

Effectiveness of synbiotics as laxative agent for constipation in children

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Abstract

Background Constipation in children can cause serious problems. Laxative is needed for the management of constipation. Oral laxative has been used frequently, even though a safe oral laxative agents for children is limited. Prebiotic and probiotic have already been proven to have laxative effect in constipation in children and adults. The effectiveness of these agents as a laxative has not been proven yet.

Objective To evaluate the effectiveness of laxative synbiotic in constipation in children compared to that of fiber foods.

Methods A randomized double blind controlled trial was conducted on children aged 6 months–14 years old who suffered from functional constipation at Dr. Sardjito Hospital, Dr. Soeradi Tirtonegoro Hospital, and Wates District Hospital from April 2007 – October 2007. Randomization was performed by computer. The outcome of recovery rate, onset therapy and side effects were evaluated after seven days of intervention.

Results Forty-three children were included in this study, but only 41 could be analyzed. Subject characteristics in both groups were comparable except for maternal educational level. The main outcome (recovery rate) was assessed by intention to treat principle. Compared with fiber foods, synbiotic increased the recovery rate with RR 2.14 (95%CI 1.14 ; 4.02) and NNT 2.9 (95%CI 2 ; 15), whereas its therapeutic onset was 15 hours faster than that of fiber foods. No important side effects were found in both groups.

Conclusions Synbiotic is safe and effective in increasing the recovery rate of functional constipation with faster therapeutic onset than that of fiber foods. [Paediatr Indones 2008;48:136-41].

Keywords: constipation, child, synbiotics, laxative agent

Constipation remains one of the main problems in Western Countries. It is estimated that the prevalence of constipation in children varies from 0.3% to 8%.¹ In children, functional constipation constitutes 97% of the cause of constipation, with equal distribution in both male and female.²

The causes of constipation can be categorized into two groups: organic and non-organic (functional).³ The management of constipation consists of three steps: 1) education, 2) feces secreting or disimpaction, and 3) maintenance. Steps two and three need oral or rectal laxative. The use of rectal laxative or enema gives a rapid effect but generates side effects such as poor psychological condition in children and trauma to the anus.⁴ The safest oral laxative is bulking and osmotic laxative. However, these kinds of oral laxatives cannot be given safely due to some serious side effects induced by the consumption of magnesium hydroxide. The suggested laxative agents that can be taken long term are lactulose and polyethylene glycol. Some studies in

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children and adults with constipation show that fiber in one's diet, classified as bulking laxative, can increase the frequency of defecation, although the result is not as good as osmotic laxative, such as magnesium, lactulose, or polyethylene glycol.^{2,5-7}

Fructooligosaccharide (FOS) and inulin are types of prebiotic that trigger the growth of intestine flora the most, especially bifidobacteria.^{8,9} Both prebiotic and probiotic have been proven to have laxative effects through the fermentation product produced in colon.^{8,10,11} Synbiotic as a mixture of prebiotic and probiotic is more effective since it contains prebiotic components which play a role as the food source for probiotic. Synbiotic can protect probiotic when it passes the digestive system, and it may help implantation and proliferation in colon.¹² Yet, a specific study on the effect of synbiotic laxative for pediatric constipation has not been conducted. This study aimed to evaluate the effectiveness of laxative synbiotic in pediatric constipation compared to that of fiber foods.

Methods

We conducted a randomized double blind controlled trial on children with constipation who visited Dr. Sardjito Hospital Yogyakarta, Dr. Soeradji Tirtonegoro Hospital Klaten, and Wates General Hospital from April 2007 to October 2007. We included children aged 6 months – 14 years with functional constipation who attended pediatric unit in one of the three hospitals by first getting informed consents from the parents. We excluded children who were (1) receiving other laxative agents, (2) having contraindication for oral intake.

Subject allocation was performed by simple randomization using computer in each hospital to either receive diet suggestion and synbiotic or placebo. Both treatments were placed into closed envelopes and given codes by appointed pharmacist. All envelopes were stored until the end of the trial.

The subjects involved in the study for a week and underwent both baseline and outcome examinations including history, physical examination, rectal *touchér* and diet counseling by nutritionist to their parents or guardians. The parents or guardians filled in a

questionnaire about types and amount of daily food and water consumption, dosage of medication for the treatment, response of therapy, and side effects that occurred. If disturbing side effects occurred or defecation had not happened within one week, the treatment was discontinued and fecal disimpaction with enema was given accordingly.

This study was approved by Research Ethics Board of Medicine and Health of Medical Faculty, Gadjah Mada University. The minimal number of subjects required with type I error of 5% and power 80% was 32 for each group.

The diagnosis of constipation was based on criteria of Rome II.¹³ Children were categorized as having functional constipation when no anatomical, endocrine, or metabolic disorders could be identified. Another criterion was when defecation less than three times a week or painful defecation and fecal retention despite three times or more defecation a week occurred in children of 4 years old or younger. For children more than four years of age, constipation was established when there were two of the following criteria: a) two or fewer bowel movements per week without laxatives; b) two or more soiling/encopresis episodes per week; c) a periodic passage of very large amount of stool once every 7-30 days; d) a palpable abdominal or rectal mass on physical examination.^{1,14}

Soiling was defined as the loss of loose stools in the underwear, or in other words stained the underwear, whereas encopresis was defined as the involuntary passage of a quantitatively normal bowel movement on the underwear.¹⁴

The treatment group received synbiotic containing 5 grams FOS and 1×10^9 CFU probiotic consisted of Lactobacillus (*L. acidophilus*, *L. casei*, *L. rhamnosus*, *L. bulgaricus*), Bifidobacterium (*Bif. infantis*, *Bif. breve*), and *Streptococcus thermophilus*. Placebo used was saccharin with the dose of 500 mg/day.

The amount of fiber foods suggested in nutritional counseling was based on the calculation of children's age (in year) plus 5 gram/day,^{15,16} which was then categorized into inadequate or adequate fiber. Recovery rate was reviewed within seven days based on the criteria of Rome II. The onset of therapy was measured in hour counted from the time the child received an intervention until the first defecation occurred. Defecation frequency was the number

of defecations in one week. Fecal consistency was considered hard when the children's feces was hard and followed by difficulty of defecation or pain while defecating. The assessment of medication compliance was based on the medication dosage taken through the questionnaire. Drug side effects included bloating, abdominal pain, or diarrhea.

Chi-squared test and student t-test were employed as appropriate. The effect of independent variables towards dependent variable was analyzed by using logistic regression analysis.¹⁷ We analyzed with intention to treat principle.

Results

Out of 43 children included in the study, two children (one in each group) dropped-out (4%) so there were only 22 children in the treatment group and 19 children in the placebo group. The basic characteristics of study subjects are presented in **Table 1**; it shows that the groups were

comparable except for maternal education, which was higher in the treatment group than that in the placebo group. The rate of recovery in the therapy group was higher than that of placebo group with RR 2.14 (95%CI 1.14; 4.02). The same result was obtained with intention to treat analysis (RR 2.06; 95% CI 1.10;3.86).

Logistic regression shows that maternal education was not a confounding factor (**Table 2**). Based on the results of this study, synbiotic recovery rate had the number needed to treat (NNT) of 2.9 (95%CI 2;15). The side effect that frequently occurred was bloating and the difference was not significant between the two groups (P=0.27). **Table 3** shows the changes of each constipation symptom based on Rome criteria as secondary outcome.

Synbiotic treated patients also showed significant changes in retention, pain when defecating, and fecal consistency. Furthermore, survival analysis indicates that patients in synbiotic treated group had their defecation 15 hours faster than those of patients in placebo group (P=0.008) (**Figure 1**). Fifty percents

Table 1. Basic characteristics of study subjects*

	Synbiotic n=22	Placebo n=19
Age, mean (SD) month	43.7 (40,2)	42.2 (16.60)
Last constipation duration, day (mean, SD)	2.4 (1.6)	2.4 (1.4)
Sex		
Male	11	10
Female	11	9
Father's education		
< Senior High School	5	8
> Senior High School	17	11
Mother's education		
< Senior High School	3	9
≥ Senior High School	19	10
Duration of constipation		
< 3 months	4	3
> 3 months	18	16
Fiber Diet		
Inadequate	21	15
Adequate	1	4
Drug consumption compliance		
Good	21	19
Bad	1	0
Liquid intake		
Inadequate	4	6
Adequate	18	13
Type of treatment		
Outpatient	19	18
Inpatient	3	1

* All subjects received suggestion to give more fiber

of children in synbiotic group has already defecated in 10 hours, while in placebo group in 25 hours.

Discussion

Prebiotic and probiotic have laxative effect through their bulking effect (bacterial mass) and product of fermentation, such as short chain fatty acid, lactic acid and hydrogen. Both of these effects can cause softening of the stool and an increasing colon transit. This study showed that synbiotic play a role as a laxative agent in children with functional constipation with a recovery rate of seven days with RR 2.14 (95% CI 1.14;4.02) and NNT 2.9 (95% CI 2;15). A seven-day evaluation was used as the bifidogenic, and the effect of synbiotic could be seen on the eight day with significant numbers of bifidobacteria and fecal consistency changes.^{18,19}

Constipation symptoms using Rome II criteria were analyzed as secondary outcome since we did not find references that used these variables to evaluate the recovery rate of constipation by giving synbiotic. We found that synbiotic could reduce constipation symptoms significantly, such as retention, pain on defecation, and hard fecal consistency.

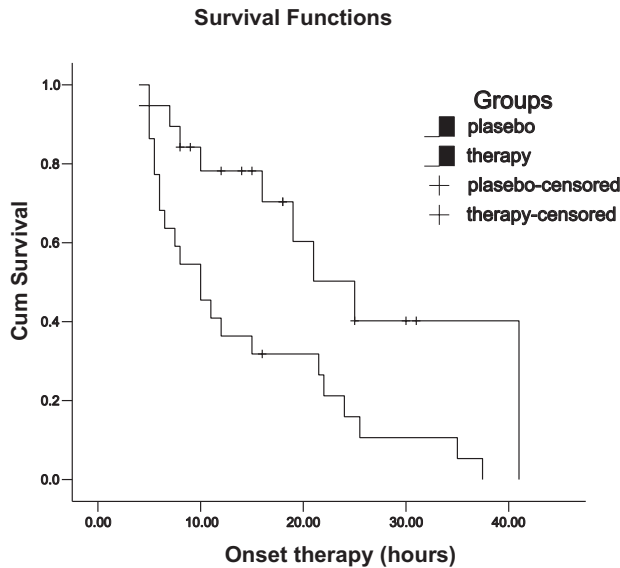


Figure 1. Survival analysis of therapy onset of synbiotic compared to placebo. Log Rank (Mantel-Cox) = 7.102; P=0.008.

Table 2. Double logistic regression of recovery rate with group 1 and group 2

Variable	Group 1		Group 2	
	OR (95% CI)	P	OR (95% CI)	P
Treatment group control = 0 experimental = 1	23.3 (2.6;210.4)	0.005	30.2 (2.97;307.9)	0.004
Mother's education ≥ Senior High School = 0 < Senior High School = 1	-	-	0.5 (0.08;2.96)	0.44

Mother's education did not influence the recovery rate of constipation treated by synbiotic.

Table 3. Number of patients experiencing constipation symptom changes¹

	Synbiotic	Placebo	x2 / t tests	P	RR (95% CI)
Defecation frequency, (mean, SD) / week	2.8 (2.3)	1.7 (0.8)	4.14	0.052	-
Stool retention	22	9	15.3	< 0.01	0.29 (0.16;0.50)
Soiling	0	2	2.43	0.21	2.29 (0.16;0.50)
Encopresis	2	3	0.43	0.43	1.35 (0.60;3.02)
Painful defecation	17	5	3.93	0.048	0.52 (0.27;0.98)
Large amount of stool once every 7 – 30 days	8	5	0.48	0.36	0.77 (0.35;1.68)
Fecal consistency	19	9	7.16	0.009	0.42 (0.23;0.77)

¹All subjects receive suggestion to give more fiber.

Synbiotic caused significant changes in retention, painful defecation and fecal consistency.

As for synbiotic influencing on other constipation symptoms still could not be proven yet due to the short time of observation.

Factors such as food fiber intake, amount of liquid consumed daily, and type of treatment did not influence the recovery rate in both groups. FOS in synbiotic had a role towards the recovery effect as it protects probiotic against digestion enzymes so that it reaches the colon in adequate amount.¹² The dosage of FOS 5 g/day had been proven in its bifidogenic effect¹⁸ and it could be given even though the children were less than one year old.¹⁹⁻²² This is because FOS is actually present in mother's breast milk, as many as 10 g/l and has been proven to give bifidogenic effect without side effects to babies.²³

We used synbiotic containing more than one species of probiotic to increase the laxative effect. Until recently, there has been no study comparing the number of probiotic strains that can give the best laxative effect. The number of live bacteria experiencing colonization in colon depended on dosage, stomach pH and previous colon macrobiotic composition.²⁴ This study used a quite large dose of probiotic and it was given along with prebiotic so that it received protection from prebiotic while passing the gastrointestinal tract. However, previous influence of gastric acidity and the composition of microbiotic could not be analyzed due to difficult examination.

The result of this study was not the same as the one conducted by Bruno,²⁵ which could not prove the effect of synbiotic on stool frequency and fecal characteristic change. This difference might be due to the fact that their subjects were healthy children, small size of sample in each treatment (n=10), the use of synbiotic with small probiotic dosage (475 mg/day), and the use of only one probiotic species (*Bifidobacterium longum*).

This study found that median therapy onset in children receiving synbiotic was faster than that in children receiving food fiber (P=0.008). If compared with a study on FOS by Garleb,²⁶ synbiotic therapy onset took relatively longer. This might be due to the fact that the methods used by Garleb's was in vitro.

Hydrogen resulted in side effects such as cramping, bloating, flatulent, and diarrhea. The side effect that came up in this study was bloating, which was not significantly different in both groups. It was

in line with a study by Bouhnik¹⁸ who found that bloating could insignificantly occur in the use of FOS up to 20 gram/day. This dosage only gave flatulence as a significant side effect.

The weakness of this study lied on the inclusion criteria. This study used clinical criteria to exclude organic constipation because of the study limitations in using the suggested diagnostic test. This study did not limit foods containing prebiotic since a lot of foods contain this substance so that it was difficult to control. However, due to its small composition in daily food (0.2-1%), its effects as confounder could be ignored.

The actual number of subjects included in this study was smaller than the previously planned. However, this study had succeeded in showing a significant recovery rate of constipation by the use of synbiotic compared to that of food fiber.

We conclude that in children with functional constipation, synbiotic is more effective than fiber food without significant side effects. Further studies on synbiotic in a longer term is needed to prove its effectiveness in managing pediatric functional constipation.

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