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Comparing the Safety and Efficacy of Two Different Synbiotics in the Treatment of Infantile Functional Constipation Resistant to Non-Pharmacological Therapy: A Randomized Clinical Trial

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ABSTRACT:
Background: Recent evidence emphasizes the positive effect of probiotics and synbiotics in the treatment of functional constipation in childhood, but no study has surveyed the effectiveness of synbiotics in improving the clinical conditions in infants ≤6 months suffering from functional constipation, so we performed this study.
Aims: Comparing the efficacy and safety of two types of synbiotics including PediLact® (Zist-Takhmir Co., Tehran, Iran) drop containing Bifidobacterium infantis, Lactobacillus reuteri, Lactobacillus rhamnosus plus fructooligosaccharides with BBCare® (Zist-Takhmir Co., Tehran, Iran) drop containing Bifidobacterium lactis BB-12 plus fructooligosaccharides in the treatment of infantile functional constipation.
Study Design: This trial was performed on infants less than 6 months of age who met the ROME IV criteria for infantile functional constipation. The patients were randomly assigned to receive PediLact drop (n = 44) or BB-Care drop (n = 45) for one month and were evaluated on the seventh day and at the end of the first month.
Results: A significant downward trend was revealed in the responsive rate of every clinical symptom in both intervention groups but BB-Care was more effective than PediLact in improving the frequency of weekly defecation. Both synbiotics also improved significantly all symptoms of constipation in all types of feeding methods after one week and one month of intervention (primary outcomes). There was no side effect of synbiotics through intervention (secondary outcome).
Conclusions: This study shows that both synbiotics improved significantly all symptoms of functional constipation after one week and one month of intervention apart from type of feeding method in infants less than 6 months of age. Due to the greater effectiveness of BB-care in increasing stool frequency, B. lactis may play a more prominent role in this age group. This study has been registered at the Iranian Registry of Clinical Trails (IRCT20160827029535N7).

KEYWORDS: Infant, Functional constipation, Synbiotics, Treatment

1.INTRODUCTION

Constipation is a common problem in children, with 3% of referrals to general pediatric clinics and 30% of referrals to pediatric gastroenterologists in developed countries for children with constipation [1]. Although the prevalence rate of childhood constipation appears to be lower in Eastern countries as a result of using a high-fiber diet, children around the world still suffer from it [2,3]. Organic causes to justify constipation are not found in 90% to 95% of children [4,5]. The rate of constipation is different, ranging from 2.5%- 79% in adults to 0.7% -29.6% in children, throughout the world [6]. About 60% of children with constipation are treated with laxatives and a significant proportion need long-term treatment [7]. In one study,52% of children still had constipation after 5 years [8]. In addition, about 30% of children with constipation, even after puberty, experience complications such as incontinence and painful bowel movements [7]. Therefore, the effectiveness of current therapeutics for the treatment of childhood constipation and their long-term impact on patients' quality of life should be reconsidered. On the other hand, the development of novel treatments for constipation in children and infants is necessary.
Previous studies have shown that probiotics are effective in treating inflammatory bowel disease, traveler's diarrhea, and constipation [5,9]. In recent years, there has been a great tendency to use probiotics in functional gastrointestinal diseases. Probiotics contain beneficial bacteria that can be used to alter the composition of gastrointestinal bacteria [10, 11]. Prebiotics

contain certain nutrients such as fructooligosaccharides and galactooligosaccharides which can be used to affect the arrangement and function of gastrointestinal bacteria. [12, 13]. In this regard, synbiotics are a mixture of probiotics and prebiotics (most often oligosaccharides selectively utilized by bacteria), which act synergistically to promote the growth and survival of beneficial microorganisms in the gut [14, 15]. It has been well demonstrated that synbiotic intake can selectively modify microbiota composition, restore microbial balance in the intestinal tract, and also improve the gastrointestinal functional state [16, 17].
At present, in Iran, only two synbiotics including BB-Care and PediLact are available to treat gastrointestinal disorders in infants. According to our last search and the last systematic review of Rodriguez's study on pediatric functional constipation in 2021, there is no clinical trial that has surveyed the effect of synbiotics in the treatment of functional constipation in infants less than 6 months of age, so the present study was performed [19].

2.MATERIALS AND METHODS

2.1. Study design

This parallel randomized double-blinded clinical trial was performed to compare the effectiveness of two different types of synbiotics including PediLact® (Zist-Takhmir Co., Tehran, Iran) drop containing Bifidobacterium infantis (B. infantis), Lactobacillus reuteri (L.reuteri), Lactobacillus rhamnosus (L. rhamnosus) plus fructooligosaccharides (FOS) and BBCare® (Zist-Takhmir Co., Tehran, Iran) drop containing Bifidobacterium lactis BB-12 (B. lactis BB-12)plus fructooligosaccharides (FOS) in the treatment of infantile functional constipation.

2.2. Participants

Ninety-two infants, less than 6 months of age with a diagnosis of infantile functional constipation who were referred to the clinics of Bahrami Hospital in Tehran from 2020 to 2021 were enrolled in this study. The infants were fed by breast, formula or both.
According to the ROME IV criteria. The infants less than 6 months of age who met at least 2 characteristics of the following criteria for 1 month including (1) Fewer than two spontaneous bowel movements per week, (2) History of excessive stool retention, (3) History of painful or hard bowel movements, (4) History of large-diameter stools, (5) Presence of a large fecal mass in the rectum, who did not response to non-pharmacological treatment (including reassurance, feeding training to gain optimal hydration of the infant, oral mineral oil and abdominal massage) were assigned to this study. Other diagnoses were ruled out based on the clinical manifestations of the patients, lab tests, and abdominal X-ray or sonography. The infants less than 6 months of age with the diagnosis of GI obstruction or surgery; receiving opiates, muscle relaxants, and sedatives; mechanical ventilation; atopy; central and peripheral nervous system abnormalities; endocrine diseases (hypothyroidism); anorectal abnormalities; Hirschsprung disease; receiving probiotics products for one week before intervention were excluded from the study. The infants with a history of using probiotics or any signs of allergy to these compounds were not included in the study. Also, patients whose parents discontinued medication or those who were not re-accessible to record treatment responses were excluded from the study.
The parents declined rectal exam so it was not performed for the diagnosis of a large fecal mass in the rectum as the fifth criteria of ROME IV criteria for diagnosis of constipation.

2.3. Clinical interventions

Ninety-two infants who met the inclusion and exclusion criteria, who did not response to non-pharmacological treatment (including reassurance, feeding training to gain optimal hydration of the infant, oral mineral oil and abdominal massage) were randomly assigned to a double-blind clinical trial into two groups. Group A received PediLact drop containing B. infantis, L. reuteri, L. rhamnosus (1×10^9 CFU per ml) plus FOS, and group B received BBCare drop containing B. lactis BB-12 (1×10^9 CFU per ml) plus FOS daily for one month. Every infant in each group received 5 drops of the synbiotic every 6 hours after feeding which was equal to 1ml of each synbiotic containing 1×10^9 CFU probiotics.
Before the intervention, a checklist including demographic data (age, gender, birth weight, weight at presentation and type of feeding) and symptoms and signs of infantile functional constipation (according to ROME IV criteria) was filled out by a clinical researcher. The same clinical researcher evaluated the clinical manifestations of patients according to ROME IV criteria after one week and one month to define the rate of clinical improvement. The response rate was considered positive if >50% of the clinical manifestations were reduced during the intervention.

2.4. Outcomes

The primary outcome was the response rate to each synbiotic. The response rate was estimated according to the times of defecation per week, the consistency of the stool according to the Bristol stool scale, cramps or pain during defecation, and stool diameter. The secondary outcome was the possible side effects of each synbiotic (the symptoms of small intestine bacterial

overgrowth including increase in gas, bloating or diarrhea; constipation or thirst; triggering allergic reactions; higher rate of infection; vomiting and skin rashes or itching) during the intervention.

2.5. Sample size

According to the study of Baştürk et al. [18], a total sample size of 83 infants was estimated using α = 0.05, β = 20%, confidence level = 95%, power = 80%, and d = 0.2. To increase the power of the study, the total sample size was increased to 92 patients. Two patients in group A and one patient in group B discontinued intervention as soon as recovery symptoms appeared. Finally, forty-four infants in group A and forty-five infants in group B, completed the study and their data were analyzed (Figure 1).

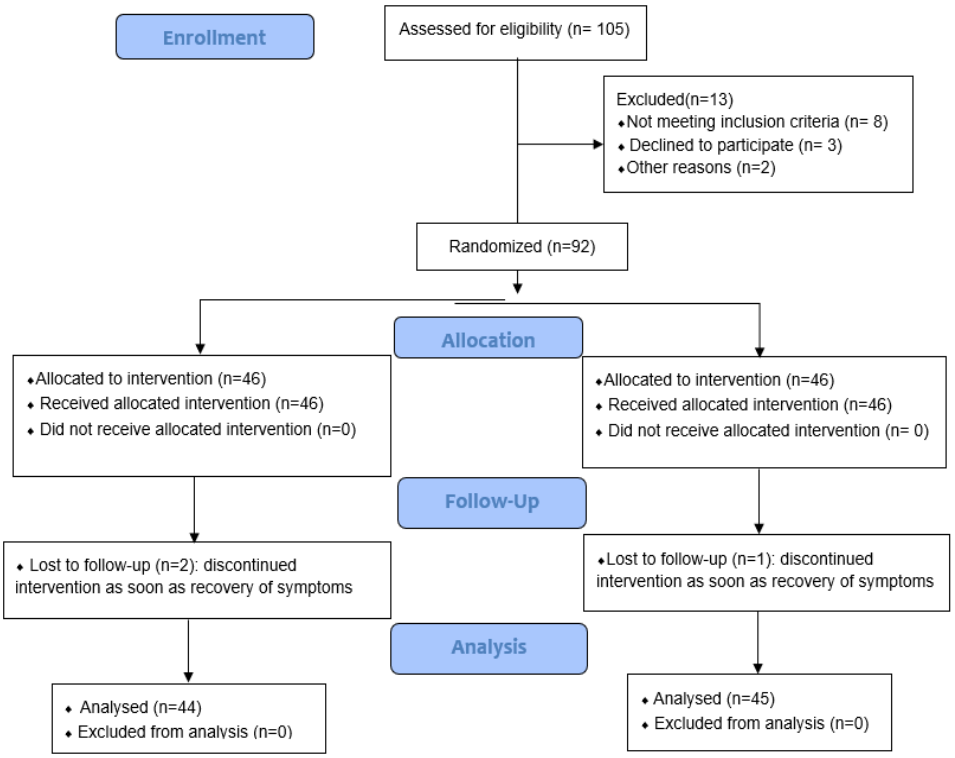

Figure 1. CONSORT Flow Diagram

2.6. Randomization

We used the random number tables from Rand Company for simple randomization. The first researcher generated the random allocation sequence, enrolled the participants, and assigned them to interventions. The second researcher evaluated the clinical manifestations of patients according to ROME IV criteria and assessed outcomes in one week and one month after the intervention.

2.7. Blinding

Both synbiotics were produced in a single drug company [Zist-Takhmir Co., Tehran, Iran] in similar bottles that were labeled with blue or red color. Group A received the synbiotic with a blue color label and group B received the synbiotic with red color label, so the infants, their parents, the caregivers who administered the synbiotics, the researcher who followed the patients, and gathered the data; and the statistician who analyzed the data, were completely unaware of patients' grouping and type of administered synbiotic.

2.8. Ethical Considerations

Written informed consent was obtained from the parents of patients who participated in this study. The details of the study protocols were approved by the ethical committee at Tehran University of Medical Sciences (IR.TUMS.MEDICINE.REC.1398.644). This study has been registered at the Iranian Registry of Clinical Trails (IRCT20160827029535N7).

2.9. Statistical analysis

The results were presented as mean ± standard deviation (SD) for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. The normality of data was analyzed using the Kolmogorov-Smirnoff test.

Categorical variables were compared using the chi-square test or Fisher's exact test when more than 20% of cells with an expected count of less than 5 were observed. Quantitative variables were also compared with the t-test or Mann U test. The multivariable logistic regression model was used to compare the efficacy of medications with the presence of baseline parameters as the confounders. For the statistical analysis, the statistical software SPSS version 16.0 for windows (SPSS Inc., Chicago, IL) was used. P- values of 0.05 or less were considered significant.

3. RESULTS

In this study, ninety-two infants were randomly assigned into two groups. Forty-six infants were classified in group A and forty-six infants in group B. Two patients in group A and one patient in group B discontinued intervention as soon as recovery symptoms appeared (Figure1).

3.1. Baseline data

The two groups were similar in baseline parameters including gender, birth weight, gestational age, type of feeding (as breastfeeding or using formula), age of onset of constipation symptoms, and history of atopy. Comparing clinical manifestations related to constipation between the two groups before intervention showed no significant difference (Table 1).

Table 1: Baseline characteristics in the PediLact and BB-Care groups

Characteristics	PediLact group N=44(%)	BB-Care group N=45(%)	P- value
Male gender, %	21 (47.7)	23 (51.1)	0.833
Mean birth weight, gr	2988.9±274.3	3112.8±315.8	0.051
Gestational age, week	38.0±0.7	38.0±0.9	0.863
Type of feeding			0.924
Breast milk	16 (36.4)	18 (40.0)	
Formula	10 (22.7)	9 (20.0)	
Breast milk and formula	18 (40.9)	18 (40.0)	
Mean age of onset of symptoms, day			0.294
< 30 days	31 (70.5)	26 (57.8)	
30 to 60 days	11 (25.0)	18 (40.0)	
60 to 120 days	2 (4.5)	1 (2.2)	

3.2. Numbers analyzed

Finally, forty-four infants in group A and forty-five infants in group B, completed the study and their data were analyzed. Data analysis was based on the intention to treat principle.

3.3. Outcomes and estimation

The effect of two drops was significant on improving all symptoms of constipation after one week and one month of intervention (Table 2).

The inter-group comparison of the related symptoms showed that BB-Care was significantly more effective in increasing the times of defecation after one week and one month of intervention. The effect of two drops was significant on improving other symptoms of constipation after one week and one month of intervention too but it was not significant between the two groups (Table 2).

Table 2. Clinical condition of patients before and after interventions

Characteristics	PediLact group N=44(%)	BB-Care group N=45(%)	P- value
Times of defecations (≤ two times/week)			
Before	34 (77.3)	37 (82.2)	0.606
One week after	25 (56.8)	17 (37.8)	**0.029**
One month after	11 (26.8)	4 (9.1)	**0.021**
P- value	<0.001	<0.001	
Cramps or painful defecation			

Before	34 (77.3)	37 (82.2)	0.606
One week after	20 (45.5)	20 (44.4)	0.811
One month after	8 (19.5)	10 (22.7)	0.999
P- value	<0.001	<0.001	
Dry or hard stool defecation			
Before	37 (84.1)	37 (82.2)	0.999
One week after	27 (61.4)	25 (55.6)	0.800
One month after	12 (29.3)	9 (20.5)	0.430
P- value	<0.001	<0.001	
Large stool defecation			
Before	16 (36.4)	20 (44.4)	0.519
One week after	6 (13.6)	5 (11.1)	0.483
One month after	5 (12.2)	4 (9.1)	0.999
P- value	0.002	<0.001	

Using a multivariable logistic regression model and with the presence of baseline confounders, BB-Care was more effective than PediLact in improving the frequency of weekly defecation in infants suffering from constipation one week after the intervention (*OR* = 2.275, 95%*CI*:1.908 to 5.700, *p* = 0.039).

In similar modeling, we could show high efficacy of BB-Care as compared to PediLact in the improvement of weekly defecation one month after the intervention (*OR* = 3.070, 95%*CI*: 1.889 to 10.603, *p* = 0.046).

Both PediLact and BB-Care drops improved all symptoms of constipation significantly after one week and one month of intervention in all types of feeding methods including breast-feeding, formula-feeding or breast-feeding plus formula-feeding too (Table 3- 5).

Table 3. Clinical condition of breast-fed infants before and after interventions

Characteristics	**PediLact group N=16(%)**	**BB-Care group N=18(%)**	**P- value 0.737**
Times of defecations (≤ two times/week)			
Before	12 (75)	6 (33.3)	0.022
One week after	10 (62.5)	3 (16.7)	0.028
One month after	5 (31.3)	3 (16.7)	0.555
P- value	0.050	0.368	
Cramps or painful defecation			
Before	10 (62.5)	15 (83.3)	0.169
One week after	8 (50)	7 (38.9)	0.515
One month after	2 (12.5)	3 (16.7)	0.732
P- value	0.002	0.000	
Dry or hard stool defecation			
Before	15 (93.8)	17 (94.4)	0.932
One week after	8 (50)	16 (88.9)	0.013
One month after	4 (25)	5 (27.8)	0.694
P- value	0.000	0.000	
Large stool defecation			
Before	5 (31.3)	9 (50)	0.268
One week after	2 (12.5)	1 (5.6)	0.476
One month after	2 (12.5)	0 (0.00)	0.122
P- value	0.050	0.000	
Total			
Before	8 (50)	11 (61.1)	0.515
One week after	0 (0.00)	0 (0.00)	1.00
One month after	0 (0.00)	0 (0.00)	1.00
P- value	0.000	0.000	

Table 4. Clinical condition of formula-fed infants before and after interventions

Characteristics	PediLact group N=10(%)	BB-Care group N=9(%)	P- value 0.737
Times of defecations (≤ two times/week)			
Before	8 (80)	7 (77.8)	0.906
One week after	1 (10)	8 (88.9)	0.001
One month after	1 (10)	5 (55.6)	0.064
P- value	0.001	0.097	
Cramps or painful defecation			
Before	9 (90)	7 (77.8)	0.466
One week after	4 (40)	3 (33.3)	0.764
One month after	2 (20)	3 (33.3)	0.707
P- value	0.011	0.035	
Dry or hard stool defecation			
Before	8 (80)	8 (88.9)	0.896
One week after	8 (80)	1 (11.1)	0.003
One month after	6 (60)	1 (11.1)	0.008
P- value	0.235	0.001	
Large stool defecation			
Before	7 (70)	5 (55.6)	0.515
One week after	2 (20)	1 (11.1)	0.596
One month after	1 (10)	1 (11.1)	0.929
P- value	0.006	0.018	
Before	6 (60)	7 (77.8)	0.405
One week after	1 (10)	0 (0.00)	0.303
One month after	2 (20)	0 (0.00)	0.156
P- value	0.030	0.001	

Table 5. Clinical condition of breast-fed plus formula-fed infants before and after interventions

Characteristics	PediLact group N=18 (%)	BB-Care group N=18 (%)	P- value 1.00
Times of defecations (≤ two times/week)			
Before	14 (77.8)	13 (72.2)	0.700
One week after	8 (44.4)	10 (55.6)	0.492
One month after	8 (44.4)	7 (38.9)	0.723
P- value	0.069	0.135	
Cramps or painful defecation			
Before	15 (83.3)	15 (83.3)	1.00
One week after	8 (44.4)	11 (61.1)	0.317
One month after	6 (33.3)	6 (33.3)	1.000
P- value	0.001	0.001	
Dry or hard stool defecation			
Before	14 (77.8)	12 (66.7)	0.457
One week after	11 (61.1)	8 (44.4)	0.317
One month after	3 (16.7)	8 (44.4)	0.047
P- value	0.001	0.497	
Large stool defecation			
Before	4 (22.2)	6 (33.3)	0.457
One week after	2 (11.1)	3 (16.7)	0.630

One month after	2 (11.1)	3 (16.7)	0.628
P- value	0.135	0.135	
Total			
Before	15 (83.3)	17 (94.4)	0.589
One week after	11 (61.1)	12 (66.7)	0.729
One month after	6 (33.3)	5 (27.8)	0.632
P- value	0.002	0.000	

4. DISCUSSION

The present study was performed on 89 infants with functional constipation according to the ROME IV criteria. Forty-four patients were treated with PediLact drop (B. infantis, L. reuteri, and L. rhamnosus plus FOS) and forty-five patients were treated with BB Care drop (B. lactis plus FOS). According to our recent research and the last review of Rodriguez's study [19] on pediatric functional constipation in 2021, the six studies of Khodadad et al, Bustarc et al., Hannah et al., Hashemi et al., Mahdavi et al., and Abedny et al. are the only clinical trials that have surveyed the effect of synbiotics on functional constipation among patients ≥ 6 months of age [14,18, 20-23]. No study has surveyed the effect of synbiotics on functional constipation among patients ≤ 6 months of age, so this study was conducted.

The present study compared the effect of two synbiotics on the treatment of infantile functional constipation. In one-week and one-month follow-up, the number of defecations per week in the BB Care group was significantly higher than the PediLact group (inter-group comparison). There was no significant difference between the two groups in terms of cramp or painful bowel movements, dry and hard stools, the large diameter of stool, and treatment-related side effects. The response rate of both drops was significant after one week and one month of treatment (intra-group comparison). This finding emphasized that the synbiotic containing B. lactis was more effective in the treatment of infantile functional constipation.

According to our recent search and the last review of Rodriguez's study [19] on pediatric functional constipation in 2021, some researchers, including Russo et al., Jose et al., Guerra et al., and Sadeghzadeh et al. found the positive effect of probiotics on pediatric functional constipation [24-27]. Some other investigations have shown the usefulness of specific strains of probiotics for the treatment of pediatric functional constipation [28-30]. Studies in children and adults have shown that probiotics, especially Lactobacilli and Bifidobacteria, increase colorectal peristalsis by producing short-chain fatty acids and lowering intraluminal pH that led to increasing stool frequency [17]. In the present study, we found a significant increase in the frequency of defecation in the BB-care group compared to the PediLact group.

Among six clinical trials that have surveyed the effect of synbiotic therapy on pediatric functional constipation, five studies have shown the positive effect of synbiotic therapy in the pediatric groups that include:1. Hannah et al. studied 41 patients aged 6 months to 14 years with functional constipation. They compared the effect of a synbiotic containing FOS and probiotics including L. casei, L. rhamnosus, S. thermophilus, L. acidophilus, L. bulgaricus, and B. infants, B. breve (1×10^{9} CFU per ml) with placebo. After 7days, there was a significant recovery rate in the synbiotic group [20]. 2. Baştürk et al. performed a clinical trial on 146 patients aged 4-18 years with the diagnosis of functional constipation based on the Rome III criteria. The first group received a sachet of synbiotic (Kidilact) /day. The second group received a sachet of placebo/day. After 4 weeks of intervention, a significant response rate ($p \leq 0.001$) was observed in all symptoms in the synbiotic group. Complete recovery was found in 48 (66.7%) in the synbiotic group versus 21 (28.3%) patients in the placebo group [17]. 3. Khodadad et al. studied 102 children aged 4-12 years with functional constipation according to Rome III criteria. They were randomly divided into three groups who received oral liquid paraffin plus placebo or oral liquid paraffin plus synbiotic or oral synbiotic plus placebo. The number of bowel movements increased in all three groups per week significantly ($P<0.001$). Other clinical symptoms of constipation decreased in all groups similarly and there was no difference between them statistically. They used a synbiotic (restore*$1x10^{9}$ CFU/1 sachet, Protexin Co, UK) containing probiotic strains of L.casei, L. rhamnosus, S. thermophilus, B. breve, L. acidophilus, B. infantis, and fructooligosaccharide as prebiotic[14]. 4. Hashemi et al. surveyed a study on 120 children aged 2-16 years with functional constipation (based on ROME III criteria). The children were randomly divided into three groups who received polyethylene glycol plus placebo or synbiotic plus placebo or polyethylene glycol plus synbiotic. They used a synbiotic Kidilact containing 10^{9} CFU/1 sachets, (colony forming units) of seven probiotics (L. casei, L.acidophilus, L. rhomnosus, L. bulgaricus, B. breve, B. infantis, and S. thermophilus) and one prebiotic (Fructooligosaccharide). The response rate was evaluated after 6 weeks. This study showed that the response rate was significant after interventions in all three groups but polyethylene glycol plus synbiotic showed the highest response rate after 6 weeks [21]. 5. Abediny et al. performed a study on 90 children aged 4-12 years with functional

constipation (Rome III) in 2013. The control group received Pidrolax powder and the intervention group received Pidrolax powder plus the synbiotic (Kidilact). Abdominal pain considerably was reduced after 2 and 4 weeks after intervention ($P < 0.05$). Their study showed that the addition of synbiotic to standard therapy was effective in the treatment of pediatric functional constipation [23].

The dose of probiotic and the type of oligosaccharide used in the studies of Khodadad et al, Bustarc et al., Hannah et al., Hashemi et al., Mahdavi et al., and Abedny et al. were similar to our study, while the probiotic strains and the age group of patients were different. On the other hand, all mentioned studies compared a synbiotic with placebo, while our study surveyed two different synbiotic that both of them had significant positive effects on infantile functional constipation who did not respond to non-pharmacological treatment (including reassurance, feeding training to gain optimal hydration of the infant, oral mineral oil and abdominal massage). The age of all previous study groups was > 6 months while the age group of our study was ≤ 6 months. In our study, both synbiotics improved significantly all symptoms of constipation in all types of feeding methods including breast-feeding, formula-feeding or breast-feeding plus formula-feeding after one week and one month of intervention. We found no side effects through the interventions in both groups of our study.

5.CONCLUSIONS

In general, the results of this clinical trial show that the use of both PediLact and BB-care synbiotics are effective in improving the clinical criteria of functional constipation in infants≤ 6 months after one week and one month of intervention apart from type of feeding method. Due to the greater effectiveness of BB-care in increasing stool frequency, B. lactis may play a more prominent role in this age group of patients.

LIMITATIONS

Similar studies are suggested to compare the synbiotics holding numerous probiotic types with synbiotics holding a similar single probiotic strain. Future studies with more participants in this age group are necessary too.

INNOVATIONS AND BREAKTHROUGHS

1.Administering and comparing two different synbiotics for the treatment of functional constipation .2. Studying the age group of under six months of age.3. The significant effectiveness of both synbiotics in the treatment of infantile functional constipation apart from type of feeding were the novelty of this study.

LIST OF ABBREVIATIONS

B. infantis: Bifidobacterium infantis; L. reuteri: Lactobacillus reuteri; L. rhamnosus: Lactobacillus rhamnosus, L. casei: Lactobacillus casei, B. Lactis BB-12: Bifidobacterium Lactis BB-12, FOS: fructooligosaccharides.

DATA AVAILABILITY

The details of data used to support the findings of this study are available from the corresponding author upon reasonable request.

CONFLICTS OF INTEREST

There was no favoritism in this research.

FUNDING STATEMENT

The authors declare that no grant was taken from financial institutions for performing this study.

AUTHORS' CONTRIBUTIONS

Concept - PAT; Design - PAT, NG, KE.; Supervision -PAT, KE. Resource – PAT; Materials - PAT, NG; Data Collection&/or Processing - PAT, NG; Analysis and/or Interpretation - PAT, NG; Literature Search - PAT, NG; Writing - PAT, NG; Critical Reviews - PAT.

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