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The Role of Metoclopramide for Treatment of Functional Constipation in Children: A Double Blind Study

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Abstract:

Background: *The treatment of functional constipation is a concern worldwide. Various studies have evaluated the effect of prokinetic agents such as cisapride in management of chronic constipation, however due to the possible lethal side effects, its consumption has been limited. In this study we assessed the effect of metoclopramide a drug with similar prokinetic effects and less side effects in management of chronic constipation.*

Method: *All pediatric patients less than 12 year of age with diagnosis of chronic functional constipation according to the ROME III criteria were included during the study period. Through this double blind study, patients were randomly divided into two groups. Group A received polyethylene glycol and placebo and group B polyethylene glycol with metoclopramide. The two groups were compared regarding their symptoms and Rome III criteria following therapy.*

Results: *Of the total 102 pediatric patients, 50 subjects completed regime A and 52 patients, regime B. The interval between defecations prior to treatment was 4.8±2.7 days in subjects of group A and 5.9±3.6 days in those of group B. Response to treatment; defined as decrease in signs and symptoms that would not fulfill Rome III criteria, and without any recurrence of fecal impaction with discontinuation of medication, was almost equal in both groups: 84% (42 of 50) in patients receiving regime A vs. 84.6% (44 of 52) in regime B group (p=0.39).*

Conclusion: *In this study we achieved no significant response from consumption of metoclopramide as a prokinetic agent in the treatment of chronic constipation of children.*

Introduction

Affecting 0.7% to 29.6% of children worldwide, constipation is considered one of the most common debilitating digestive problems in the pediatric population [1]. The majority of children with constipation have functional constipation, and only less than 5% are believed to have an underlying etiology [2]. A complete medical history and a careful physical examination are usually sufficient for diagnosis of functional constipation; however due to diversity in the definition of constipation by physicians and patients, and in order to make an accurate diagnosis of the disease, there was a need for a global agreement on the definition of chronic functional constipation. It was then that the ROME II (1999) and following that the ROME III criteria (2006) were described

for diagnosis of functional constipation [3-5]. Management of the disorder is composed of three steps: disimpaction, maintenance therapy, and follow up. Maintenance therapy itself consists of non-pharmacologic management (eg; behavioral therapy and dietary changes) and pharmacologic interventions for prevention of disimpaction [2]. Osmotic laxatives (eg; lactulose and polyethylene glycol "PEG"), stimulant laxatives (eg; bisacodyl, Senna) and mineral oil are the main drugs used as maintenance therapy in children [6-8]. Recently a few studies have evaluated the effect of prokinetic agents such as cisapride in functional constipation [9-14]. However considering the fact that severe side effects such as arrhythmias have been reported from consumption of cisapride, in this study we decided to assess the effect of metoclopramide a substance with similar prokinetic effects, in the management of chronic functional constipation of children.

Method

In a two year interval; between March 2008 and March 2010, all pediatric patients less than 12 year of age with diagnosis of chronic functional constipation according to the ROME III criteria (Table 1) [3] whom had referred to the Pediatric Gastroenterology Clinic affiliated to Shiraz University of Medical Sciences, were enrolled in this study.

An informed consent was obtained from all parents or legal guardians, and the study was approved by the ethical committee of our university.

In this double blind clinical trial study, in order to compare the efficacy of different maintenance regimes in the therapy of chronic functional constipation, patients were randomly divided into two groups. At the first visit a questionnaire including the patient's demographic features such as sex and age, his/her clinical signs and symptoms (eg; frequency of defecation, withholding behaviors, hard and bulky stool, difficult defecation, and fecal incontinence), duration of symptoms, and the interval between each defecation, was completed for all patients.

There were two different maintenance treatment regimens; which after disimpaction, patients were randomly assigned to. Regime A was PEG (0.6 gr/Kg/day) for 12 weeks with placebo for 4 weeks, while regime B included PEG (0.6 gr/Kg/day) for 12 weeks with metoclopramide (0.15 mg/Kg/day) for 4 weeks. Each regime was previously packed by our pharmacist with a special code, so that neither the patient nor the physician knew what regime was consigned to each subject before data analysis. Patients in both groups regularly received educations regarding dietary

Table I. Rome III Criteria for the Diagnosis of Chronic Functional Constipation in Children	
Infants and toddlers	**Children with developmental age 4 to 18 years**
At least two following present for at least <u>one month</u>	*At least two of the following present for at least <u>two months</u>*
Two or fewer defecation per week	Two or fewer defecation per week
At least one episode of incontinence after acquisition toileting skills	At least one episode of fecal incontinence per week
History of excessive of stool retention	History of retentive posturing or excessive volitional stool retention
History of pain full or hard bowel movement	History of pain full or hard bowel movement
Presence of a large fecal mass in the rectum	Presence of a large fecal mass in the rectum
History of large - diameter stool that may obstruct the toilet	History of large - diameter stool that may obstruct the toilet

changes and behavioral modifications of toilet sitting through family training.

Subjects were followed every 4 weeks through a 6 month interval. At each follow-up visit patients were asked about their symptoms (eg; frequency of defecation, withholding behaviors, hard and bulky stool, difficult defecation, and fecal incontinence), the interval between their defecations and any possible complaints during the consumption of their medication (eg; extrapyramidal symptoms, headache, diarrhea, flatulence, abdominal cramps, nausea). Also in the course of these visits the patient's compliance was assessed.

Response to treatment; defined as decrease in signs and symptoms that would not fulfill Rome III criteria, and without any recurrence of fecal impaction with discontinuation of medication.

Data collected from patients; through our questionnaire forms, were coded and entered into the computer using the SPSS program. Statistical analysis was performed using the

chi-square and Fisher's exact test for evaluation and comparison of the two regimens regarding their response to treatment. A p value <0.05 was considered to be significant.

Results

In this study a total of 102 pediatric patients with mean age of 5.2±3.2 years, diagnosed as having chronic functional constipation according to the ROME III criteria were included. Fifty subjects completed regime A and 52 patients, regime B. There was no significant demographic difference between the two groups (Table 2).

Table II. Demographic Characteristics of the Study Population

	Regime A (PEG + Placebo) (n=50)	Regime B (PEG + Metoclopramide) (n=52)	p
Age in years, mean ± SD	5.27 ± 3.29	5.11 ± 3.18	p>o.o5
Sex (Male/Female)	0.85:1	1.16:1	p>o.o5

The mean duration of symptoms prior to the first visit was 2.54±2.14 years in group A vs. 2.06±1.7 years in group B. Hard and bulky stool passing was the most common complaint among our patients in both groups (Table 3). The interval of between defecations prior to treatment was 4.8±2.7 days in subjects of group A and 5.9±3.6 days in those of group B.

None of our patients in both groups complained of any side effects during the course of treatment.

Six months after start of therapy the interval between defecations had declined to 1.8±1.4 days in group A and 1.7±0.8 days in group B. (p= 0.23)

Response to treatment,; defined as one to two soft and easy defecation of stool per day, with no relapse of symptoms with discontinuation of treatment, was almost equal in both groups: 84% (42 of 50) in patients receiving regime A vs. 84.6% (44 of 52) in regime B group (p= 0.39).

Discussion

Prokinetic agents such as cisapride, erythromycin, and metoclopramide which enhance gastrointestinal motility by increasing the frequency and strength of the small intestinal contractions have long been studied for their effect in

Table 3. Common Symptoms of Pediatric Patients with Chronic Functional Constipation

Symptoms	Regimes			
	Regime A		Regime B	
	Prior to treatment	Six months after treatment	Prior to treatment	Six months after treatment
Hard and Bulky stool	42 (84%)	8 (16%)	49 (94.2%)	8 (15.4%)
Abdominal Pain	25 (50%)	1 (2%)	13 (28%)	0
Fecal Incontinence	14 (28%)	1 (2%)	20 (38.4%)	2 (3.8%)

treatment of chronic constipation especially in the adult population [10-14].

Although some previous studies had shown cisapride to be beneficial in children with constipation [11,12]; in 1997 Odeka et al. showed no significant effect in stool frequency and gastrointestinal transition time after 10 weeks of cisapride consumption in children with chronic functional constipation [13]. However in 2000 through a double blind placebo control study, Nurko et al. also recommended the consumption of cisapride as an alternative for treatment of children with constipation [14]. Its fatal cardiac arrhythmic side effect has caused limitations in use of the drug. As an overall the North American Society for Pediatric Gastroenterology Hepatology and Nutrition states that the benefits of cisapride do not outweigh its risks [15].

As of the use of erythromycin for treatment of constipation, randomize control trials have only been conducted in children. Bellomo-Brandao et al. demonstrated erythromycin estolate to be a useful treatment for severely constipated children [16]. This is while Venkatasubramani et al. suggested that erythromycin lactobionate has no colon prokinetic effect in children with chronic intractable constipation [17].

Metoclopramide a chemically related drug to cisapride has been commonly used for nausea, vomiting and mostly tested for its effect on upper gastrointestinal mobility [18]. Its efficacy in treatment of chronic functional constipation; as a prokinetic agent, has neither previously been studied in adults nor children. So, we didn't include a third group that treated with metoclopramide alone.

In this study we evaluated the effect of metoclopramide as an adjunctive therapy with PEG in management of chronic functional constipation.

Our research demonstrated no significant difference in response to treatment and alleviation of symptoms in chronic functional constipation, between the two treatment regimes (PEG and placebo vs. PEG and metoclopramide).

In this study we achieved no significant response from consumption of metoclopramide as a prokinetic agent in the treatment of chronic constipation of children. We recommend further and larger randomized clinical trials with possibly longer duration of therapy, and also perhaps studies which could evaluate the effect of metoclopramide on colon motility in children with chronic constipation using colon manometry.

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