Original Article

The Efficacy of the Administration of *Bifidobacterium lactis* for Treatment of Infantile Colic: A Double-Blind, Randomized, Placebo-Controlled Clinical Trial

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Abstract

Background: Although there is evidence regarding the effectiveness of probiotics for infantile colic (IC), there are not many studies regarding the efficacy of Bifidobacterium animalis subsp. Lactis BB-12®, (BB-12®), for the treatment of IC. This trial aimed to evaluate the efficacy of this subspecies of probiotic administration on IC.

Materials and Methods: In this double-blind randomized, placebo-controlled clinical trial, infants with IC diagnosis, exclusive breastfeeding, gestational age of more than 37 weeks, and birth weight of more than 2500 grams were included. The selected infants were randomly allocated into the two groups of "BBcare" group, treated with BB-12® and the control group was treated with a placebo, 5 drops per day, for 6 weeks. The mean of crying time, vomiting episodes, and frequency of defecation at baseline and during follow-ups (40 and 60 days after intervention) were compared between the two studied groups.

Results: In this study, 40 and 38 neonates in "BBcare" and placebo groups completed the study. In the "BBcare" group frequency of defecation, crying time, and vomiting episodes decreased significantly during intervention till 60 days after probiotic administration ($P < 0.05$). In the placebo group, there was a significant increase in crying and vomiting episodes between baseline and 60 days after intervention ($P < 0.05$). Between-group analyses indicated that mean of crying time, and vomiting episodes and number of defecations, 60 days after intervention were significantly lower in "BBcare" group ($P < 0.05$).

Conclusion: The findings of our study offer compelling signals for the effectiveness of BB-12® in the management of some intestinal problems. Although these findings could be supportive evidence for the important role of gut microbiota as the goal of intervention to improve bowel movement and comfortable defecation in IC, further studies are needed in this field, especially for the evaluation of different types of probiotics in combination with each other's and with different dosages.

Keywords: Bifidobacterium lactis, infantile colic, treatment

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Introduction

Near 25% of infants suffer from a functional gut disturbance, which is named infantile colic (IC). This benign disorder presents between 1 and 4 months of life and is considered an origin of major distress for the infant, parents, and their families.[1] There is no absolute association between IC and kind of feeding, socioeconomic standing, and gestational age, and occurs equally between both sexes.

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Since now, the etiology and pathogenesis of IC remain unknown and are supposed to be multifactorial, but, recent research proposes that alterations of gastrointestinal microorganisms can contribute to the advance of this condition.[2] Based on available data, there are reports about a lower variety and constancy of gastrointestinal microbiota in neonates with IC, during the first 2 weeks of life.[3] Given the role of dysbiosis in the pathogenesis of IC, some studies have evaluated the effectiveness of different probiotics for managing of the disorder.

Most of the available reviews and articles focusing on the effectiveness of Lactobacillus reuteri strains, there is a notable gap in research specifically addressing Bifidobacterium animalis subsp. lactis BB-12® (BB-12®).[4-6] BB-12®, an important probiotic, which modifies the configuration of the gastrointestinal microbiota and improves the immune system function.[7] These facts probably make BB-12® potentially helpful for the treatment of infantile colic. In a previous trial, a low lactose relatively hydrolysate formula comprising these prebiotics prompted beneficial in decreasing the time of crying in infants with colic.[8]

Our study aims to fill this gap by examining the unique effects of BB-12® in a defined population, which we believe could provide insights into its efficacy relative to other strains.

Moreover, we acknowledge that the effectiveness of probiotics can vary significantly based on factors such as study population and geographic region. Thus, this trial aimed to evaluate the efficacy of BB-12® administration on infantile gut problems.

Materials and Methods

This double-blind randomized, placebo-controlled clinical trial was conducted from December 2018 to December 2019 in the pediatric department of Amin Hospital, affiliated with Isfahan University of Medical Sciences.

The protocol of this study was approved by the Ethics Committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1397.298) with a project number of 397266.

The trial was carried out in collaboration with a team of general pediatricians and health staff, working in the Amin hospital outpatient clinic in the north area of Isfahan. All inspectors connected in the study attended an inspector conference during which the trial protocol was represented and deliberated, and all explanations and procedures, as well as the important factors in the controlling of IC, were shared; including parental training, assurance, and concern.[9]

In this study, all infants aged less than 2 months old who were referred to Amin Hospital outpatient clinic for irritability and exertion during defecation were enrolled using the simple sampling (available) method.

Infants with IC diagnosis (crying for more than three hours a day for more than 3 days a week starting from at least one week ago), exclusive breastfeeding, gestational age of more than 37 weeks, and birth weight of more than 2500 grams were included. Those with a history of organic causes of crying (such as otitis, UTI, Fisher, esophagitis, and reflux diagnosed by a pediatrician), insufficient weight gain (less than 150 grams per week), and the presence of blood in the stool were not included.

From selected infants, those with a history of antibiotic consumption before or during the study and poor parental cooperation were excluded.

The selected infants were randomly allocated in the two groups, using random allocation software. One group was treated with BBcare drop (BB-12®) 5 drops per day, as intervention group and the other group was treated with placebo drops at 5 drops per day, as the placebo group, for 6 weeks. The mean of crying time, vomiting episodes, and frequency of defecation at baseline and during follow-ups (40 and 60 days after intervention) were compared between the two studied groups.

Data collection and intervention

Written informed consent was obtained from the parents of all selected infants.

Selected infants were examined physically by a pediatrician. Using a questionnaire, demographic, anthropometric, medical history (history of recent infection, diseases, and medication use), and clinical findings (vital signs, hydration, growth, nutritional status, otoscopic examination, oral cavity, abdomen, respiratory, and lymph node evaluation) were recorded.

Then, infants were followed for a 1-week as a pre-enrolment course. If after this time the diagnosis of IC was established, the infants were randomized to one of the following study groups:

- Intervention or BB-12®: Parental assurance and teaching plus BBCare® drop (Zist takhmir, Pardis, Tehran, Iran), which is composed of 15 ml of a mixture containing Bifidobacterium Lactis. One drop of this product holds a minimum of 1000,000,000 CFU Bifidobacterium Lactis plus fructooligosaccharides (FOS).
- Placebo Group: Parental assurance and teaching plus placebo (oil maltodextrin suspension).

Parents were asked for administration to their infants 5 drops of the allocated study product, once a day, for 30 days directly in the mouth before feeding in the morning.

Instructions for care and upholding the product were offered according to the manufacturer's suggestion. Study products were made by Zisttakhmir pharmaceutical company. The infant's parents, researcher, staff persons achieving the appraisals, and study analysts were blinded to the characteristics of the treatment at every stage, i.e. allocation, interference, and statistical investigation. The covering, weight, appearance, taste, and smell of the study product and the placebo were very similar and made sure in the blind conditions. The bottles restraining the placebo or the probiotic were tagged with successive numbers without any mention of the group task. We provided a diary for the infant's parents and asked them to complete it daily with data relating to the consumption of a

daily dose of the trail product, duration and amount of weeping episodes, number of intestinal movements, and firmness of the infant's stool (according to the Bristol stool scale),[10] duration of sleep, potential adverse events.

During 6 weeks the infants were followed up and visited by the trial pediatrician for 4 times. Unplanned visits were done if necessary. The pediatricians completed a full examination of the infants at each visit and evaluated and collected data from the trial diary. Compliance was judged by assessing the diary delivered by the parent. We assessed the alterations in dietary behaviors and imaginable influences of maternal nutritional factors, by evaluating data from a 7-day diet diary composed during the week before treatment. Moreover, potential changes in maternal food were measured during the last week of the trial. All diaries were evaluated by expert dietitians ignorant of the study goals. At each visit, the infants' parents were requested to report any adverse and side effects, unpredicted symptoms, or unpredicted events connected or not to the treatment. Parents were educated to avoid any treatment with pre/probiotics or any herbal and chemical anti-colic drugs during the trial.

Stool consistency was assessed as the number and the proportion of infants with a minimum of one stool sample of each kind per week rendering to the Bristol scale. Regular demographic and anamnestic characteristics were similar matching the two study groups. All infants were from people of middle socioeconomic rank and lived in northern areas of Isfahan. All studied infants were breastfed during the whole study period. None of the subjects received any drugs for colic before the study entry and throughout the study period. Seven-day food diaries were obtainable from all mothers of the babies included in the trial, and no dietary alterations were detected during the week before treatment.

Using the data which is recorded by parents, the crying time, vomiting episodes, and frequency of defecation in the two groups before, during and 40 and 60 days after intervention were compared.

Statistical analysis

Data was analyzed using SPSS version 21 software. Quantitative and qualitative data were reported as mean (SD) and number (percentages), respectively. Comparison of the studied variables in the studied groups and within groups during follow-ups were performed using a student *t*-test for quantitative data and a Chi-square test for qualitative data. $P < 0.05$ is considered a significant level.

Results

In this study from initially enrolled neonates, 40 and 38 neonates in BB-12® and placebo groups completed the study. Characteristics of the neonates are presented in Table 1. There were no significant differences regarding studied variables in the two studied groups ($P > 0.05$).

Table 1: Characteristics of patients with infantile colic in BB-12® and placebo groups

Variables	BB-12® group *n*=40	Placebo group *n*=38	*P*
Female/male [*n* (%)]	16 (45%)/24 (55%)	13 (48%)/25 (52)	0.127
Normal vaginal delivery [*n* (%)]	18 (32.5%)	20 (30.5%)	0.731
Gestational age (weeks)*	38.7 (1.2)	38.7 (1.1)	0.962
Birth weight (kg)*	3.4 (0.6)	3.1 (0.2)	<0.001
Age (days)*	25.52 (6.42)	23.90 (1.97)	0.124
Exposure to passive smoking [*n* (%)]	10 (22.5)	10 (21.4)	0.934
Familial risk for allergy [*n* (%)]	8 (17)	9 (15)	0.807

*Mean (SD)

The mean of crying, vomiting episodes, and defecation number at baseline and during follow-ups (40 and 60 days after intervention) are presented in Figures 2–4. Within-group analysis indicated that there were significant differences in the mean of crying and vomiting episodes and the number of defecations in the BB-12® group ($P < 0.05$). In the placebo group, there were significant differences between the mean of crying and vomiting episodes ($P < 0.05$), but there was no significant difference between the mean number of defecations in the placebo group ($P > 0.05$).

There was a significant difference between groups regarding the mean of crying and vomiting episodes at baseline ($P < 0.05$). It was higher significantly in the BB-12® group than in the placebo group ($P < 0.05$).

There were no significant differences between groups regarding the mean of crying and vomiting episodes and the number of defecations, 40 days after intervention ($P < 0.05$).

Between-group analyses indicated that there was a significant difference between groups regarding the mean of crying and vomiting episodes and number of defecations, 60 days after intervention ($P < 0.05$). It was lower in BB-12® group than the placebo group ($P < 0.05$).

The frequency of different types of stool consistency is presented in Table 2. In the placebo group, the stool consistency did have not significant changes during follow-up periods ($P > 0.05$). In the BB-12® group, the stool consistency changed significantly ($P < 0.05$).

The anthropometric parameters improved within the regular range from one visit to the next visit and they were the same in the two groups. There was no report of antibiotic consumption.

Discussion

In this study, we evaluate the effectiveness of BB-12® probiotic strain on the management of IC. Our results indicated that the probiotic has a proper effect on crying and vomiting episodes for

Table 2: The frequency of different forms of stool consistency (according to the Bristol stool scale) at baseline and during follow-ups (40 and 60 days after intervention) in BB-12® and placebo groups

Groups/follow-ups	Baseline	40 days after intervention	60 days after intervention	*P*
BB-12®				
- Sausage-shaped but lumpy	0 (0%)	0 (0%)	0 (0%)	<0.001
- Sausage shaped with cracks	6 (15%)	17 (42%)	26 (65%)	
- Sausage shaped but soft	25 (62%)	22 (55%)	11 (27%)	
- Fluffy shaped	9 (22%)	1 (2.5%)	3 (7.5%)	
Placebo				
- Sausage-shaped but lumpy	0 (0%)	1 (2.5%)	4 (10%)	0.680
- Sausage shaped with cracks	16 (40%)	16 (40%)	18 (45%)	
- Sausage shaped but soft	22 (55%)	21 (52%)	7 (17%)	
- Fluffy shaped	2 (5%)	2 (5%)	11 (27%)	
P-value Mann-Whitney	0.406	0.974	0.003	

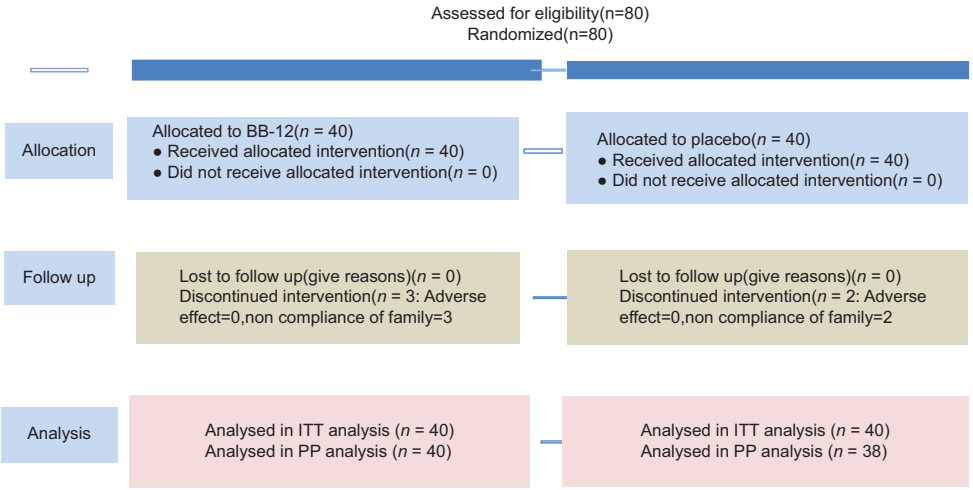

Figure 1: The consort diagram of the study

long-term use (60 days after using the probiotic). In the BB-12® group number of defecation, crying, and vomiting episodes decreased significantly during intervention till 60 days after probiotic administration, whereas in the placebo group, there was a significant decrease in crying and vomiting episodes between baseline and 60 days after intervention.

The role of probiotics in the treatment of IC has been investigated in several studies.[11-20]

The results of a recent systematic review and meta-analysis of clinical trials have demonstrated that probiotics could reduce crying episodes in infants with IC. They concluded that based on available data, we could not concisely assume that probiotics could improve IC by modulation of the immune system or modulation of microbiota because most of the reviewed studies reported their data based on associations and recommended to plan further clinical trials based on causations.[21]

Most of the trials evaluated the effectiveness of *L. reuteri* for IC, especially in exclusively breastfed infants. However, some studies did not show any significant efficacy for *L. reuteri*.[4-6,14,22,23]

Recently, Vaz *et al*.[24] conducted a systematic review and meta-analysis to assess the effectiveness of probiotics and symbiotics for treating infantile colic (IC). The study examined 15 probiotic strains, including *Lactobacillus reuteri* DSM 17938, which were given either alone or alongside prebiotics. The results showed an average decrease of 51 minutes in daily crying time, with notable variations among subgroups infants delivered vaginally experienced a 39.30-minute reduction, while exclusively breastfed infants had a reduction of 74.28 minutes. These findings indicate that probiotics are generally effective, especially for exclusively breastfed infants, although data on formula-fed and caesarean-born infants is still limited.

In the literature review, we found only two studies regarding the effectiveness of BB-12® on IC and its related symptoms including the daily average of crying. In the first trial, Vlieger *et al*.[25] compared a formula supplemented with containing *Lactobacillus paracasei*, and *Bifidobacterium animalis*, Lactis with the same formula without the probiotics in infants with IC. Their results did not indicate a significant difference in the duration of crying and sleeping hours between the two studied groups during the first three months of life.

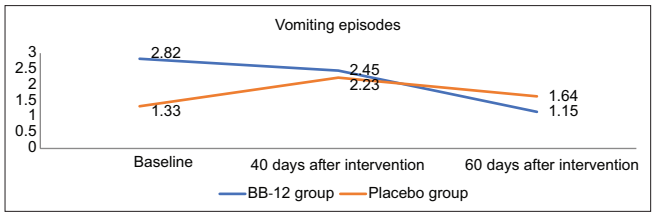

Figure 2: The mean of vomiting episodes number at baseline and 40 and 60 days after intervention in BB-12® and placebo groups

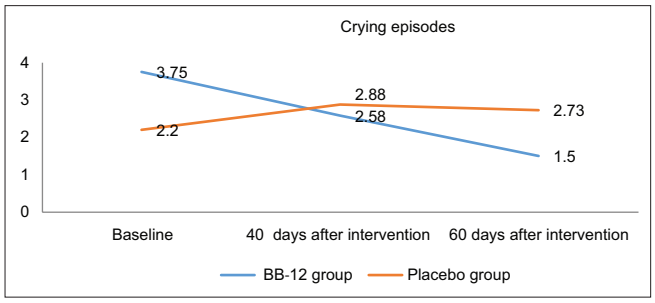

Figure 3: The mean of crying episodes number at baseline and 40 and 60 days after intervention in BB-12® and placebo groups

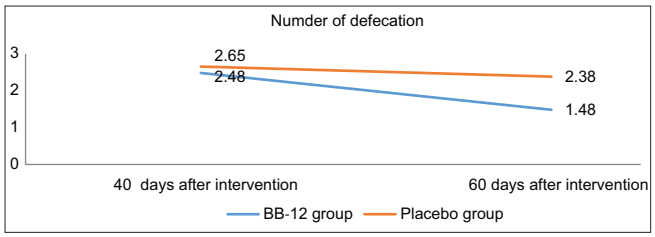

Figure 4: Mean number of defecation at baseline and 40 and 60 days after intervention in BB-12® and placebo groups

Recently, Nocerino and colleagues[17] reported that using the *Bifidobacterium animalis* subsp. lactis BB-12 strain in infants with IC results in a significant decrease in daily crying episodes. They indicated that its effectiveness was observed at the end of the 2nd week of administration. They also did not report any relapse after the intervention. They suggested that the effect could derive from immune and non-immune mechanisms associated with a modulation of gut microbiota structure and function.[19]

Our findings were similar to their study. In addition, we report its effectiveness on vomiting episodes of neonates with IC. At this time, there is no comprehensive study on the effect of BB-12® on infant vomiting which can be caused by allergy, gastroesophageal reflux, and colic. Based on the high probability role of immune allergic reactions in gastrointestinal problems including vomiting and the possible effect of probiotics in diminishing this process, there is a strong need for more research on this issue in the future

The explanation for this inconsistent evidence and various results in previous studies is uncertain, and there is a necessity to explore the causes behind such controversial consequences, principally with accumulating probiotic marketing, variation of strains used, and poorly understanding of colic pathogenesis considering the role of BB-12® on the infantile colic, little study has been done and more studies are needed in the future.

About the role of BB-12® recommendation on daily bowel movements and pattern of infant defecation, our study strongly showed the beneficial effects of this probiotic strain. Previous studies support a clinically relevant benefit of the probiotic strain BB-12®, on defecation frequency in healthy subjects with low defecation frequency and abdominal discomfort.[22] A study about the effects of *Bifidobacterium lactis* supplementation on colonic transit time and gastrointestinal symptoms in adults with functional constipation conducted by Alvin Ibarra *et al*.[26] did not strongly show the effectiveness of this probiotic.[7] Another study indicated that BB-12 has a beneficial action on transit time and stool consistency.[17] Probiotics (I.e: BB-12) may intermingle with the immune system in several ways, e.g. by provoking local and systemic antibody production, aggravating immune cell activity, modifying signals in epithelial and immune cells, and stimulating phenotypic alterations in dendritic cells. However, the main mechanism of this effect is still unclear; and a causal relationship between the modulatory effect of probiotics on microbiota and the immune system has not been confirmed.[21]

Previous findings indicate that BB-12® modifies the proliferation of human peripheral blood mononuclear cells and cytokines expression,[22,27] with protective action against gastrointestinal infections in infants and children. In the setting of IC, these properties could be responsible for a helpful shaping of gut microbiota arrangement. It is recognized that a confident modulation of LL-37, HBD-2, and sIgA expressions into the gut lumen leads to a positive effect on gut microbiota structure and butyrate production.[23] These effects seem mainly significant in IC, where dysbiosis with augmented presence of proteobacteria and reduced presence of Bifidobacteria with declined rate production have been established.[28]

The limitations of the current study were the small number of previous research studies related to this type of probiotic, short-term follow, and the inclusion of exclusively breastfeeding infants. It is suggested that future trials can help in clarifying the action of BB-12® in infant colic and intestinal homeostasis.

The strengths of this study were its well-designed methods (the placebo-controlled, randomized double-blind trial), the use of a validated procedure for IC diagnosis, and the use of a well-defined probiotic strain.

Conclusion

The findings of our study offer compelling signals for the effectiveness of BB-12® in the management of some intestinal problems. Though these findings could be supportive evidence for the important role of gut microbiota as the goal of intervention to improve bowel movement and comfortable defecation in IC, further studies are needed in

this field, especially for the evaluation of different types of probiotics in combination with each other's and with different dosages. It is important to emphasize that this study evaluated a particular well-characterized probiotic strain and that these outcomes cannot be generalized for other probiotic strains.

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Author contributions

All authors (MAP, FF, AK, SH, RK) have participated in the conception of the study as well as in the analysis and interpretation of data, elaboration, or critical reviews of the report, and they have read and approved the final version of the manuscript. The authors confirm there are no concerns of financial involvement with organizations, entities, or individuals with an interest in the subject matter or materials discussed in the manuscript, and no conflict of interest.

Ethics approval and consent to participate

The protocol of the study was approved by the ethics committee of Isfahan University of Medical Sciences with the ethics code of IR.MUI.MED.REC.1397. 298

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Conflicts of interest

There are no conflicts of interest.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to privacy/ethical restrictions but are available from the corresponding author upon reasonable request.

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