http:// ijp.mums.ac.ir
Original Article (Pages: 5357-5367)

The Effect of Adding Synbiotics to Polyethylene Glycol in Childhood Functional Constipation: A Randomized Clinical Trial Study

M Mahdavi[1], *MR Esmaeili dooki[1], S Mehrabani[1], M Hajiahmadi[1], AA Moghadamnia[2], L Moslemi[1]

[1]Non-Communicable Pediatric Diseases Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, IR Iran.
[2]Department of Pharmacology, Faculty of Medicine, Babol University of Medical Sciences, Babol, IR Iran.

Abstract

Background
This study aimed to determine effects of synbiotics on treatment of functional constipation in children aged 2-10 years old.

Materials and Methods
This randomized single blind clinical trial study carried out on children who had functional constipation based on the Rome III criteria. The polyethylene glycol + synbiotic group (P+S group, n=38) received the synbiotic with polyethylene glycol 0.6 gr/kg daily for 4 weeks followed by tonly polyethylene glycol for the following four weeks. The polyethylene glycol group (P group n=41) received polyethylene glycol for eight weeks. Then 8 after treatment, frequency of defecation, stool consistency, pain during defecation, fecal constipation and the percentage of patients who needed to continue their drug after 12 weeks treatment were compared between two groups.

Results
The differences in the mean frequencies of defecation (P=0.36), stool consistency (P>0.05), pain during defecation (P>0.05), incontinence (P>0.05) between the two groups at the end of eight weeks were not significant (P>0.05). The end of 12 weeks, 27.8% of (P + S) group and 15.6% of (P) group needed to continue medication more than one time /week (P>0.05).

Conclusion
In this study, adding synbiotic to polyethylene was not more effective than only polyethylene in the treatment of childhood functional constipation.

Key Words: Childhood, Functional constipation, Polyethylene glycol, Synbiotic.

*Please cite this article as: Mahdavi M, Esmaeili dooki MR, Mehrabani S, Hajiahmadi M, Moghadamnia AA, Moslemi L. The Effect of Adding Synbiotics to Polyethylene Glycol in Childhood Functional Constipation: A Randomized Clinical Trial Study. Int J Pediatr 2017; 5(7): 5357-67. DOI: **10.22038/ijp.2017.23141.1990**

Corresponding Author:

Mohammd Reza Esmaeili dooki, MD, Non-Communicable Pediatric Diseases Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, IR Iran.

Email: esmaeilidooki@yahoo.com

Received date: Apr.13, 2017; Accepted date: Jun.22, 2017

1- INTRODUCTION

Functional constipation is a common disorder in children (1). It has a prevalence from 0.7 to 29.6% in various parts of the world (2). In Iran, the prevalence of functional constipation in school-age children is 21%, while the prevalence of fecal incontinence as a side effect of constipation is 27.5% (3, 4). According to the Rome III criteria, any definition of constipation depends on stool consistency, stool frequency, and the level of difficulty with defecation (5). Functional constipation involves continuous, hard, irregular, and incomplete defecation with no primary evidence of anatomic, endocrine, or metabolic causes (6).

The goal of treatment in pediatric constipation is to create a suitable model for soft defecation, with no pain and no fecal incontinence, and to prevent the recurrence of the disease (7). In order to achieve this goal, after providing relevant information to the patient and his/her parents, as well as following the disposal of fecal mass (if any) in the colon in order to prevent the re-accumulation of feces, various drug therapies are used in addition to a recommended diet and laxatives. The principle drugs used today in the treatment of children with functional constipation include polyethylene glycol (PEG), which is a colorless and odorless chemical compound (8, 9).

Yet, a high percentage of patients with functional constipation do not experience a good response to PEG or else, they experience side effects such as bloating, diarrhea, and abdominal pain (10). The intestinal microbiota in healthy subjects is different to that in patients with chronic constipation, who exhibit a disturbed intestinal microbial balance (i.e., dysbiosis) (11). Probiotics as small organisms treat different gastrointestinal diseases (12). They produce lactic acid, acetic acid, and other acids that reduce the colon PH. A low colon PH strengthens the peristalsis of the colon and thereby reduces the intestinal transit time, which in turn has a beneficial effect on the treatment of constipation (13, 14). Prebiotics are yeast components that change the composition or activity of the intestinal microflora, and they also have beneficial effects for the host (15). In addition, synbiotics, which are a mixture of probiotics and prebiotics, may also be useful in strengthening these effects. However, there exist conflicting reports regarding the therapeutic effects of probiotics and prebiotics on functional constipation (16).

Therefore, the current study was designed to assess the effects of the synbiotic in combination with polyethylene glycol in therapeutic regimens for children more than two years old with functional constipation.

2- MATERIALS AND METHODS

2-1. Allocation of patients

This study was a randomized single blind clinical trial that was approved by the ethics committee of Babol University of Medical Sciences (MUBABOL.REC.94.114) and parents of children signed an informed consent. The study was pre-registered in Iranian Registry of Clinical Trials (IRCT) website (IRCT ID: 2015072723363N1).

The study carried out on 79 children with functional constipation. The children were referred to Amirkola Children's Hospital (Babol, Mazandaran, Iran) from September 2015 to February 2016. By regarding the data derived from others paper and with the confidence of 95% and test power of 90%, 30 children were estimated as the sample size in each group. After obtaining informed consent from their parents, the children were assigned in two groups, using computerized random-number table, the polyethylene glycol + synbiotic (P+S)

group and the polyethylene glycol (P) group.

The inclusion criteria for the study were: aged between 2- and 10-year-old and diagnosed with functional constipation according to the Rome III criteria (7). A pediatric gastroenterologist assessed the children in relation to the inclusion criteria. The exclusion criteria for the study were: aged less than two-year-old or more than 10-year-old, where any organic causes of constipation such as neurologic, anatomic, allergic, metabolic and endocrine disorders, drug celiac disease and cystic fibrosis were present, taking other drugs that can cause diarrhea or constipation, and a history of using polyethylene glycol, probiotics, and/or prebiotics during the previous year, changing residence and drug intolerance.

Patients who suffered from other illnesses during treatment and who were forced to use drugs that had a profound impact on bowel movements (such as antibiotics and antihistamines) were also excluded from the present study (**Figure. 1**).

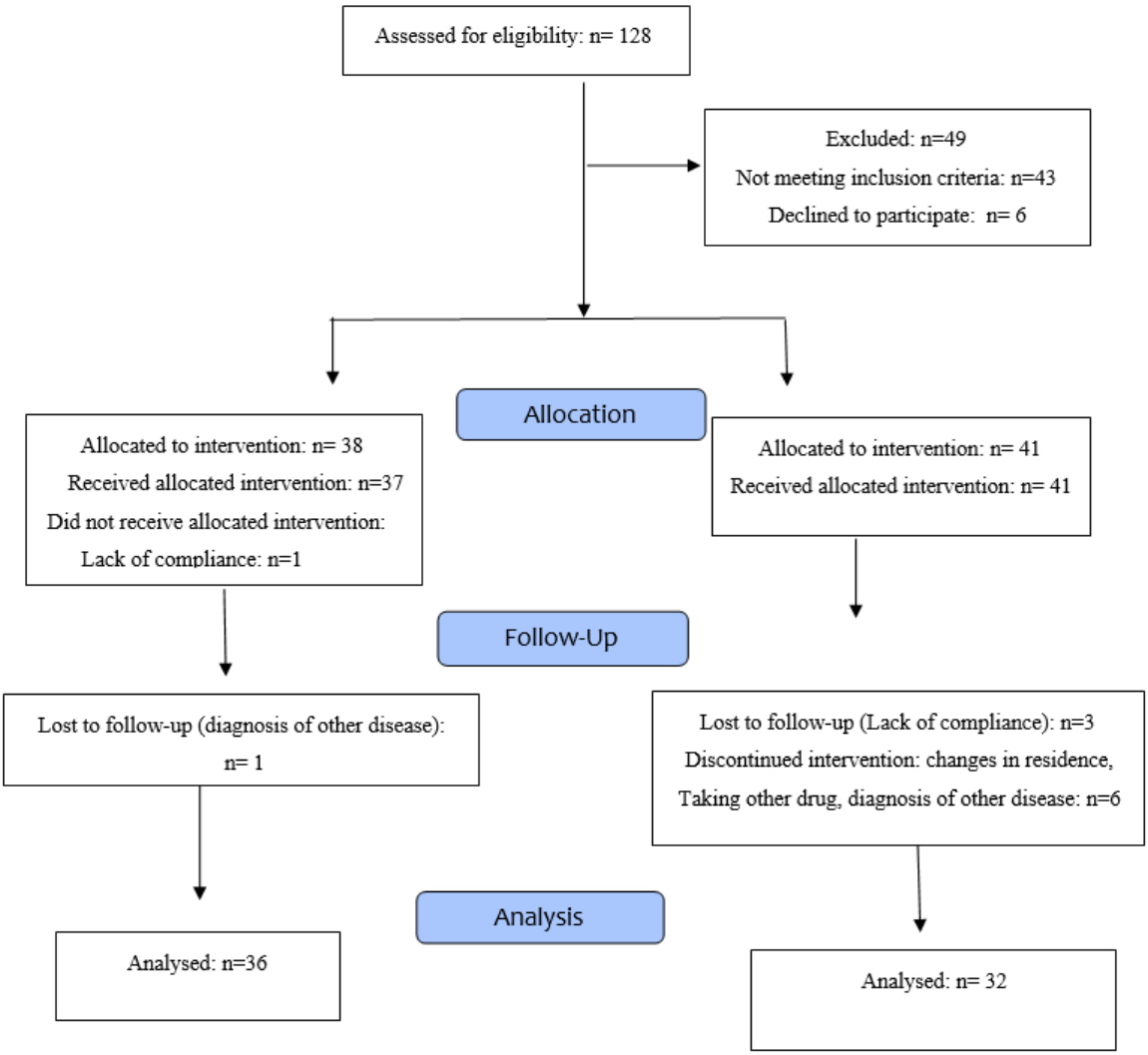

Fig1: Consort diagram

2-2. Intervention

For the first four weeks, 38 children from the P + S group received synbiotic (Kidilact, ZistTakhamir Company, Tehran, Iran) in combination with polyethylene glycol 4,000 (Pidrolax, Sepidaj Company, Karaj, Iran), before receiving solely PEG for the second four-week period. The Kidilact was in sachet form and it contained 10^9 CFU (colony forming units), seven probiotics (Lactobacillus casei, Lactobacillus acidophilus, Lactobacillus rhomnosus, Lactobacillus bulgaricus, Bifidobacterium breve, Bifidobacterium infantis, and Streptococcus thermophilus) and one prebiotic (Fructooligosaccharide). The second group, the P group, received polyethylene glycol alone for eight weeks. The daily dose of one sachet of Kidilact was dissolved in 100 ml of water or juice according to the child's preference and it was used immediately after preparation. The daily 0.6 gr/kg dose of polyethylene glycol was also dissolved in water or juice according to the child's preference.

2-3. Measurment of outcomes

The primary outcome of this study is a comparison of the number of bowel movements per week, incontinency per week, withholding per week, stool consistency, pain during defecation, acceptance of the drug, and the side effects between the two groups at the end of the fourth and eighth weeks. The secondary outcome is a comparison between the two groups of frequency of defecation, stool consistency and the need for the continued use of anti-constipation drugs for more than one time per week. All patients who were referred to Amirkola Children's Hospital due to functional constipation and who met the inclusion criteria had their demographic information as well as their average number of defecations, fecal incontinency, withholding, pain, and stool consistency over the last week recorded in a questionnaire. The parents of the patients were trained based on a visual analog scale (VAS) to assess their children's pain intensity and stool consistency (17-20). The pain-related scores ranged from (0) no pain to (100) maximum pain, while the scores for stool consistency ranged from (0) was soft and comfortable to (100) exhibited maximum rigidity (21). All patients were advised to change their laxative diet and to sit on the toilet 20–30 minutes after each meal for 5–10 minutes. If, at the start of the study, there was fecal impaction, it was resolved using mineral oil or a normal saline enema.

The effectiveness of the drug and drug tolerance were assessed via a questionnaire filled out by the patients' parents. The patients were followed for 12 weeks and three questionnaires were given to parents over this period. At the end of four and eight weeks of treatment, the patients were evaluated in terms of their response to treatment, while at the end of 12 weeks of treatment, they were evaluated in terms of frequency of defecation, stool consistency and the need to continue with the drug more than one time per week.

The patients' parents were asked to assess the following: the number of bowel movements per week, the number of incidents of fecal incontinency per week, withholding per week, stool consistency based on the VAS (from 0 = soft and comfortable to 100 = exhibited maximum stiffness), and pain during bowel movements based on the VAS (from 0 = no pain to 100 = maximum pain). They were asked to collect the relevant data on a weekly basis. The parents also were asked to record their children's acceptance and tolerance of the drugs, which were classified on a scale from one to seven: (1) receiving the medication easily and with passion, (2) taking the drug without resistance, (3) taking the drug with objections, (4) taking the drug after encouragement, (5) forced to take the drug, (6) not taking the drug even with force

(tolerates), and (7) definitely not taking the drug (vomiting) (21, 22). The parents were asked to visit or telephone the therapist if their children experienced any side effects, including abdominal pain, diarrhea, nausea, vomiting, and other skin symptoms. Any experienced side effects were also recorded in the questionnaire.

2-4. Statistical analysis

All analyzes were performed according to intention to treat (ITT) that all participants in the study were based on the group which have been attributed to it regardless of what happened later. Statistical analyses were performed using SPSS version 19.0 (SPSS Inc., Chicago, IL, United States) software and SAS ® version 9.1 (SAS Institute, Cary North Carolina). Continuous variables are presented as mean ± standard deviation (SD). Independent samples t-test was used to evaluate baseline differences in continuous variables between the two groups. To test within group changes from baseline to end of treatment, Paired t-tests was performed. The Wilcoxon signed ranks test or the Mann-Whitney test were used if non-parametric tests were required based on data distribution. Chi-square test or Fisher's exact test was performed to compare percentages. $P < 0.05$ was considered statistically significant for all analyses.

3- RESULTS

This study involved 79 children aged 2- to 10-year-old who had functional constipation. The patients were divided into two groups, with 38 patients in the synbiotic plus polyethylene glycol (S + P) group and 41 patients in the polyethylene glycol alone (P) group. Five patients at the end of eight weeks and five others at the end of 12 weeks were excluded from the study due to changing residence, the use of other medications, and being diagnosed with other diseases such as common colds. In addition, one patient was excluded due to drug intolerance. This means that 11 patients did not fully complete the study. The average age in the S + P group was 45.94±14.73 months, while in the P group it was 54.43± 27.29 months (P=0.59) (**Table.1**). Although the percentage of patients who needed to continue using their allocated drug after eight weeks and to 12 weeks was lower in the P + S group, the difference was not statistically significant (P=0.23) (**Table.2**).

The level of drug acceptance in two groups was also not significantly different (P=0.71). Five patients protested about taking the synbiotic, while two patients were forced to take it. One patient was not able to handle the synbiotic. In addition, seven patients took the Pidrolax after their parents forced them to. The side effects experienced were not significantly different between the two groups.

In the P + S group, two patients experienced abdominal pain, two patients had diarrhea, and one suffered from nausea. In the P group, one patient had diarrhea and two experienced abdominal pain. The symptoms of patients in each group at the end of four and eight weeks of treatment were compared with the respective group's baseline. Significant improvements in terms of all symptoms were seen (P-value in most cases is <0.001) (**Table.2**).

Table-1: Demographic information concerning the two groups

Variables	Group 1 (S + P)	Group 2 (P)	P-value
Number	38	41	
Age (months)	42	48	0.59
Weight (kg)	14.42	15.9	0.44
Height (cm)	98	100	0.46

BMI (kg/m²)		15.51	15.91	0.93
Gender	Female	18 (47.3%)	24 (58.5%)	0.22
	Male	20 (52.6%)	17 (41.4%)	
Duration from onset of disease to start of treatment (months)		17.10	23.34	0.14
Fecal impaction (%)		4 (10.5%)	3 (7.3%)	0.61
Blood in stool (%)		4 (10.5%)	3 (7.3%)	0.61

Table-2: Outcome measurements at baseline and after four, eight, and 12 weeks of treatment

Outcome measurement	PEG + Synbiotic	PEG	P-value
Baseline(N)	38	41	
At 4 weeks(N)	37	41	
At 8 weeks(N)	37	36	
At 12 weeks(N)	36	32	
Defecation/Week*			
Baseline	1.78	2.02	0.49
At 4 weeks	6.31	6.53	0.67
At 8 weeks	7.21	6.77	0.36
At 12 weeks	5.55	6.34	0.12
Consistency of stool (VAS)*			
Baseline	88.67	85.60	0.46
At 4 weeks	7.63	9.26	0.67
At 8 weeks	2.97	3.33	0.86
At 12 weeks	13.88	15.31	0.79
Severity of pain (VAS)*			
Baseline	88.15	85.12	0.50
At 4 weeks	4.73	6.58	0.58
At 8 weeks	3.51	3.33	0.93
At 12 weeks	13.48	15.45	0.81
Withholding/week*			
Baseline	0.97	0.73	0.27
At 4 weeks	0	0	0.99
At 8 weeks	0	0	0.99
At 12 weeks	0	0.02	0.13
Fecal incontinence/week*			
Baseline	2.57	1.19	0.06
At 4 weeks	0.289	0.02	0.005
At 8 weeks	0.02	0	0.32
At 12 week	0.11	0	0.22
Adverse effects (%)			
Baseline	–	–	–
At 4 weeks	5 (13.21%)	3(7.3%)	0.47
At 8 weeks	0	0	0.99
At 12 weeks	0	0	0.99
The need for Pidrolax at the end of 8 weeks (%)	6 (27.8%)	5(15.6%)	0.23

*Non-normally distributed data are shown as median.

4- DISCUSSION

This study involved an open, randomized clinical trial designed to compare the use of a mixture of probiotics and prebiotics (i.e., synbiotic) and polyethylene glycol and polyethylene glycol alone for the treatment of functional constipation. The performance and response to treatment between the two groups were compared based on the Rome III criteria and an intention-to-treat (ITT) analysis. There were no significant differences between the two groups for any of the criteria related to the primary study outcome, including number of bowel movements per week, drug acceptance rate, and side effects. The criteria related to the secondary outcome, including constipation recurrence and the need to continue taking medication at the end of eight weeks of treatment were not significantly different between the two groups. Lactobacillus is an important component of intestinal microflora that is frequently used in probiotics (23).

The abnormal flora of the gastrointestinal tract in children with constipation include high levels of clostridia and Escherichia coli that are rarely found in healthy children (11). It remains unclear whether this dysbiosis is a secondary consequence of functional constipation or a basic pathogenesis that is associated with functional constipation. The idea of using lactic acid-producing bacteria in the treatment of functional constipation stems from reports of dysbiosis in the flora of patients with functional constipation. It has been suggested that a low PH in the colon caused by probiotics may be associated with normal intestinal function (23). However, some studies have found that employing probiotics and prebiotics for the treatment of functional constipation has led to different results (16). In this study, less than one-third of patients required the continuation of treatment more than one time per week after eight weeks. In several studies concerning the treatment of pediatric functional constipation, at least half of all patients needed treatment for more than a year (6, 25). Sadeghzadeh et al. conducted a study involving 56 children (aged 4–12 years) with constipation who were randomly divided into two groups: one group received lactulose + Protexin, while the other group was given lactulose + a placebo every day for four weeks. The number of stool disposals, abdominal pain, incontinency, and weight gain were compared at baseline, after one week, and at the end of four weeks for both groups. In the fourth week, the number of bowel movements and stool consistency significantly improved in both groups. At the end of the first week, incontinency and abdominal pain were significantly improved in the intervention group. However, at the end of this study, the differences were not significant (P=0.161 and P=0. 125) and significant weight gain was seen at the end of the first week in the intervention group (26).

In a study conducted by Aleksandra et al., 84 children with functional constipation (aged 2–16 years) participated in a double-blind investigation. A group of 43 patients received 1 cc/kg of 70% lactulose with 10 grams of colony forming units Lactobacillus rhamnosus (LGG) daily. Another group of 41 patients received a placebo twice daily for 12 weeks. The success of the treatment for fecal incontinency was similar in both groups at the end of the 12^{th} week. The two groups were not significantly different at the end of weeks four, eight, and 12 in terms of incontinency, bowel movements, and side effects (23). The results of the present study are similar to those of the two abovementioned studies. In this study, we also observed that no serious complications caused the treatment to be stopped. Only one patient in the S + P group could not tolerate either of the two medications. In a double-blind study by

Ahmad Khodadad et al. conducted at the Children's Medical Center of Tehran on 102 children (aged 4-12 years) with functional constipation, the patients were divided into three groups: group A received liquid paraffin oil + a placebo daily, group B received one sachet of synbiotic + a placebo daily, and group C received 1.5 cc/kg liquid paraffin oil + a sachet of symbiotic per day. The frequency of bowel movements, stool consistency, stool frequency, abdominal pain, the painful bowel movements per week, success of treatment, and side effects in both groups before and after treatment were evaluated. The number of bowel movements per week increased in all groups (P>0.001), although there was a difference between the groups and the increase was higher in group C (P= 0.03). Stool consistency, the number of stool disposals, fecal incontinency, abdominal pain, and the number of painful stools per week decreased in all groups compared to the baseline. There were no significant differences between the groups. The success of treatment was similar in all the groups and there was no significant difference in this regard (P=0.6) (27). It should be noted, however, that the synbiotic used in this study was different to that used in our study.

In the present study, stool consistency, the number of stool disposals, and incontinency were significantly lower in the two groups after treatment than before the study began. However, no difference was observed between the two groups. In a study conducted by Houda-L-Noor et al. in Amsterdam on 20 children (aged 4–16 years) with functional constipation, the patients received 4×10^9 colony forming units once a day over a period of four weeks. The preliminary results included the measurement of bowel movements per week and stool consistency. The secondary outcomes included the frequency of fecal incontinency per week, abdominal pain, and side effects. Their study showed the positive impact of a mixture of probiotics on functional constipation (28). However, unlike the present study, their study did not involve a control group. In a study by Coccorulle Paola et al. involving 44 children with functional constipation, the patients were randomly divided into two groups. Group A received a probiotic supplement containing Lactobacillus reuteri DSM 17938 (L. reuteri), while group B received a placebo. The children who received the probiotic had significantly more bowel movements than the children who received the placebo, although the stool consistency between the two groups was not significantly different. The study showed that the L. reuteri probiotic had a positive effect on bowel movements in patients with chronic constipation, although it had no effect on stool consistency (29). The mean age of the patients was about eight months and hence they were infants. In our study, the children were older. In the group that received the synbiotic, the age mean was approximately 45 months. Their study was different from our study in terms of the findings concerning the frequency of bowel movements. Another difference concerns the fact that members of the first group were given a placebo. Both groups received polyethylene glycol, which can affect the results.

In a double-blind study by Koebnick et al., 70 randomly assigned patients received 65 mL of the Lactobacillus casei Shirota (LCS) probiotic, while another 70 received the same dose of a placebo. At the end of the first week, the group that received the probiotic exhibited a reduced severity of constipation and improved stool consistency (P<0.001). Further, the incidence of severe and very severe constipation was lower in the LCS group. At the end of the treatment period, 89% of the LCS group and 56% of the placebo group reported beneficial effects in terms

of the consistency of their stools and no side effects were seen in either group. However, it should be noted that this study was conducted on adults (30). Merit et al. conducted a study in Amsterdam on 159 children with constipation. They randomly assigned 79 children to a group that received milk containing Bifidobacterium lactis DN-173010, probiotic and 80 children to a group that received a placebo twice a day for three weeks. Eleven children did not return for follow up, so 74 children were studied in each group. The frequency of stools per week increased from the level before treatment in both groups. However, there was no significant difference in this increase between the probiotic group (2.9 ± 3.2) and the control group (2.6 ± 2.6). No side effects were observed (31). The reasons for the differences in terms of the treatment effects of the probiotics and prebiotics in these studies might be due to differences in the dose, the type of probiotics and prebiotics, the length of the treatment, and the differing ages of the patients. In our study, the number of children who needed to continue treatment after the end of eight weeks was lower in the synbiotic + polyethylene glycol group, although the difference was not significant. In both groups, more than two-third of patients with a dose reduction or the gradual discontinuation of the drug required the continuation of treatment at least once per week.

4-1. Limitations of the study

Self-reporting method to complete questionnaire was a potential limitation in this study. The lack of placebo in the polyethylene glycol group during the first 4 weeks intervention, was another limitation in this study.

5- CONCLUSION

Hence, based on the findings of this study, adding a synbiotic for one month at the beginning of the treatment period not only failed to result in a better treatment response but was also unable to prevent the early recurrence of constipation following the gradual discontinuation of polyethylene glycol. Then, it is suggested, further studies were designed with longer duration, and a combination of probiotics or prebiotics with different dose and type, as well as detecting normal stool flora in healthy children and children with functional constipation and then choosing the type of probiotic based on the stool flora, might help to improve the treatment efficacy.

6- CONFLICT OF INTEREST: None.

7- REFERENCES

1. Loening-Baucke V. Constipation in children. N Engl J Med 1998; 339(16):1155-6.

2. Mugie SM, Benninga MA, Di Lorenzo C. Epidemiology of constipation in children and adults: a systematic review. Best Pract Res Clin Gastroenterol 2011;25(1):3-18.

3. Esmaeili Dooki MR, Sorkhi H, Variji Z, Mirzapour M, Alizadeh-Navaei R, Hoseini SR, et al. Pediatrics Functional Constipation and school-Whether are linked? Caspian Journal of Pediatric. 2015;1(1):13-6.

4. Sohrabi S, Nouraie M, Khademi H, Baghizadeh S, Nasseri-Moghaddam S, Malekzadeh R. Epidemiology of uninvestigated gastrointestinal symptoms in adolescents: a population-based study applying the Rome II questionnaire. J Pediatr Gastroenterol Nutr 2010; 51(1):41-5.

5. Rasquin-Weber A, Hyman P, Cucchiara S, Fleisher D, Hyams J, Milla P, et al. Childhood functional gastrointestinal disorders. Gut. 1999;45(2):60-8.

6. Thompson WG, Longstreth G, Drossman D, Heaton K, Irvine E, Müller-Lissner S. Functional bowel disorders and functional abdominal pain. Gut. 1999;45(2):43-7.

7. van Ginkel R, Reitsma JB, Büller HA, Taminiau JA, Benninga MA. Childhood constipation: longitudinal follow-up beyond

puberty. Gastroenterology 2003;125(2):357-63.

8. North American Society for Paediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) Neurogastroenterology and Motility Committee. Polyethylene Glycole 3350 (PEG3350) Frequently Asked Questions. January 2015, Available at: http:naspghan. Inform 2.

9. Wang Y, Wang B, Jiang X, Jiang M, Xu C, Shao C, et al. Polyethylene glycol 4000 treatment for children with constipation: A randomized comparative multicenter study. Exp Ther Med. 2012; 3(5):853-6.

10. Pashankar DS, Loening-Baucke V, Bishop WP. Safety of polyethylene glycol 3350 for the treatment of chronic constipation in children. Arch Pediatr Adolesc Med. 2003;157(7):61-4.

11. Zoppi G, Cinquetti M, Luciano A, Benini A, Muner A, Minelli EB. The intestinal ecosystem in chronic functional constipation. Acta Paediatr. 1998;87(8):836-41.

12. Szymański H, Pejcz J, Jawień M, Chmielarczyk A, Strus M, Heczko P. Treatment of acute infectious diarrhoea in infants and children with a mixture of three Lactobacillus rhamnosus strains–a randomized, double-blind, placebo-controlled trial. Aliment Pharmacol Ther 2006;23(2):247-53.

13. Di Lorenzo C. Pediatric anorectal disorders. Gastroenterol Clin North Am 2001;30(1):269-87.

14. Agrawal A, Houghton LA, Morris J, Reilly B, Guyonnet D, Goupil Feuillerat N, et al. Clinical trial: the effects of a fermented milk product containing Bifidobacterium lactis DN-173 010 on abdominal distension and gastrointestinal transit in irritable bowel syndrome with constipation. Aliment Pharmacol Ther 2009;29(1):104-14.

15. Feigelson HS . Pediatric Gastrointestinal and liver Disease. Prebiotic, synbiotics, and fermented products. Philadelphia: Elsevier; 2006. pp. 177-91.

16. Tabbers M, DiLorenzo C, Berger M, Faure C, Langendam M, Nurko S, et al. Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN. J Pediatr Gastroenterol Nutr 2014;58(2):258-74.

17. Philip BK. Parametric statistics for evaluation of the visual analog scale. Anesthesia and Analgesia 1990;71(6):710.

18. Dexter F, Chestnut DH. Analysis of statistical tests to compare visual analog scale measurements among groups. The Journal of the American Society of Anesthesiologists 1995;82(4):896-902.

19. Todd KH. Clinical versus statistical significance in the assessment of pain relief. Annals of emergency medicine 1996;27(4):439-41.

20. Kelly A. The minimum clinically significant difference in visual analogue scale pain score does not differ with severity of pain. Emergency Medicine Journal 2001;18(3):205-7.

21. Mozaffarpur SA, Naseri M, Esmaeilidooki MR, Kamalinejad M, Bijani A. The effect of cassia fistula emulsion on pediatric functional constipation in comparison with mineral oil: a randomized, clinical trial. DARU Journal of Pharmaceutical Sciences 2012;20(1):1.

22. Esmaeilidooki MR, Mozaffarpur SA, Mirzapour M, Shirafkan H, Kamalinejad M, Bijani A. Comparison between the cassia Fistula's with Polyethylene Glycole (PEG4000) in the pediatric functional constipation: A randomized clinical trial. Iran Red Crescent Med J. 2016; 18(7): e33998.

23. Banaszkiewicz A, Szajewska H. Ineffectiveness of Lactobacillus GG as an adjunct to lactulose for the treatment of constipation in children: a double-blind, placebo-controlled randomized trial. J Pediatr 2005;146(3):364-9.

24. Salminen S, Salminen E. Lactulose, lactic acid bacteria, intestinal microecology and mucosal protection. Scand J Gastroenterol Suppl 1996; 222:45-8.

25. Wyllie R, Jeffery S, Kay M. PediatricGastrointestinal. 5thed.Philadelphia: Elsevier; 2016 .Vol 2. pp. 124-36

26. Sadeghzadeh M, Rabieefar A, Khoshnevisasl P, Mousavinasab N, Eftekhari K. The Effect of Probiotics on Childhood Constipation: A Randomized Controlled Double Blind Clinical Trial. Int J Pediatr 2014. Available at: http://dx.doi.org/10.1155/2014/937212

27. Khodadad A, Sabbaghian M. Role of synbiotics in the treatment of childhood constipation: a double-blind randomized placebo controlled trial. Iran J Pediatr 2010;20(4):387-92.

28. Noor-L-Houda B, Marloes B, Olivia L, Marc B. The role of a probiotics mixture in the treatment of childhood constipation: a pilot study. J Nutr. 2007.; 6(1): 17-23.

29. Coccorullo P, Strisciuglio C, Martinelli M, Miele E, Greco L, Staiano A. Lactobacillus reuteri (DSM 17938) in infants with functional chronic constipation: a double-blind, randomized, placebo-controlled study. J Pediatr 2010;157(4):598-602.

30. Koebnick C, Wagner I, Leitzmann P, Stern U, Zunft HF. Probiotic beverage containing Lactobacillus casei Shirota improves gastrointestinal symptoms in patients with chronic constipation-The aim of the present study was to investigate the effect of a. Can J Gastroenterol 2003;17(11):655-60.

31. Tabbers MM, Chmielewska A, Roseboom MG, Crastes N, Perrin C, Reitsma JB, et al. Fermented milk containing Bifidobacterium lactis DN-173 01 ،in childhood constipation: a randomized, double-blind, controlled trial. Pediatr 2011;127(6):e1392-e9.