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Original Article

Selenium and functional constipation in children

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Abstract

Background Constipation is a common problem in children, with approximately 90 to 95% of constipation cases having functional constipation. Oxidative stress may be a causative factor in gastrointestinal diseases, alleved by intervention with antioxidants. Selenium is an essential trace element and acts as a cofactor of gluthathione peroxidase, which protects membranes from oxidative damage.

Objective To determine the effect of selenium on functional constipation in children.

Methods We conducted a single-blind, randomized clinical trial from November to December 2012 at the Al-Kautsar Al-Akbar Islamic Boarding School in Medan, North Sumatra. Subjects were children aged 12 to 17 years with functional constipation, diagnosed according to the ROME III criteria. Patients were randomly allocated into either the selenium group (n=57) or the placebo group (n=57). Subjects were clinically evaluated for frequency of defecation, stool consistency, severity of abdominal pain, and side effects during the 2 weeks of treatment (days 7 and 14) and 1 week after treatment had stopped (day 21).

Results A total of 114 subjects were eligible to participate. The average frequency of defecation observed on day 14 was 1.5 (SD 0.75) days per defecation (P=0.0001) in the selenium group and 2.4 (0.84) days per defecation in the placebo group, a statistically significant difference (P=0.0001). There was no significant difference in frequency of defecation on the 7th day of treatment. But after day 7, there were significant differences between the groups at days 14 and 21. Normal stool consistency was found in 45 subjects (78.9%) on day 7 and in 57 subjects (100%) on day 14 of treatment in the selenium group, significantly more than those in the placebo group (P<0.05). In placebo group, normal stool consistency was found in 27 subject (47.4%) with (P=0.001) on day 7 and in 38 subject (66.7%) on day 14 of treatment (P=0.0001). On day 14, the selenium group had significantly more subjects without pain than the placebo group [47 subjects (82.5%) *vs.* 10 subjects (17.5%), respectively (P=0.0001)]. Severity of abdominal pain after 14th day of treatment is without pain 47 subject (82.5%) and mild pain 10 subject (17.5%) (P=0.0001). We found no side effects of selenium treatment in our subjects.

Conclusion Selenium is effective in improving clinically functional constipation, in terms of increased frequency of defecation, normalization of stool consistency, and less severe abdominal pain. **[Paediatr Indones. 2016;56:111-17.]**

Keywords: *childhood functional constipation, antioxidant, selenium, defecation frequency*

In the last 15 years, the concept of free radical-mediated oxidative stress (OS) has gained tremendous scientific momentum, from studying its role in the pathophysiology of disease to its therapeutic implications. Almost all gastrointestinal (GI) diseases have been evaluated for underlying OS as a causative factor and intervention with antioxidants have been attempted. The GI tract is bombarded with diets accompanied by free radicals, pro-oxidants, and various xenobiotics that are metabolized mainly in the liver and in smaller quantities at other sites of the GI tract.[1] A balance between pro-oxidants and antioxidants is critical to the body's defensive mechanisms and benefits from aerobic gut organisms.

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Imbalances leading to more pro-oxidants may result in a destructive process called oxidative stress.[2]

A randomized, controlled clinical study in China reported a relationship between chronic constipation and potential oxidative stress in children.[3,4] Constipation is a common problem accounting for 3% of all pediatrician visits and 10-15% of children treated by pediatric gastroenterologists have chronic constipation. Most (90-95%) constipation in children over the age of 1 year is functional constipation, with only 5-10% having an organic cause or abnormal pathology.[5]

Since the recognition of selenium (Se) as an essential micronutrient in animals in 1957, there has been an increasing interest in this trace element.[6] Traces of dietary selenium prevented liver necrosis in rats fed with a diet deficient in vitamin E.[7] Most organ systems in the body require selenium. Selenium is best known for its role as a cofactor of glutathione peroxidase, which protects membranes from oxidative damage. Selenium deficiency exposes most tissues to peroxidative damage.[8] A meta-analysis study in China in 2012 found that supplementation with organic selenium increased glutathione peroxidase activity in adults.[9] The purpose of this study was to assess the effect of selenium on clinical improvement of functional constipation in children.

Methods

We conducted a single-blind, randomized clinical trial from November to December 2012 at the Al-Kautsar Al-Akbar Boarding School in Medan, North Sumatra Province. Children aged 12-17 years, who met the diagnosis of functional constipation according to the ROME III criteria,[10] and had no organic abnormalities were included. We excluded children who used several types of drugs (antacid, anticolinergic, anticonvulsan, antidepresan, diuretic, iron preparation, muscle relaxant, narcotics and psycotropic drugs) or laxatives within the 3 days prior to the start of the study. All subjects' parents provided informed consent. This study was approved by the Research Ethics Committee of the Faculty of Medicine, University of Sumatra Utara.

Children who met the inclusion criteria underwent initial data collection on aspects of functional constipation including frequency of defecation, stool consistency, and abdominal pain severity. Subjects were randomized into either the treatment group (n = 57) that received selenium or the control group (n = 57) that received placebo. The treatment group received 40 micrograms selenium per day for those aged 11-14 years, and 50 micrograms per day for those aged 15-17 years, given once per day after breakfast for two weeks. The control group was similarly given one capsule daily after breakfast for two weeks. Patients did not know the identity of the supplements that they were given.

Monitoring was done on days 7, 14 and 21 to assess the frequency of defecation, abdominal pain severity, and stool consistency. Stool consistency was evaluated using the Bristol Stool Scale and classified as hard (types 1-2), normal (types 3-6), or liquid (type 7). Abdominal pain experienced by patients with constipation was assessed by the Wong-Baker FACES pain scale assessment, namely: no pain (scale 0), mild pain (scales 1-3), moderate pain (scales 4-6), or severe pain (scales 7-10).

Data processing was done using the *SPSS version 15.0* software, with a significance level of $P<0.05$. Mann-Whitney test was used to assess the relationship between frequency of defecation and selenium, while the nominal Chi-square test was used to assess stool consistency and abdominal pain.

Results

Of 530 students examined, 124 had functional constipation, and 4 of these refused to participate in the study. The remaining 120 were included in the study. Simple randomization with closed envelopes was used to divide subjects into two groups. Initially, the selenium group had 61 subjects and the placebo group had 59 subjects, but during the study, 6 children did not continue, so the two groups had 57 subjects each.

Table 1 shows the mean age in both groups was 13.5 years, with a majority of females (50.9% in the selenium group and 66.7% in the placebo group). The nutritional status categories of the selenium and placebo groups were normoweight (73.7% *vs.* 78.9%, respectively), overweight (17.5% *vs.* 14%, respectively), and obese (7% *vs.* 3.5%, respectively).

The Mann Whitney test revealed significantly

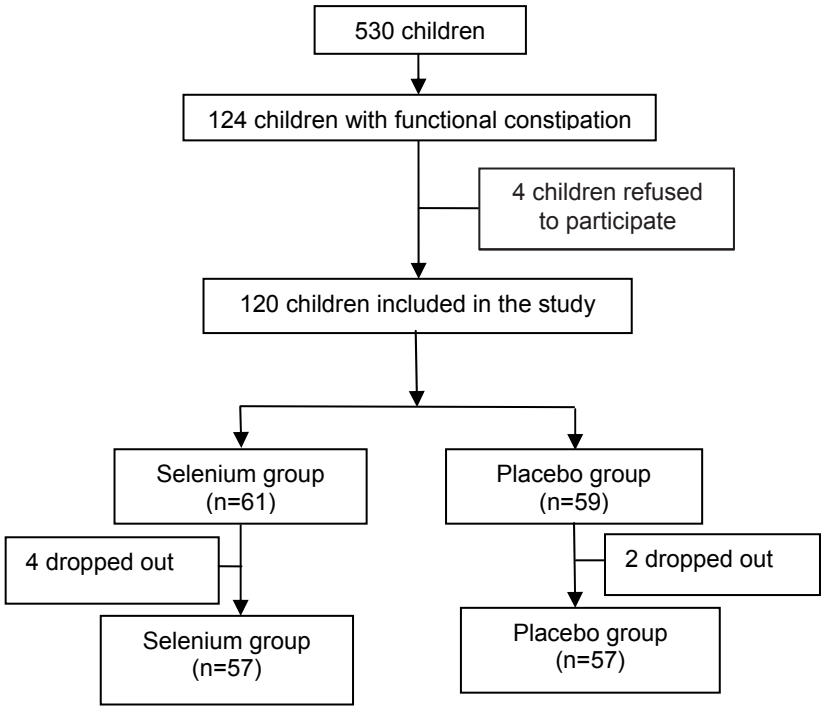

Figure 1. Study profile

Table 1. Basic characteristics of subjects

Characteristics	Selenium group (n = 57)	Placebo group (n = 57)
Gender, n (%)		
Male	28 (49.1)	19 (33.3)
Female	29 (50.9)	38 (66.7)
Mean age (SD), years	13.5 (1.41)	13.5 (1.45)
Mean body weight (SD), kg	46.5 (8.15)	44.6 (7.17)
Mean body height (SD), cm	153.3 (6.55)	152.3 (6.23)
Nutritional status		
Mild malnutrition	1 (1.8)	2 (3.3)
Normoweight	42 (73.7)	45 (78.9)
Overweight	10 (17.5)	8 (14.0)
Obese	4 (7.0)	2 (3.5)

more frequent defecation in the selenium group than in the placebo group after treatment at days 14 and 21 ($P<0.05$) (**Table 2**). However, there was no significant difference in frequency of defecation between groups at day 7.

The Chi-square test revealed significant differences in stool consistency between the two groups on days 7, 14, and 21 ($P<0.05$) (**Table 3**). The selenium group had significantly less hard stool consistency than did the placebo group.

Chi-square test revealed significantly less severe abdominal pain in the selenium group than in the

Table 2. Mean frequency of defecation in the selenium and placebo groups

Mean frequency of defecation (SD)	Selenium group (n=57)	Placebo group (n=57)	P value
Day 7, days/defecation	3 (0.77)	3.1 (0.99)	0.609
Day 14, days/defecation	1.5 (0.75)	2.4 (0.84)	0.0001
Day 21, days/defecation	1.6 (0.593)	2.1 (0.63)	0.0001

placebo group on days 7, 14, and 21 ($P < 0.05$) (**Table 4**). We found no side effects of selenium treatment in our subjects.

Table 3. Stool consistency in the selenium and placebo groups

Stool consistency	Selenium group (n=57)	Placebo group (n=57)	P value
Day 7, n (%)			
Hard	12 (21.1)	30 (52.6)	0.001
Normal	45 (78.9)	27 (47.4)	
Day 14, n (%)			
Hard	0	19 (33.3)	0.0001
Normal	57 (100)	38 (66.7)	
Day 21, n (%)			
Hard	5 (8.8)	32 (56.1)	0.0001
Normal	52 (91.2)	25 (43.9)	

Table 4. Abdominal pain severity in the selenium and placebo groups

Abdominal pain	Selenium group (n=57)	Placebo group (n=57)	P value
Day 7, n (%)			
Scale 0	14 (24.6)	9 (15.8)	0.013
Scale 1-2	33 (57.9)	28 (49.1)	
Scale 3-4	7 (12.3)	20 (35.1)	
Scale 5-6	3 (5.3)	0	
Day 14, n (%)			
Scale 0	47 (82.5)	10 (17.5)	0.0001
Scale 1-2	10 (17.5)	33 (57.9)	
Scale 3-4	0	13 (22.8)	
Scale 5-6	0	1 (1.8)	
Day 21, n (%)			
Scale 0	44 (77.2)	11 (19.3)	0.0001
Scale 1-2	12 (21.1)	36 (63.2)	
Scale 3-4	1 (1.8)	10 (17.5)	
Scale 5-6	0	0	

Discussion

Constipation is a common problem, accounting for 3% of pediatric clinic visits and up to 25% of pediatric gastroenterologist visits.[11] In two recent community-based studies using similar criteria, 5 and 18% of children were thought to be constipated.[11,12] Moreover, about one-third of these children continued to have constipation into adulthood, despite treatment and follow-up.[11] A 2013 systematic review of 19 prospective studies on the epidemiology of functional constipation in children around the world stated that prevalence ranged from 0.7 to 29.6%.[13] The negative effects of functional constipation on social function include school performance, sports and other activities, as well as general behavior that can affect quality of life.[11] Generally, constipation is found in approximately 16-37% of school-aged children and in about 4% of preschoolers. Up to 90-95% of the condition is considered to be functional constipation in children over the age of 1 year, with only 5-10% of constipation caused by organic abnormalities.[5] A retrospective study in 2007 reported the prevalence of constipation in children aged 4 to 17 years to be 22.6%.[14] A community-based study in 2008 found that the prevalence of constipation for children under 4 years of age was 28.8%.[15] In addition, a longitudinal study in 2003 reported that 18% of children aged 9 to 11 years suffered from constipation.[11]

We found the prevalence of constipation in the Al-Kautsar Al-Akbar Boarding School subjects to be

23.3% (124 students who met the ROME III criteria from a total of 530 students). The mean age of students with functional constipation was 13.5 years in both groups. We included children aged 11 to 17 years as the study subjects, based on the high prevalence of functional constipation in school-aged children, and being in the age group with low prevalences of organic causes and pathological disorders. Furthermore, this age group may experience an even greater negative impact on their school achievement and quality of life due to constipation.

In our study, more female students (58.7%) had functional constipation than male students (41.2%). Other epidemiological studies have shown no differences in prevalence of constipation between boys and girls, in contrast to the adult literature in which the prevalence was found to be higher in women.[13,16,17] Furthermore, a systematic review concluded that female gender is a risk factor for constipation, in which women had the condition 3 times more than men.[18]

Nutritional status in the selenium and placebo groups were as follows: 73.7% *vs.* 78.9% normoweight, respectively; 17.5% *vs.* 14% overweight, respectively; and 7% *vs.* 3.5% obese, respectively. Less physically active individuals tend to experience more constipation.[13] A retrospective study found that constipated children tended to weigh more, but the group of children with higher body weight and constipation was significantly more male-dominated.[19] A retrospective study reported that in constipated children, 22% were obese, while in the control group, only 11% were obese.[14] Fishman *et al*. found 23% of children with obesity suffered from constipation. The etiology of constipation in obese children is unclear, but hormonal changes or hyperglycemia may play an important role.[20]

Treatment of functional constipation includes fecal evacuation in the event of scybala, maintenance therapy in the form of medication, behavior modification, parental education, and follow-up consultation.[5,21,22] If treatment with behavior modification (such as toilet training and physical activity) shows no change in two weeks, medical treatment (laxative such as lactulose, polyethylene glycol, bisacodyl, etc) can be given immediately. The goal of treatment is to soften the stool consistency, so as to facilitate defecation. Treatment is given for 2 weeks, followed by a reassessment. If constipation persists for more than 2 months of regular treatment, the dose may be reduced if the frequency of defecation is found to be more than 3 times per week and no symptoms of constipation are found.[23]

This study suggests that selenium therapy is effective in improving functional constipation, in terms of the frequency of defecation, stool consistency, and severity of abdominal pain. The age-appropriate dose of selenium according to the RDA in 2000,[24,25] is 40 ug per day for children aged 11-14 years and 50 ug per day for children aged 15-17 years. After 14 days of treatment, the mean frequency of defecation was significantly higher in the selenium group than in the placebo group (1.54 *vs.* 2.46 days/defecation, respectively). Also, after 14 days of treatment, significantly more subjects in the selenium group had normal stool consistency than in the placebo group (100% *vs.* 66.7%, respectively).

Two randomized clinical trials in China reported a relationship between chronic constipation and oxidative stress in children.[3,4] A meta-analysis conducted in China in 2012, stated that supplementation with organic selenium can increase the activity of glutathione peroxidase in healthy adults.[9] A randomized clinical trial in Israel found that *Ziziphus jujube* plants, that contain betulinic acid, oleanolic acid, maslinic acid, glucose, sitosterol, stigmasterol, desmasterol, resin, catechol, tannins, essential oils, 13 types of amino acids, selenium, calcium, phosphorus, iron, cAMP, and cGMP, were an effective and safe treatment for functional constipation.[26]

We found significant differences in abdominal pain between the two groups. After 14 days of treatment, the selenium group had 82.5% with no pain and 17.5% with mild pain, while the placebo group had only 17.5% with no pain, 57.9% with mild pain, and 1.8% with severe pain. The Wong-Baker FACES pain scale assessment (WBS) is generally preferred by parents and patients to report pain perception and is used in children aged 3 to 18 years. Six hand-drawn faces range from smiling to crying. Facial image analysis was developed based on children's faces representing different degrees of pain, with a scale numbered 0 to 5.[27] An observational study reported that the WBS showed a moderate correlation with other pain scales in school-aged patients.[28]

We did not perform plasma selenium measurements. A study by Dwipoerwantoro assessed the effect of selenium deficiency on the enzymatic

antioxidant defense system (superoxide dismutase/SOD, chatalase/CAT, gluthathione peroxidase/GPX) and non-enzymatic molecules (gluthathione/GSH, thiobarbituric acid reactive substances/TBARS, and thiols) in the liver and muscle tissue of rats. The selenium-deficient group had significantly decreased plasma glutathione peroxidase (GPX) activity (95%) compared to the control group (74%).[29]

Excessive exposure to selenium in humans may cause nausea, vomiting, and diarrhea. Selenosis can cause acute and chronic changes in nails and hair, peripheral neuropathy, fatigue, and restlessness. Garlicky breath also indicates selenium poisoning.[6] We found no side effects in our subjects after administration of selenium.

In our study, the healing process was assessed by clinical improvements in frequency of defecation, stool consistency, and abdominal pain. Subjects were treated for 14 days, and assessed at days 7, 14, and 21. We did not assess other factors that affect functional constipation, such as physical activity, fluid and fiber intake, nutrition, and availability of bathroom faciliites. A Chinese study found that the levels of vitamin C and vitamin E, as well as superoxide dismutase and catalase activity were significantly decreased in patients with chronic constipation.[4] Further studies are needed to compare the effects of selenium against other antioxidants such as vitamin C and vitamin E. Furthermore, a study is needed to assess the overall effectiveness of selenium as initial and maintenance therapy, as well as factors that affect the healing and recurrence of constipation.

In conclusion, selenium given for 2 weeks is effective in clinical improvement of functional constipation in children, in terms of higher frequency of defecation, normalization of stool consistency, and less severe abdominal pain.

Conflict of interest

None declared.

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