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Effect of Fructooligosaccharides on Constipation in Pediatric Patients

ผลของฟรักโทโอลิโกซาคคาไรด์ต่อภาวะท้องผูกในผู้ป่วยเด็ก

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The objective of this study was to compare the efficacy of fructooligosaccharide (FOS) with milk of magnesia (MOM) in treating children with chronic constipation. The study enrolled 54 children with chronic constipation at Gastroenterology Clinic, Queen Sirikit National Institute of Child Health. The subjects were assigned randomly to receive either 5 g/day of FOS (n=25) or 1.2-2.4 g/day of MOM (n=29) for 6 weeks. The efficacy of the laxatives was evaluated by improvement of the symptoms which can be observed by the pattern of defecation (frequency, stool consistency and symptoms during defecation). Drug safety was evaluated by observing adverse effects. Dietary pattern and nutritional status assessment were also included in the study.

The constipation symptoms improved significantly both in FOS and MOM group, both after 2 weeks and after 6 weeks of the treatment. Compared with the baseline, stool frequency and consistency improved significantly ($p<0.001$). No straining, anal pain or blood-streaked stool was observed. The efficacy of FOS and MOM in treatment of constipation were not significantly different ($p=0.361$). Neither MOM nor FOS interfered with growth status of the subjects. Adverse effects of FOS were abdominal pain, flatulence, flatus, and nausea. The results of this study suggested that FOS could be alternative choice for treating chronic constipation in pediatric patients.

Keywords: Fructooligosaccharides, milk of magnesia, chronic pediatric constipation.

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** สถาบันสุขภาพเด็กแห่งชาติมหาราชินี

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การศึกษานี้มีวัตถุประสงค์เพื่อศึกษาประสิทธิผลของฟรักโทโอลิโกซาคคาไรด์ในผู้ป่วยเด็กท้องผูกเรื้อรัง เปรียบเทียบกับการรักษาด้วยมิลค์ออฟแมกนีเซีย (milk of magnesia) ซึ่งทำการศึกษาแบบทดลองในผู้ป่วยเด็กท้องผูกเรื้อรังจำนวน 54 ราย ที่คลินิกโรคทางเดินอาหาร สถาบันสุขภาพเด็กแห่งชาติมหาราชินี แบ่งผู้ป่วยเป็น 2 กลุ่ม คือ กลุ่มที่ได้รับการรักษาด้วยมิลค์ออฟแมกนีเซีย (25 ราย) ปริมาณ 1.2-2.4 กรัมต่อวัน และกลุ่มที่ได้รับการรักษาด้วยฟรักโทโอลิโกซาคคาไรด์ (29 ราย) ปริมาณ 5 กรัมต่อวัน เป็นระยะเวลา 6 สัปดาห์ ตัวชี้วัดประสิทธิผลของการรักษาได้แก่ รูปแบบการถ่ายอุจจาระ (ความถี่ ลักษณะ และอาการของการขับถ่ายอุจจาระ) และอาการข้างเคียงที่เกิดขึ้นในแต่ละวัน ตลอดระยะเวลาการศึกษา นอกจากนี้ กลุ่มตัวอย่างได้รับการประเมินรูปแบบการรับประทานอาหาร และภาวะโภชนาการด้วย

หลังจากการได้รับการรักษา 2 และ 6 สัปดาห์ พบว่า ภาวะท้องผูกดีขึ้นทั้งสองกลุ่ม คือ จำนวนครั้งในการถ่ายอุจจาระต่อสัปดาห์เพิ่มขึ้น ลักษณะอุจจาระนิ่มขึ้น ไม่มีการเบ่งถ่ายอุจจาระ รวมทั้งไม่พบการเจ็บปวดและอุจจาระมีเลือดปนขณะถ่ายอุจจาระ เมื่อเปรียบเทียบกับก่อนรักษาอย่างมีนัยสำคัญ ($p< 0.001$) โดยที่ประสิทธิผลของการรักษาด้วยฟรักโทโอลิโกซาคคาไรด์ต่อภาวะท้องผูกไม่แตกต่างกับการรักษาด้วยมิลค์ออฟแมกนีเซีย ($p=0.361$) นอกจากนี้ การรักษาด้วยฟรักโทโอลิโกซาคคาไรด์และมิลค์ออฟแมกนีเซียไม่มีผลรบกวนการเจริญเติบโตของกลุ่มตัวอย่าง สำหรับอาการข้างเคียงจากการรับประทานฟรักโทโอลิโกซาคคาไรด์ ได้แก่ ปวดท้อง ท้องอืด ผายลม และคลื่นไส้ ซึ่งอาการที่เกิดขึ้นนี้ไม่รุนแรง จากผลการศึกษาแสดงให้เห็นว่าฟรักโทโอลิโกซาคคาไรด์ สามารถเป็นอีกทางเลือกหนึ่งในการรักษาผู้ป่วยเด็กท้องผูกเรื้อรัง

คำสำคัญ : ฟรักโทโอลิโกซาคคาไรด์ มิลค์ออฟแมกนีเซีย ผู้ป่วยเด็กท้องผูกเรื้อรัง

Introduction

Constipation is a common problem in general population affecting both adults and children. Approximately 3 percent of general pediatric outpatient visits and 25 percent of pediatric gastroenterology consultations are related to difficulties with defecation[1-3] The causes are varied with age. Approximately 90-95 percent of constipation in children is idiopathic.[4] Most constipated patients had insufficient intakes of dietary fiber and water, poor bowel habit or stool withholding.[5-7]

The treatment program consists of clearing any existing impaction, preventing re-impaction, and establishing a regular bowel habit. After the initial bowel cleanout, increase in dietary fiber and fluid intakes, toilet training and long-term daily laxative therapy are started.[8] Laxative therapy such as mineral oil (lubricant laxative), magnesium hydroxide

(milk of magnesia; MOM) and lactulose are commonly used in children.[9] Caution must be applied when MOM is used in infants because it may induce magnesium poisoning.[10] Fructoligosaccharides (FOS) are prebiotic, non-digestible carbohydrates completely fermented in the colon. They can increase fecal weight, decrease intestinal transit time, increase water holding capacity of stool and fecal weight adsorption in feces, like osmotic laxatives. They also benefit the host by selectively stimulate the growth and activity of the resident microflora.[11,12] Some studies showed that FOS led to improvement of constipation in adult patients.[13,14]

However, there is still no study on FOS treatment in children aged between 4-12 years old with chronic constipation. While different laxatives are available, there are few published studies conducted in children that compare different laxatives regarding their efficacy or safety. Therefore, this study was designed to compare the efficacy of FOS versus MOM which are laxatives that are commonly used in children.

Method

Subjects. Pediatric patients attended at the Pediatric Gastroenterology Outpatient Clinic at Queen Sirikit National Institute of Child Health for the first time with the problem of constipation were recruited in this study. The patients were eligible for the study if they were between 4 and 12 years and had a presence of constipation by duration of more than 3 months with or without fecal incontinence. Constipation was defined as having at least two symptoms of the following Rome III criteria[15]: frequency of bowel movement is less than 3 stools/week; having more than 1 episode of fecal incontinence/week; history of retentive posturing (withholding behavior); feeling pain or hard bowel movements; presence of large fecal mass; passing of large diameter stools that may obstructed the toilet. Also, they must not receive any constipation-induced medicines and were not treated with other laxatives during 2 weeks before participating in the study. Children with organic causes of defecation disorders were excluded from this study. These causes included chronic intestinal pseudo-obstruction, Hirschsprung's disease, previous surgery involving the colon or anus, thyroid function disorder, seizure, gastrointestinal diseases, and dysfunctions of liver, pancreas and spleen.

The study protocol was approved by the Institute Ethics Committee of the Queen Sirikit National Institute of Child Health, Bangkok. Written informed consent was obtained from all parents and from children aged above 7 years old.

The number of patients enrolled in this study was calculated as followed:

$$n = \frac{Z^2pq}{d^2}$$

While n = number of sample

Z = 1.96 (α = 0.05)

p = proportion of MOM treatment were improved in pediatric constipation from Loening-Baucke et al (2006)[16] were 0.55

q = 1-p

d = standard error from p = ±0.20

The number of pediatric patient in this study was

$$n = \frac{(1.96)^2(0.55)(0.45)}{(0.2)^2} = 23.76 \approx 24$$

Add 10 percent drop out

n = 24+ (24*0.10) = 26.40 ≈ 27

Experimental Procedure. All parents were received questionnaire containing items describing children's bowel habits. The pattern of defecation included age at the time of development of constipation, presence of retentive behavior, frequency of defecation per week, presence of fecal continence/week, size and consistency of stools defecated into toilet, passage of bowel movements that obstructed the toilet, presence of abdominal pain, urinary incontinence during the day or night, and presence of blood in stool. The nutrition status of each subject was also assessed. Such data as the subject's weight, height and dietary intake pattern (24-hour recall) were collected.

The subjects then were assigned to receive either 5 g/day of FOS or 1.2-2.4 g/day of MOM for 6 weeks. However, the laxative dosage was adjusted if necessary. One normal saline enema daily for three days was given to the subject who was impacted for clearing any rectal fecal remains. All subjects returned to the clinic twice during the study, at 2 weeks, at 6 weeks after the treatment began. At each follow-up visit, each subject was assessed for the nutritional status, pattern of defecation (stool consistency, defecation per week, symptoms during defecation), and adverse effects of the laxatives. The subject's compliance was assessed by counting the amount of returned laxatives.

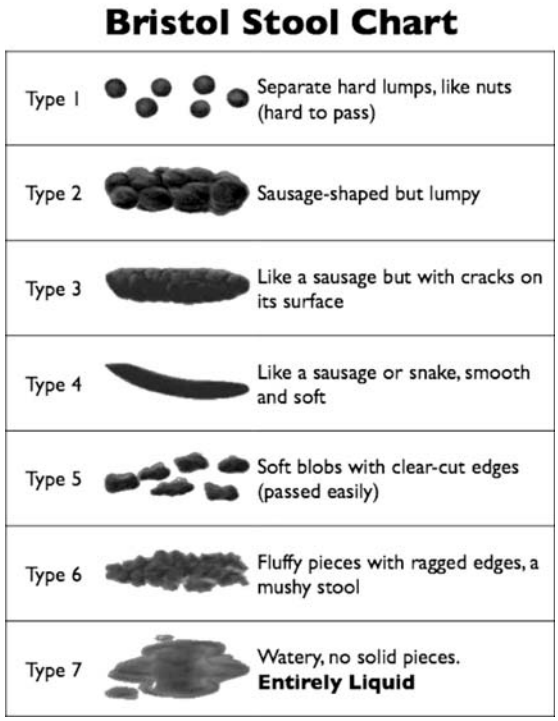

Fig 1: The Bristol Stool Form Scale[17]

Outcomes. The outcomes of this study were the improvement in frequency of

defecation and stool consistency, and overall treatment success at six weeks. An increase in frequency of defecation to three or more per week was considered improved. The stool consistency was interpreted using Bristol Stool Form Scale (Figure 1)[17]. The ideal stools are types 3 and 4 (especially type 4). The stool consistency was considered to have improved if it was described as type 4 (4 points or approximately) and abdominal pain, pain at anus or other symptoms of constipation were not found.

Statistical Analyses. Comparisons of outcome variables were made between the initial and follow-up data within and between groups. Statistical analyses included determination of means and standard deviation, independent t-test, repeated measure ANOVA and chi-square test, with significance accepted at the 5 percent level. Results was expressed as mean ± SD or percentage.

Results

Characteristics of the Subjects. A total of 63 patients were enrolled in this study and were assigned to one of the two groups. Nine subjects were either lost to follow-up or failed to complete the study, leaving 54 subjects who participated in the study throughout 6 weeks. Twenty-five subjects (16 males and 9 females) and 29 subjects (18 males and 11 females) were treated by FOS and MOM respectively. The demographic data of the subjects are summarized in Table 1. Following the inclusion criteria, all subjects had defecation less than 3 times per week and most of them had feces described as separated hard lumps like nut, and pain on defecation. The baseline characteristics of the two groups were not significantly different ($p>0.07$).

Pattern of Defecation. The key variables in this study were changes in defecation pattern after the treatment, including the frequency of defecation and stool consistency.

Frequency of Defecation. The frequency of defecation in the FOS and MOM groups increased after the interventions. After two weeks, the frequency of defecation increased significantly ($p<0.001$) form baseline. Similarly, after six weeks, it also increased significantly ($p=0.001$) from week 2. However, there was no difference between the FOS and MOM groups either at baseline, after 2 weeks or 6 weeks of treatment (Table 2).

Stool Consistency. Before the intervention, the stools of all subjects looked lumpy and hard (type 1 and 2). The stools looked smoother and softer (type 4-6) both after 2 weeks and at the end of the treatment (Table 2).

Nutritional Status and Dietary Pattern. There were no significant differences in weight, height, and BMI between the FOS and MOM groups. The growth charts showed normal growth status in both groups (data were not

Table 1 Baseline characteristics of the subjects

Characteristics	FOS Group (n = 25)	MOM Group (n = 29)	p-value*
Males, n (percent)	16 (64)	18 (62)	0.884
Age, mean ± SD (years)	6.68 ± 2.50	6.21 ± 2.37	0.755
Normal nutritional status, n (percent)	24 (96)	27 (93)	0.643
Dietary pattern intake, n (percent)			
1-2 times/week of vegetable intake	21 (84)	28 (97)	0.113
< 4 glasses per day of water intake	21 (84)	28 (97)	0.113
Carbonated beverage intake	19 (76)	22 (76)	0.991
Soft drink intake	18 (72)	21 (72)	0.973
Fruit juice intake	13 (52)	21 (72)	0.121
Snack intake	22 (88)	28 (97)	0.121
No exercise, n (percent)	22 (88)	23 (79)	0.411
Frequency of defecation, mean ± SD (times/week)	1.36 ± 0.49	1.28 ± 0.45	0.208
Stool consistency scales, mean ± SD	1.80 ± 0.58	1.55 ± 0.69	0.073
Symptoms of constipation, n (percent)			
- Presence of straining during defecation	19 (76)	26 (90)	0.534
- Presence of pain at anus during defecation	18 (72)	21 (72)	0.807

*p-value from student t-test for variables age, frequency of defecation and stool consistency score and symptoms of constipation ; p-value from chi-square test for variables sex, dietary pattern

shown). Dietary patterns of the subjects in both groups before the intervention were not significantly different. After the intervention, the amount of protein and fat intakes in the MOM group significantly increased. The increase in the proportion of dietary fiber intake was observed in both groups (data were not shown).

Adverse Effects. No serious adverse effects were observed during 8 weeks of the study. However, 10 subjects (18.52 percent), 6 in FOS group (24.0 percent) and 4 in MOM group (13.79 percent), reported adverse effects such as abdominal pain, decrease appetite, diarrhea, flatulence, nausea, flatus, and vomiting.

Discussion

In this study, most of the pediatric constipated patients were school-age children, of which the average age was 6 years old. The proportion of boys and girls was approximately 2:1. This was consistent with the studies by Lorenzo[18] and Abi-Hanna and Lake[19] that childhood constipation in school-age probably occurred in boys more than girls. Causes of constipation in school-age children included inadequate fluid intake and/or consumption of diet lacking of fiber, because most of them often consumed carbonated beverages, soft

Table 2 The pattern of defecation of the subjects

Outcome Variables	FOS Group (n=25)	MOM Group (n=29)
Frequency of defecation		
Baseline	1.36 ± 0.49	1.28 ± 0.45
After 2 weeks	4.03 ± 1.34[a]	4.34 ± 1.25[a]
After 6 weeks	5.14 ± 1.24[a,b]	5.87 ± 1.11[a,b]
Stool consistency		
Baseline (cases) (percent)		
Type 1	24 (96.0)	29 (100)
Type 2	1 (4.0)	-
Type 3	-	-
Type 4	-	-
Type 5, 6, 7	-	-
After 2 weeks (cases) (percent)		
Type 1	-	-
Type 2	-	-
Type 3	2 (8.0)	1 (3.5)
Type 4	12 (48.0)	12 (41.4)
Type 5,6,7	11 (44.0)	16 (55.1)
After 6 weeks (cases) (percent)		
Type 1	-	-
Type 2	-	-
Type 3	-	-
Type 4	18 (72.0)	18 (62.1)
Type 5, 6, 7	(28.0) 11	(37.9)

The frequency of defecation on baseline, after 2 weeks and after 6 weeks were analyses by ANOVA statistics. Between duration of intervention was using Post Hoc analysis: least significant difference (LSD).

[a]Different from baseline with $p<0.05$

[b]Different from 2-week treatment period with $p<0.05$

drinks, fruit juices, and snacks. Their physical inactivities may be related to reduced colonic motility.[20] These causative factors were also found in this study.

FOS treatment increased the frequency of defecations from 1 to 4 times/week at the end of second week and to 5 times/week at the end of sixth week. The stool consistency was less likely to be described as "hard", and more likely to be described as "*soft*" or "*loose*". However, the stool consistency was almost likely a sausage or snake, smooth and soft when they were treated using FOS. This was consistent with other clinical trials. Kleessen et al[21] studied in constipated elderly patients who received 20-40 g/day of FOS for 19 days.

The result showed an increase in frequency of defecation and softer stool consistency. Chen et al[14] studied in constipated elderly patients receiving 10 g/day of FOS for 30 days. It was found that their stool outputs increased significantly. In case of infants, addition of 1.5-3 g/day of FOS led to an increase in stool outputs and softer stools.[22-24] Furthermore, the subjects in this study who received FOS could pass the stool easily without abdominal pain, pain at anus, or blood-streaked stool. Their incomplete feeling during defecation and frequency of withholding were reduced. These results showed that FOS supplementation could improve the symptoms of constipation.

This study found that MOM and FOS has similar efficacy in treatment constipation in pediatric patients. The adherence of each treatment was not different. Several researches had studied about efficacy of other prebiotic (lactulose) or various laxatives in pediatric constipation. One study compared efficacy of polyethylene glycol (PEG) 3350 with lactulose. No differences in stool frequency and consistency were found between the two laxatives, but PEG 3350 could significantly reduced the total colonic transit time.[25] When the treatment was extended to 8 weeks, it was found that PEG 3350 was more effective than lactulose.[26]

The adverse effects of FOS observed in this study included abdominal pain, flatulence, decrease appetite, diarrhea, nausea, flatus, and vomiting that were similar to MOM treatment. All of these effects were also found in the study of Carabin and Flamm.[27] Nonetheless, these adverse effects were common but partly depend on the dosage of FOS.[21]

However, the effective treatment of chronic constipation includes not only using laxatives but also behavioral modification (dietary advice, toilet training, and increased intake of fluids). In this study, the subjects and their parents also received advices about dietary intake and behavioral modification. A proper dietary pattern includes increasing fluid and dietary fiber intakes to meet the recommended amounts for children older than 2 years (age plus 5 g/day).[28,29] These advices may help to relieve constipation and consequently promote food intake since decreased appetite was frequently found in constipated patients. This study showed increases in intake of total energy, protein, fat, carbohydrate, dietary fiber, and fluids in all subjects. In addition, the amounts of dietary fiber intake in all subjects were in the recommended range, and no difference was found between the FOS and MOM groups.

The subjects in both groups increased in weight and height along their growth curve. Most constipated children often have decreased appetite from vague chronic abdominal pain. The weight loss may be found in these patients[4] but did not interfere with their development.[30]

Conclusion

Results of the study showed that both FOS and MOM were effective and safe in the treatment of children with constipation. Therefore, FOS may be used as alternative treatment for constipation. However, the dosage of FOS may be adjusted according to tolerance of each patient. In addition, good eating habit and various food intake are important for children with constipation problem.

Limitation

The number of participants was calculated by using standard error (d) of 20%, so the sample size was too small. In addition, FOS powder supply was sufficient for approximately 30 patients and the study had limitation of reward budget. However, the duration of research was limited from the Ethics Committee of the Queen Sirikit National Institute of Child Health.

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