Original Article

A Randomized Controlled Trial in Efficacy of Itopride Hydrochloride with Polyethylene Glycol (PEG) and PEG Alone in Bowel Preparation for Colonoscopy

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ABSTRACT

Aims: To compare the efficacy of colon cleansing for colonoscopy between itopride hydrochloride plus polyethylene glycol group and polyethylene glycol alone.

Methods: This was a randomized controlled trial comparing the efficacy of colon cleansing for colonoscopy between itopride hydrochloride plus polyethylene glycol (PEG) and polyethylene glycol alone in patients undergoing an elective colonoscopy at the Division of Gastroenterology, Department of Medicine, Faculty of Medicine, Vajira Hospital, Navamindradhiraj University, Bangkok, between January 2014 and December 2014.

Results: A total of 82 patients were enrolled, 41 (50%) in the itopride hydrochloride plus polyethylene glycol group (combination group), and 41 (50%) in the polyethylene glycol alone group (PEG group). In the combination group, 24 patients (58.5%) achieved an optimal bowel preparation (Ottawa scale ≤ 4) with an average score of 3.9 ± 2.69. In the PEG group, 17 patients (41.5%) achieved optimal bowel preparation with an average score of 4.83 ± 2.66. The difference was not statistically significant (p=0.12). The number of patients in the combination group with total fluid score of 0 was statistically higher than that in the PEG group (41.5% vs. 19.5%, p = 0.03). In the combination group, 2 cases of abdominal discomfort (4.9%) and 2 cases of nausea and vomiting (4.9%) were reported (p=0.24), whereas in the PEG group, 5 cases of abdominal discomfort (12.2 %) and 4 cases of nausea and vomiting (9.8 %) were noted (p=0.24, 0.39). The difference was not statistically significant.

Conclusion: Colonic bowel preparation by adding itopride hydrochloride 50 mg to the split-regimen of 2-liter PEG increased the number of patients with minimal colonic fluid residue with statistical significance.

Key words : Itopride Hydrochloride, Polyethylone Glycol, PEG, Colonoscopy

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INTRODUCTION

Colonoscopy is the current standard for evaluation of the colon. The accuracy and safety of colonoscopy depends on the quality of colonic preparation[1]. Sub-optimal bowel preparation decreases the sensitivity in detecting polyps in the colon and the chance of successful complete colonoscopy[2,3]. Cost as well as potential side effects during bowel preparation, such as nausea, abdominal discomfort and, including reasonable costs, must be considered[4].

In 1980, Davis *et al* formulated a polyethylene glycol (PEG) regimen[5]. PEG is an osmotically balanced electrolyte lavage solution which is safe and effective in cleansing the colon[6], but the large amount of water content in the 4-liter standard volume, may give rise to nausea, vomiting and abdominal discomfort. A study comparing 2-liter PEG and 4-liter PEG showed no significant difference in the overall colon cleanliness[7-11]. In that study, however, cleanliness in the right colon and the sensitivity in detecting right colon polyps was significantly less with 2-liter PEG than with 4-liter PEG[10,11]. Other studies have been conducted with the addition of a number of laxatives and stimulant laxatives to enhance the quality of bowel preparation, the results being similar, that is, the outcome does not appear to be significantly improved[12-15].

Itopride hydrochloride is benzamide's derivative, working by stimulating the contraction of colons through D2 receptor antagonist and acetylcholinesterase inhibition. Previous studies have demonstrated that the drug stimulated the colon to contract more strongly resulting in forward movement and eventual passage of fecal matter[16]. A study using itopride hydrochloride combined with polyethylene glycol to enhance the effectiveness of bowel preparation, a randomized controlled trial with 2 controlled groups by Mishima Y *et al* in 2008[17], did not show a significant improvement of bowel preparation. Itopride hydrochloride in that study, however, helped reduce nausea, vomiting and abdominal discomfort. In another study by Kim HJ *et al* in 2012[18], itopride hydrochloride was shown to significantly increase cleanliness of the colon.

Our study was designed to assess the effectiveness of itopride hydrochloride for quality bowel preparation for colonoscopy in patients at the Department of Medicine, Faculty of Medicine, Vajira Hospital, Navamindradhiraj University, Bangkok. Data was collected over a 1-year period for preparing a guideline for colonoscopy bowel preparation.

Objectives

Primary objective

To compare colon cleanliness for colonoscopy between itopride hydrochloride plus polyethylene glycol and polyethylene glycol alone.

Secondary objective

To assess the efficacy of itopride hydrochloride in reducing side effects from the administration of PEG e.g. abdominal discomfort, nausea, vomiting.

MATERIALS AND METHODS

Patients aged 18 to 70 undergoing an elective colonoscopy at the Division of Gastroenterology, Department of Medicine, Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Bangkok, between January 2014 and December 2014 were enrolled in the study. Exclusion criteria included allergy to PEG and benzamide's derivative, severe co-morbidity (congestive heart failure, previous colectomy or bowel resection, unstable angina and acute coronary syndrome, massive ascites, megacolon, suspected bowel obstruction), and pregnancy or breast feeding. The study protocol was approved by the Navamindradhiraj University Research Ethics Committee. A written informed consent was obtained from all participants.

Sample calculation

The outcome of treatment interest was related to the assessment of preparatory bowel cleansing using the Ottawa bowel preparation scale. The total score and the segmental score were determined. If the total score was less than or equal to 4, bowel preparation was considered optimal. If the total score was over 4, bowel preparation was sub-optimal. This was based on a study by Kim HJ *et al* in 2012[18]. The proportion of patients with adequate bowel preparation after using itopride hydrochloride and PEG was as high as 72%. When calculating the differences of the proportions in the two groups at 25% and the superiority limit was assumed to be at least 5% ($\delta = 0.05$), the calculation algorithm of a suitable sample size was to compare the proportions in the two groups for superiority, whereby according to Z table, the standard value was 1.64 at the significance level of 0.05 and the power of

80%. In this study, the sample size used was at least 70 patients per group. Therefore, the total sample size was 140 patients.

The Ottawa bowel preparation scale[19]

Score of 0 to 4 points per segment:

- Excellent (0 point): Mucosa clearly visible. Minimum liquid remains.
- Good (1 poin): Some liquid remains. Good view of the mucosa.
- Fair (2 points): Blow liquid or semisolid. No precise wash. Reasonable view of the mucosa.
- Poor (3 points): Blow sucks needing wash. Low vision of the mucosa.
- Inadequate (4 points): Blow solids that impede vision.

Amount of liquid in the entire colon, from 0 to 2 points:

- Low (0 point)
- Moderate (1 point)
- Large (2 points)

Study design

After giving consent, patients were divided into 2 groups at the ratio of 1:1 by alternate sequencing of 1. The first group for bowel preparation using itopride hydrochloride plus PEG, and the second group for PEG alone. Two days before the scheduled colonoscopy, all patients would consume easily digestible and refined foods such as porridge, congee with fish or egg. High-fiber foods e.g. brown rice, vegetables and fruits were to be refrained. One day before the scheduled colonoscopy, patients were admitted and consumed only food provided in the hospital, which was liquid diet without fiber, e.g. clear fruit juice (no pulp), honey, clear and colorless sweet soup and plain congee.

Group 1; patients received 1 liter of PEG (NIFLEC®) at 6PM in the evening of the pre colonoscopy day and another 1 liter at 5.30AM on the day of colonoscopy. Two-hundred mL of PEG was taken every 10 minute and the whole 1 liter was finished within 1 hour. One tablet of itopride hydrochloride 50 mg (Ganaton®) was also taken 30 minutes before taking each liter of PEG.

Group 2; patients received 1 liter of PEG (NIFLEC®) at 6PM in the evening of the pre-colonoscopy day, and another 1 liter at 5.30AM on the day of colonoscopy. PEG was taken in a similar manner.

All patients completed a questionnaire on side effects of medications e.g. abdominal distension, nausea, vomiting, headache, dizziness. Patients underwent colonoscopy between 9AM and 12AM. The quality of bowel preparation was evaluated using a recorded CD. Two gastroenterologists who did not perform the colonoscopy completed the Ottawa bowel preparation scale[19]. If their opinions differed, an operation by the third endoscopist was sought.

Statistical analysis

There was strict control and supervision of data entry and access to study data. Patients demographic data were summarized in frequency for categorical variables and in mean ± standard deviation for continuous variables. Chi-square test or Fisher's exact test and student's t test were used to compare differences between the groups for categorical and continuous variables, respectively. Values of $p < 0.05$ were regarded as statistically significant. All analyses were performed using SPSS 18.0 statistical software.

RESULTS

There were 82 study patients, 41 (50%) in the itopride hydrochloride plus PEG group and 41 (50%) in the polyethylene glycol alone group. Table 1 shows the comparison of baseline data of the two groups. There were 19 males (46.3%) with an average age of 66.51 years in group 1. There were 20 males (48.8%) with an average age of 64.37 years in group 2. There were no statistically significant differences regarding gender, age, body weight, underlying diseases, indication for colonoscopy, and timing of bowel preparation. The indication for colonoscopy included anemia, chronic diarrhea, screening for colon cancer and gastrointestinal bleeding, etc. In this study, more polyps were detected in the itopride hydrochloride-PEG combination group than in the PEG alone group, without statistical significance.

Table 2 shows the primary outcome: bowel preparation scores by the Ottawa scale. In the combination group, 24 patients (58.5%) had an optimal bowel preparation (Ottawa scale of ≤ 4) with the average score of 3.9 ± 2.69. In the PEG group, 17 patients (41.5%) had optimal bowel preparation with the average score of 4.83 ± 2.66. The difference was not statistically significant (p=0.12).

Table 3 shows the number of patients with excel-

Table 1. Baseline characteristics.

	Itopride hydrochloride + PEG (N=41)	PEG alone (N=41)	*p*- value
Sex, male, n (%) (yrs)	19 (46.3)	20 (48.8)	0.83
Age, mean (SD)	66.51 (12.28)	64.37 (15.89)	0.49
Weight, mean (SD) (kgs)	59 (12.5)	57.9 (9.95)	0.67
Height, mean (SD) (cms)	159.3 (8.32)	159 (7.72)	0.87
BMI, mean (SD) (kg/m^2)	23.16 (4.19)	22.9 (3.46)	0.76
Diabetic mellitus, n (%)	10 (24.4)	15 (36.6)	0.23
Hypertension, n (%)	20 (48.8)	23 (56.1)	0.51
Dyslipidemia, n (%)	13 (31.7)	15 (36.6)	0.64
Coronary artery disease, n (%)	7 (17.1)	8 (19.5)	0.78
Cerebrovascular disease, n (%)	2 (4.9)	0 (0)	0.15
Chronic kidney disease, n (%)	2 (4.9)	4 (9.8)	0.39
Indication			0.69
Surveillance, n (%)	4 (9.8)	5 (12.2)	
Anemia, n (%)	19 (46.3)	22 (53.7)	
GI bleeding, n (%)	0 (0)	2 (4.9)	
Diarrhea, n (%)	8 (19.5)	4 (9.8)	
Chronic abdominal pain, n (%)	2 (4.9)	3 (7.3)	
Constipation, n (%)	5 (12.2)	3 (7.3)	
Follow up, n (%)	3 (7.3)	1 (2.4)	
Protein loosing enteropathy, n (%)	0 (0)	1 (2.4)	
Time to scope, mean (SD)	3.47 (0.83)	3.78 (0.91)	0.17
Findings			
Normal, n (%)	13 (31.7)	17 (41.5)	0.36
CA colon, n (%)	2 (4.9)	6 (14.6)	0.14
Polyp, n (%)	17 (41.5)	9 (22)	0.06
Diverticulum, n (%)	7 (17.1)	7 (17.1)	1
Angiodysplasia, n (%)	2 (4.9)	1 (2.4)	0.56

Table 2. Primary outcome: Ottawa bowel preparation scores.

	Itopride hydrochloride + PEG (N=41)	PEG alone (N=41)	*p*- value
Left side score, mean (SD)	1.32 (0.76)	1.51 (0.98)	0.32
Transverse score, mean (SD)	0.85 (0.82)	1.17 (0.86)	0.09
Right side score, mean (SD)	0.76 (0.73)	1 (0.81)	0.16
Overall fluid score, mean (SD)	0.9 (0.86)	1.15 (0.8)	0.17
Overall score, mean (SD)	3.9 (2.69)	4.83 (2.66)	0.12
Good bowel preperation, n (%)	24 (58.5)	17 (41.5)	0.12

Table 3. Excellent scores (score = 0).

	Itopride hydrochloride + PEG (N=41)	PEG alone (N=41)	*p*- value
Left side colon, n (%)	6 (14.6)	7 (17.1)	0.76
Transverse colon, n (%)	16 (39)	11 (26.8)	0.24
Right side colon, n (%)	17 (41.5)	12 (29.3)	0.25
Overall fluid score, n (%)	17 (41.5)	8 (19.5)	0.03
Overall score, n (%)	2 (4.9)	3 (3.7)	0.64

Table 4. Secondary outcome: Side effects.

	Itopride hydrochloride + PEG (N=41)	PEG alone (N=41)	*p*- value
Discomfort, n (%)	2 (4.9)	5 (12.2)	0.24
Nausea, n (%)	2 (4.9)	4 (9.8)	0.39
Dizziness, n (%)	3 (7.3)	1 (2.4)	0.31
Insomnia, n (%)	4 (9.8)	4 (9.8)	1

lent segmental score (segmental score 0). In the combination group, higher numbers of patients had a clean right colon, and transverse colon but the number was not statistically significant (41.5 % vs. 29.3, p=0.25; 39% vs. 26.8%, p=0.24). In addition, the number of patients in the combination group with total fluid score of 0 was statistically higher than that in the PEG group (41.5% vs. 19.5%, p = 0.03).

Table 4 shows side effects associated with bowel preparation. In the combination group, 2 cases of abdominal discomfort (4.9%) and 2 cases of nausea and vomiting (4.9%) were observed, while in the PEG group, 5 cases of abdominal discomfort (12.2 %) and 4 cases of nausea and vomiting (9.8 %) were noted (p=0.24 and p=0.39). The difference however, was not statistically significant.

Discussion

It is well known that, the quality of bowel preparation for colonoscopy increases the chance of detecting polyps in the colon. Adding a stimulant laxative is one method to improve bowel cleansing[12-15]. Our study showed that adding itopride hydrochloride 50 mg tablet in two divided doses to 2-liter of PEG resulted in improved colon cleansing. In the itopride hydrochloride combination group, the segmental scores of left side colon, the transverse colon, the right side colon and the total score were better than those in the PEG group, although the difference not statistically significant. In this study, there was a statistically insignificant higher rate of polyp detection in the combination group (41.5 % vs. 22%; p=0.06). Moreover, in this latter group, there was a statistically significant higher proportion of patients with a total liquid score of 0 (41.5 % vs. 19.5%; p= 0.03), suggesting that itopride hydrochloride helps improve the cleanliness of bowel preparation by stimulating colonic preparation action and fecal clearance. In two previous studies by Kim HJ *et al* in 2008(18), the addition of itopride hydrochloride was shown to statistically significantly improve the total score. However, in that study, 2 liters of PEG combined with 100 mg of itopride hydrochloride was given twice that a higher total dose (4 liters) of PEG than in our study. Another study by Mischima Y *et al* in 2008[17], on the other hand, demonstrated that the addition of itopride hydrochloride 50 mg to 2-liter polyethylene glycol prior to colonoscopy did not improve the bowel preparation score, but in that study only a single bowel preparation was given in the morning before the colonoscopy procedure in the afternoon.

Side effects from the use of 2-divided PEG regi-

men (total 2 liters) in the study by Cristian Ell *et al* in 2008 included abdominal discomfort (15.7%) and of nausea and vomiting (22%)[7]. In our study, abdominal distention (12.2%) and nausea and vomiting (9.8%) were noted, which were a little less than in the previous study, and apparently less in the itopride hydrochloride combination group. It can be concluded that the use of itopride hydrochloride combined with PEG may help reduce side effects from the use of PEG alone (9.8% vs. 22%; p=0.13). The main limitation in this study was the small number of study cases, which could affect data analysis with consequent inconclusive result. A larger number of patients is required for future study to establish the conclusion.

Bowel preparation by adding itopride hydrochloride 50 mg per time to the split-regimen of 2-liter PEG statistically significantly increase the proportion of patient with minimal residual liquid in the colon. Cleansing of the segmental colon is also improved with lower side effects. This regimen is potentially an alternative regimen in bowel preparation for colonoscopy.

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