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ORIGINAL ARTICLE

Red Sugar versus Polyethylene Glycol 3350 in Pediatric Functional Constipation: A randomized and Active-Controlled Trial

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KEYWORDS

Microbial Contamination; Chemical Contamination; Confectionery Products; Cream-Filled Pastry; Iran

ABSTRACT: Functional constipation is a prevalent problem in children. This study was designed to compare the efficacy and safety of molasses with polyethylene glycol (PEG) in childhood constipation. This randomized single-center trial was conducted in Amir Al-Momenin Hospital, Semnan, Iran. 110 constipated children aged from 2 to 8 years were randomly assigned to 2 g kg^{-1} PEG or 2 ccs/kg molasses. Children were treated for 1 month, and frequency of defecation, frequency of encopresis, abdominal pain, appetite, fecaloma, and pain at defecation were compared. The safety of both treatments was also studied. After 1 month of treatment, both drugs had an equal effect on the frequency of defecation and the frequency of encopresis per week ($P < 0.05$). Both drugs were effective in relieving defecation pain to some extent. Molasses had a better effect on appetite status ($P < 0.05$). Molasses caused a lower rate of side effects; diarrhea ($P < 0.01$), nausea ($P < 0.05$), and vomit. Our study showed that red sugar was as effective as PEG 3350 for treating childhood functional constipation.

INTRODUCTION

Functional constipation is a common digestive issue in children [1]. Functional constipation is defined as a delay or difficulty in defecation lasting for more than two weeks. Concurrent problems like hypothyroidism, celiac, neuropathic and myopathicintestinal, and pseudo–obstruction may be existing in some patients [2, 3]. Abdominal pain, perianal inflammation, rectal bleeding, and weight loss are important complications of functional constipation [4]. Constipated children are treated by laxatives, polyethylene glycol, and mineral oil. Polyethylene glycol (PEG) as an osmotic drug is able to increase water content of stool and hence make it soft. PEG is helpful for painful defecation in a constipated child. Bloating, diarrhea, and nausea are usual side effects of PEG[5, 6]. Rarely, it may cause colonic ulcerations [7-9]. At present, PEG is widely used for treating pediatric constipation with moderate efficacy. Several investigations have shown superiority of PEG to lactulose [10-12]. During recent years, herbal medicines have gained prominence in treating

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many disorders. Most of them are categorized as traditional medicines. One of such compounds with evidenced efficacy in constipation is red sugar (molasses) obtained from sugarcane. Molasses is discussed in Avicenna's Canon of Medicine and its laxative effects have been evidenced in Canon of Medicine [13]. Our previous study provided evidence for red sugar role in pediatric constipation [14]. In addition, laxative effects of red sugar (molasses) have been discussed elsewhere [15, 16]. Molasses can increase the motility of the intestinal tract and through a partial inhibition of water absorption can improve the constipation. Till now, limited randomized trials have been performed to test new medications in pediatric constipation. This was our goal. In the current study, we aimed at comparing efficacy of red sugar with PEG 3350 in treating childhood constipation.

MATERIALS AND METHODS

Study design

This single center, randomized, open-label, parallel-group, and active-controlled study was conducted in Amir Al-Momenin Hospital, Semnan, Iran. Simple randomization method was used. Children aged 2 to 8 years with functional constipation were included in the study. Functional constipation was defined as less than 3bowel movements per week; encopresis more than once a week; large amounts of stool every 7–30 days, passing of stools so large that they obstructed the toilet, and retentive posturing, and palpable abdominal or rectal mass. Exclusion criteria were cases with nonfunctional constipation, hypothyroidism, history of colon chronic intestinal pseudo-obstruction, previous surgery of the colon oranus, and Hirschsprung's disease. Patients were discontinued from the study for these reasons: safety, lost to follow-up, and voluntary discontinuation.

Treatment phase

A simple evaluation form was designed to record number of defecations, consistency and size of stool, abdominal pain, abdominal or rectal mass, fecal incontinence, appetite status, and use of drugs. These forms were filled out by parents and were returned to us at each visit. Clinic visit was done at 15, and 30 days after initiation of treatment. If not possible, it was done by telephone. Prior to trial, children were evaluated for number of defecations, consistency and size of stool, abdominal pain, abdominal or rectal mass and then were received enema to clear any remaining stools. One hundred and seventeen participants were randomized 1:1 to oral solution PEG3350 2 g $kg^{-1}day^{-1}$ or oral solution of red sugar 2 cc/kg/day for 1 month [14].

Efficacy assessment

The primary outcome was treatment success which was defined as three or more bowel movements per week, and 2 episodes of encopresis per month. Abdominal pain, appetite, compliance with drugs, and untoward effects of the drugs were the secondary outcomes. Efficacy was evaluated every week by blinded pediatricians. In cases with diarrhea, dose of both drugs had a 50% decrease. In cases without improvement, dose of both drugs had a 50% increase. Follow up was done until 4 weeks after termination of the treatment by telephone.

Safety assessment

For assessment of adverse effects of the drugs, patients were monitored for diarrhea, nausea, and rash, and fever every week at clinic visits or by telephone. Parents were asked to report any severe adverse events during the treatment.

Data analysis

The total number of 125 patients was calculated for randomization according to the assumption of 10% dropout in number of the study patients with an 80% power at an alpha level of 0.05. A sample size of 110 patients was considered. Student t test, x^2 test and non-parametric tests were used to study differences between groups. $P<0.05$ was

considered as statistical significance. Analysis was carried out using SPSS software version 18.0, Chicago, USA.

RESULTS

Baseline characteristics

Of the 125 patients who were included 8 patients did not enter the randomized treatment. A total of 117 patients were studied between September 2015 and February 2017. Seven patients were lost to follow up and 110 patients were analyzed. Figure 1 shows patients flow through. Baseline characteristics of study subjects are presented in Table 1. The mean age was 3 years with an excess of girls (51.9%vs 48.1%). No significant differences were noted in the demographic data at baseline.

Table 1. Baseline characteristics of the patients.

Characteristics	Red sugar	PEG 3350
Age (years)	3.1 ± 1.5	2.9 ± 1.1
Age range (years)	2-8	2-8
Male (number)	24 (43.6)	29 (52.7)
Fecaloma	9 (16.3)	7 (12.7)
Pain during defecation	31 (56.3)	34 (61.8)
Loss of appetite	50 (90.9)	45 (81.8)
Fecal impaction	19 (34.5)	22 (40)
Abdominal pain	28 (50.9)	24 (43.6)

Data are shown in mean ± SD or number (percent)

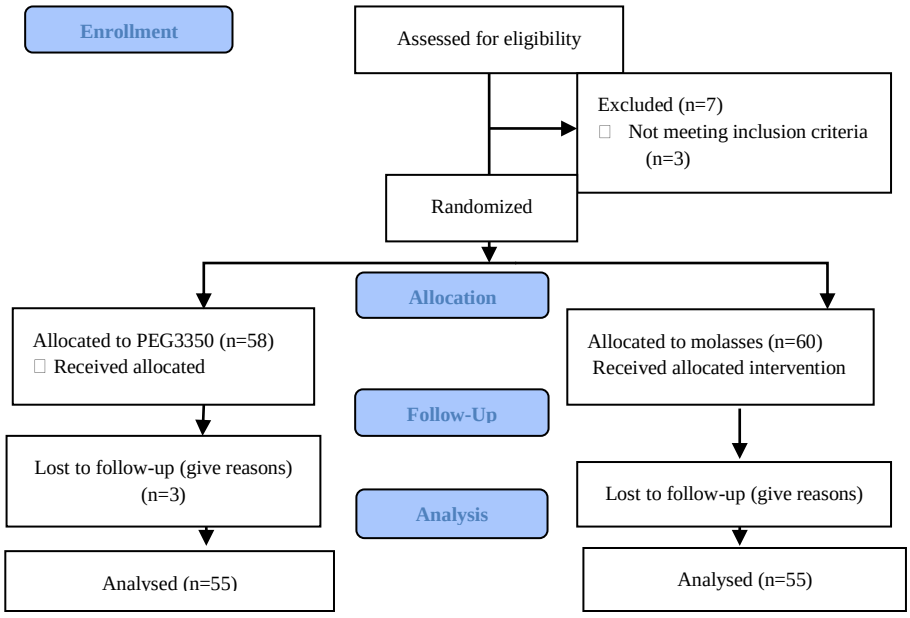

Figure 1. Consort diagram detailing the study subjects.

Efficacy

Changes in frequency of defecation and frequency of encopresis after 1 month of therapy and 1 month of follow up are presented in Table 2. Both treatments had cause significant increase in weekly frequency of defecation (P <

0.05). In addition, both treatments could significantly reduce frequency of encopresis per week compared to baseline values (P < 0.05). 50 % of children in red sugar treatment group and 45% of children PEG treatment group, had lost their appetite to varying degrees. Both drugs were effective to stimulate appetite; however children treated by molasses, showed better improvement in appetites compared to PEG after 1 month of treatment (P < 0.05). About 11% of patients treated by PEG showed watery stool. This effect was not seen in molasses group (P < 0.05). Moreover, no case of fecaloma was seen in both treatment groups. Compared to baseline values, both drugs could significantly reduce abdominal pain (P < 0.01).

Table 2. Improvement in frequency of defecation (per week) and frequency of encopresis (per week) following the treatments

	Frequency of defecation		Frequency of encopresis	
	Red sugar	**PEG 3350**	**Red sugar**	**PEG 3350**
Baseline	3.5 ± 3.9	3.9 ± 3.2	10.1 ± 4.0	11.2 ± 3.0
30 days	8.6 ± 2.4	9.1 ± 3.2	3.9 ± 5.0	3.4 ± 2.1
60 days	8.8 ± 3.4	8.9 ± 2.7	3.5 ± 2.1	3.7 ± 3.3

Data are shown in Mean ± SD. *All parameters had significant improvement compared to baseline values (P < 0.05).

Rate of response

From total of 110 subjects who received treatments, 8 (7%) patients were not responsive to the PEG therapy and 9 (8.1%) patients did not respond to the molasses treatment.

Safety

After 1 month of treatment, no serious side effect was observed in both groups. As shown in Figure 2, diarrhea was the most common side effect. However, rate of diarrhea was higher with PEG than with molasses (P < 0.01).In addition, patients treated by PEG, showed higher rate of nausea compared to molasses (P < 0.05). No patient was withdrawn due to severe adverse effects in either group.

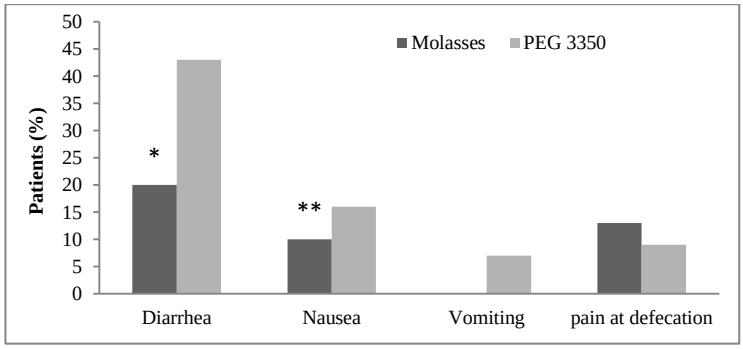

Figure 2. Side effects after 4 weeks of treatment in the molasses group and the PEG 3350 group; * P <0.01, **P < 0.05

DISCUSSION

To our knowledge, the present study is the first to compare efficacy and safety of red sugar (molasses) with PEG3350 in pediatric constipation. Our results show that molasses is as effective as PEG in treating pediatric constipation. Both drugs caused an increase in number of defecation, reduced fetal incontinence, improved stool consistency, increased appetite, and relieved defecation pain without occurrence of fecaloma. Taken together, both treatments had similar effects. PEG is moderately effective in childhood constipation. Although functional constipation is very common, there is still lack of evidence supporting benefits of different treatments. PEG, lactulose, milk of magnesia, and paraffin are the only medicines that have been clinically tested and practiced till now [17]. Calcium, magnesium, manganese, potassium,

copper, iron, B vitamins and phenolic compounds are present in molasses obtained from *SACCHARUMOFFICINARUM*L [18]. Recent works have provided evidence for milk and molasses enema in child hood constipation with acceptable outcomes[19, 20]. It is likely that red sugar has osmotic effect and can increase bowel motions without overt adverse effect. Efficacy of PEG in functional constipation is well studied. Voskuijl's work showed superiority of PEG 3350 to lactulose in a total of 91 children with functional constipation for 8 weeks of treatment. Bad palatability was more common in children treated by PEG in that work. In line with our findings, diarrhea, and nausea were other side effects of PEG therapy[11]. Another study by Rafati showed that PEG 3350was as effective as liquid paraffin with better safety profile[21]. It was demonstrated by Dupont's investigation that PEG has similar or greater efficacy than lactulose for childhood constipation[10]. In accordance with previous studies, PEG therapy was not associated with serious adverse effects. Diarrhea is usually the most common reported side effect of PEG. We found that children with soft stool had higher chance for diarrhea after receiving PEG. Of note, children on molasses had better appetite status which is of clinical importance especially in children with weight problems. Because of its sweet taste, children and their parents had no complain about red sugar; however, some children complained about taste of PEG.

CONCLUSIONS

Conclusion: Our study showed that red sugar was as effective as PEG 3350 for treating childhood functional constipation.

Study limitation

The present study has a number of limitations that should be acknowledged. Due to limited number of patients, our findings can be confirmed in larger studies. Long-term follow up of patients should be done to investigate safety and efficacy of two treatments.

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ETHICAL CONSIDERATION

The project was approved by local Ethics Committee and informed consent letters were taken from parent(s) or legal representatives. The clinical trial registry number of this study was IRCT2015061722794N1.

Conflict of Interest

The authors declare not having any personal or financial support or involvement with organizations with financial interest in the subject matter or any actual or potential conflict of interest.

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