the treatment of infantile colic. The etiology of colic is multifactorial. Management of infantile colic is challenging and there is no definitive treatment.

Probiotic is a term driven from a Greek word meaning "for life". Probiotics are useful living microorganisms that balance the bowel's flora. A prebiotic is a food or dietary product that provides energy for useful bacteria and may induce their growth or activity. Synbiotics are a mixture of both prebiotics and probiotics that have a synergistic effect on the growth or activity of non-pathogenic bacteria [21]. Some researchers have studied mixed probiotic strains and suggested the possibility of an inhibitory effect between different strains [26].

Several researchers, including Bird et al., Dryl and Szajewska, and Pärtty et al., found the positive effect of probiotics on infantile colic [17-19]. Some other researchers, like Vandenplas and Savino, and Pandey et al., reported that prebiotics were useful for the management of infantile colic, too [20, 21]. Many investigations have shown the usefulness of specific strains of probiotics for the treatment of infantile colic. For example, studies conducted by Sung et al. and Savino et al. showed that *L. reuteri DSM17938* was effective and safe for the management of infantile colic [27, 28].

To the best of our knowledge, few clinical trials have studied the effectiveness of synbiotics for the treatment of infantile colic [22, 23], which was the reason why this study was conducted.

The present study compared the effect of two synbiotics on the treatment of infantile colic. The positive response rate was significant after 1 week and 1 month of intervention in both groups (inter-group comparison). There was a significant difference in the response rate between 1 week and 1 month of intervention in both groups, with an "intra-group p-value" of 0.000. This finding indicates the positive effects of both synbiotics on infantile colic. Group B experienced a significantly higher response rate after 1 week and 1 month of intervention compared to group A (inter-group comparison) (**Tab. 2** and **Tab. 3**). This finding emphasizes the larger effect of the symbiotic containing *B. lactis* in treating infantile colic.

In 2014, Kianifar et al. studied 50 breastfed infants aged ≤ 4 months with infantile colic. They compared the effect of a synbiotic containing *L. casei*, *L. rhamnosus*, *S. thermophilus*, *B. breve*, *L. acidophilus*, *B. infantis*, *L. bulgaricus* (1×10^9 CFU per ml) plus FOS with placebo. After 1 month, there was a significant reduction of > 50% in the crying time in the synbiotic group compared to the placebo group ($p < 0.01$). The rate of symptom recovery was significant in the synbiotic group after 1 week, but it was not significant after 1 month [22]. The dose of probiotic and the type of oligosaccharides used in this study were similar to our study, while the probiotic strains were different. On the other hand, Kianifar et al. compared a synbiotic containing seven strains with placebo, while the present study compared two different synbiotics and showed their positive effects on infantile colic. Kianifar et al. also reported a significantly higher rate of symptom recovery in the synbiotic group after 1 week, but it was not significantly higher after 1 month. This finding is in contrast to the results of the present study, where both the synbiotics had a significant positive response rate after 1 week and 1 month, with a higher response rate after 1 month of intervention.

In 2017, Vijayalakshmi et al. studied 50 infants of whom 25 were treated with standard treatment alone, and 25 received a synbiotic along with standard treatment. They used a synbiotic containing a combination of *L. sporogenes* (5×10^7 CFU per ml), *S. faecalis* (3×10^7 CFU per ml), *C. butyricum* (2×10^6 CFU per ml), and *B. mesentericus* (1×10^6 CFU per ml). The results showed that the synbiotic was an effective treatment and could be used along with the standard treatment for managing infantile colic [23]. The dose and the type of probiotic strains of this study were different from the present study.

Limitations

The present study was limited to term infants with infantile colic. Further studies are recommended to compare the effect of these two drops in premature infants. Similar studies with more participants in this age range are required to confirm the findings. The two products used in this study were the first two synbiotic agents produced in Iran and other products were not available, which was a limitation of this study. Further studies are recommended to compare synbiotics containing multiple probiotic strains with synbiotics containing a similar single probiotic strain. Administering and comparing two different synbiotics for the treatment of infantile colic was the novelty of this study.

Conclusion

This study showed that both synbiotics were effective for the treatment of infantile colic. However, the synbiotic containing *B. lactis* was significantly more effective than the synbiotic containing *B. infantis*, *L. reuteri*, and *L. rhamnosus* in infantile colic.

Neither synbiotic was associated with adverse effects.

Established facts and novel insights of this study are presented in **Tab. 4**.

Table 4. Established facts and novel insights.

Established facts	Infantile colic is common in the first 4 months of life.
	The etiology of infantile colic is multi-factorial with no definite treatment.
	Previous studies have shown that probiotics and prebiotics can reduce symptoms of colic.
Novel insights	The effect of synbiotics on infantile colic is an unexplored area of research.
	The present study showed that both synbiotics were effective in the treatment of infantile colic.
	However, the synbiotic containing *B. lactis* was significantly more effective than the synbiotic containing *B. infantis*, *L. reuteri*, and *L. rhamnosus* in infantile colic.

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Declaration of interest

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