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Original Article

Can prucalopride improve the efficacy and tolerability of colonoscopy preparation?

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Abstract: Objective: Adequate bowel cleansing is an important determinant for the colonoscopy. Polyethylene glycol (PEG)-based solutions are used commonly in bowel preparation, but their poor palatability and large volumes (4L) affect the patient's compliance. Studies found that prokinetic agents improved preprocedure tolerability and efficacy in patients. The high affinity and selectivity for 5-hydroxytryptamine receptor-4 (5-HT_4) agonist differentiates prucalopride from older generation compounds and minimizes the potential for target-unrelated side effects. The study aimed to compare the efficacy and safety of adjunctive prucalopride for bowel preparation before colonoscopy. Materials and methods: In a randomized controlled trial setting, 175 outpatients were randomized to receive either 3-L polyethylene glycol (PEG) + 2 mg of prucalopride (prucalopride group) or 3-L PEG + placebo (PEG group). The bowel preparation efficacy was scored by a blinded endoscopist using the Ottawa scale. Mean scores for each bowel segment, composite mean scores, and rates of "good preparation (prep)", "excellent prep", and "inadequate prep" interpreted from the Ottawa scale were compared between the two groups. Results: An "excellent prep" and a "good prep" were more often observed in the prucalopride group than in the PEG group (P=0.003, P=0.006). Vomiting frequencies were significantly lower (P=0.034), the time of first defecation was significantly shorter (P=0.008) and the defecation frequency was significantly higher (P=0.000) in the prucalopride group than in the PEG group. Frequencies of symptoms (nausea, bloating etc) and willingness to repeat the same regimen were similar in both groups. Conclusions: Prucalopride may be an effective and safe adjunct to PEG that leads to an improved quality of bowel preparation.

Keywords: Prucalopride, 5-HT_4-receptor agonist, polyethylene glycol (PEG) electrolyte solution, colonoscopy, bowel preparation

Introduction

Colorectal cancer (CRC) continues to be one of the leading causes of death worldwide [1]. CRC is a common malignant tumor in China [2]. With the changing in eating habits and continuous improvement in people's living standards, the incidence of CRC has increased year by year; higher growth of CRC incidence has been reported in larger cities [2]. CRC develops in a series of well-defined steps, from normal mucosa to adenomatous polyp through varying degrees of dysplasia and finally to adenocarcinoma. Colorectal adenoma is the most important precancerous disease of CRC [3]. By identifying and removing precursor lesions, colonoscopy has emerged as the gold standard for screening and surveillance of colorectal neoplasia, and has been shown to reduce mortality from CRC [4]. However, colonoscopy is dependent on adequacy of bowel preparation for the complete visualization of the colonic mucosa. Unfortunately, up to 20%-25% of all colonoscopies are reported to have an inadequate bowel preparation [5], which has potential adverse consequences, such as missed pathological abnormalities, need for repeated procedures, and increased procedure-related complications [6].

In the past few years, to get the best preparation of bowel, many studies have been performed with varying uses of PEG, such as split-dose PEG and PEG with adjuncts, or other bowel preparation regimens, such as sodium phosphate, sodium sulfate solution, sodium picosul-

fate, magnesium citrate, etc., in an effort to improve the patient tolerability and/or efficacy of the bowel preparation [7-12]. While none has provided optimal safety and efficacy profiles, each represents unique strengths and weaknesses (in terms of efficiency, ingested volume, taste, adverse events, and time required for preparation). In 2014, the US Multi-Society Task Force recommended split-dose 4-L PEG with electrolytes as bowel preparation regimen for colonoscopy [13]. However, given its large volume, it may not be suited for all patients; and current regimes require patients to take the preparation from the afternoon of the preceding day. This effectively prevents the patient from working or going out during this period, effectively making colonoscopy a 2-day procedure. The polyethylene glycol (PEG)-electrolyte solution has been widely used in China as lavage solutions for bowel cleansing [14]. For adequate bowel preparation, about 3000 mL of this solution is usually required. May be because of its taste, fluid volume ingested, or side effects such as nausea, bloating, and vomiting, we have encountered patients with insufficient bowel cleansing in practical works. To address these concerns, investigators continue to search for perfect bowel preparation with respect to quality and patient satisfaction. Tajika et al [15] and Kim et al [16] found that mosapride and itopride, 2 prokinetic agents currently in clinical development, improved preprocedure tolerability with significant reductions in nausea, vomiting, bloating, and abdominal pain, and improved efficacy in patients through reducing residual fluid in the colon. Unfortunately, former 5-HT_4 receptor agonists were less selective and less specific, which caused in potential adverse cardiac effects or reduced intestinal prokinetic activity due to interactions with other 5-HT receptors.

Prucalopride is a selective, high-affinity, 5-hydroxytryptamine receptor-4 (5-HT_4) agonist with gastrointestinal prokinetic properties [17]. Several Studies [18-20] found that prucalopride is effective in improving stool frequency, reducing abdominal and stool-related symptoms associated with constipation, and can accelerate colonic transit time (CTT) in some patients, with mean CTT reduced by 12 h from baseline after 4-12 weeks of treatment. Prucalopride is approved in many countries for the symptomatic treatment of chronic constipation (CC) in women, in whom laxatives have failed to provide adequate relief at a recommended daily dose of 2 mg or 1 mg once daily for patients who are over 65 years old [19]. Simon Nennstiel et al [21] found that prucalopride reduced the number of reflux episodes and improves subjective symptoms in gastroesophageal reflux disease. One Study [22] proved that prucalopride was safe and well tolerated by patients (men or women) in the Asia-Pacific region. However, as adjunct for colonic cleansing, the efficacy and tolerability of a PEG-electrolyte solution with prucalopride has not been studied.

The present study investigated the cleansing efficacy and tolerability of prucalopride as an adjuvant to PEG-electrolyte solution for colonoscopy preparation.

Methods

This study was a randomized, prospective, double-blind, clinical trial, and was reviewed and approved by the ethics committee of the Liaocheng People's Hospital (ID: 2014087). Outpatients 20-65 years of age who were scheduled for an elective colonoscopy for various reasons (**Table 2**) at the Gastroenterology Clinic, Liaocheng People's Hospital (Shandong, China), were consecutively enrolled in the study. A gastroenterologist assessed the patient eligibility, and written informed consent was obtained from each patient prior to inclusion. Exclusion criteria were as follows: pregnancy, breast feeding, severe constipation (<2 bowel movements a week), presence of significant cardiac, renal, hepatic, or metabolic comorbidities; presence of ascites or bowel obstruction; known allergy to PEG-electrolyte solution; history of gastric stapling or bypass procedure; history of prior colonic or rectal surgery; and refusal to consent to participate in the study.

The patients who consented to the study were then randomly allocated to one of the two interventions by a computer-generated number list. They were randomly assigned to two subgroups by the envelope method. With the exceptions of the unblinded research assistant, all other individuals participating in this study, including the patients, the endoscopists and endoscopy nurses, were blinded to the allocated treatment group. Comparisons between the 3-L PEG (recommended by Chinese Medical Association of Gastroenterology for adequate bowel preparation) + 2 mg (general recommended dose for

Table 1. Bowel preparation quality of Ottawa scale

	Scores
Cleanliness of each part of the colon: Rt, Mid, Lt	
No liquid	0
Minimal liquid, no suction	1
Suction required to see mucosa	2
Wash and suction required	3
Solid stool, not washable	4
Overall quantity of fluid	0 (mild), 1 (moderate), 2 (severe)

Total score (0-14), cleanliness (Rt + Mid + Lt) + overall quantity of fluid. Rt = Right; Mid = middle; Lt = left.

Table 2. Baseline Demographics, indications for colonoscopy, and previous history of colonoscopy in two groups

Demographic data	PEG group	Prucalopride group	*P* value
n	93	82	
Mean age (SD)	47.7 (11.1)	48.6 (10.8)	0.56
Gender, n (%)			
Male	54 (58.1)	38 (47)	0.121
Female	39 (41.9)	44 (53)	0.121
Mean BMI (SD)	24.5 (3.1)	24.0 (3.0)	0.224
Indication n (%)			
Screening	29 (31.2)	25 (30.5)	0.921
Hematochezia	10 (10.8)	8 (9.8)	0.829
Abdominal pain	14 (15.1)	10 (12.2)	0.583
Change in bowel habits	16 (17.2)	12 (14.6)	0.644
Surveillance	10 (10.8)	8 (9.8)	0.829
Positive FOBT	4 (4.3)	3 (3.7)	0.829
Weight loss	7 (7.5)	8 (9.8)	0.599
Anemia	3 (3.2)	4 (4.9)	0.578
Others	4 (4.3)	4 (4.9)	0.855
Previous colonoscopy n (%)			
None (first time)	74 (79.6)	67 (81.7)	0.721
≥2	19 (20.4)	15 (18.3)	0.721

BMI, Body mass index; n, sample size; FOBT: fecal occult blood test; SD, standard deviation.

treating chronic constipation) [19] of prucalopride (prucalopride group, n=100) and 3-L PEG + placebo (PEG group, n=100) [14] were made in an investigator blind fashion. After randomization, patients were required to complete a questionnaire before colonoscopy. The quality of preparation was assessed and the Ottawa scale scores were assessed by endoscopists (**Table 1**) at the time of insertion of the colonoscope before any cleansing maneuvers.

Bowel preparation methods

The day before colonoscopy, all patients were instructed to eat low residue diet including breakfast. On the day of colonoscopy, one prucalopride tablet (2 mg) (Janssen Cilag S.p.A. company, Xi'an, China) or identical-looking placebo tablet were administered orally with water at 6:30 am. After 30 min, both the groups were instructed to drink 0.25 L of PEG-electrolyte solution (create a feeling of God Pharmaceutical Co., Ltd. Beijing, China) every 10 min (**Figure 1**). Colonoscopies were performed from 14:00, and the start times were recorded for each patient.

Evaluation of bowel preparation

Bowel-cleansing efficacy was measured by endoscopists using the Ottawa scale [23] (**Table 1**). To ensure that their findings consistency, investigators performed calibration exercises involving more than 40 colonoscopies prior to study commencement based on their interpretation of scale anchors. This scale assesses cleanliness and fluid volume separately. Cleanliness was assessed separately for the right colon (caecum, ascending), mid colon (transverse, descending), and the rectosigmoid on a 5-point scale. Fluid quantity was rated from 0 to 2 for the entire colon. As per one study [24], a total score of >8 on the Ottawa scale was considered to indicate an inadequate preparation and a score of ≤7 was deemed adequate. Preparations with a total score of ≤4 were considered excellent, provided that no individual colonic segment received a score higher than 1. The quality of preparation was assessed at the time of insertion of the colonoscope before any cleansing maneuvers by two colonoscopies

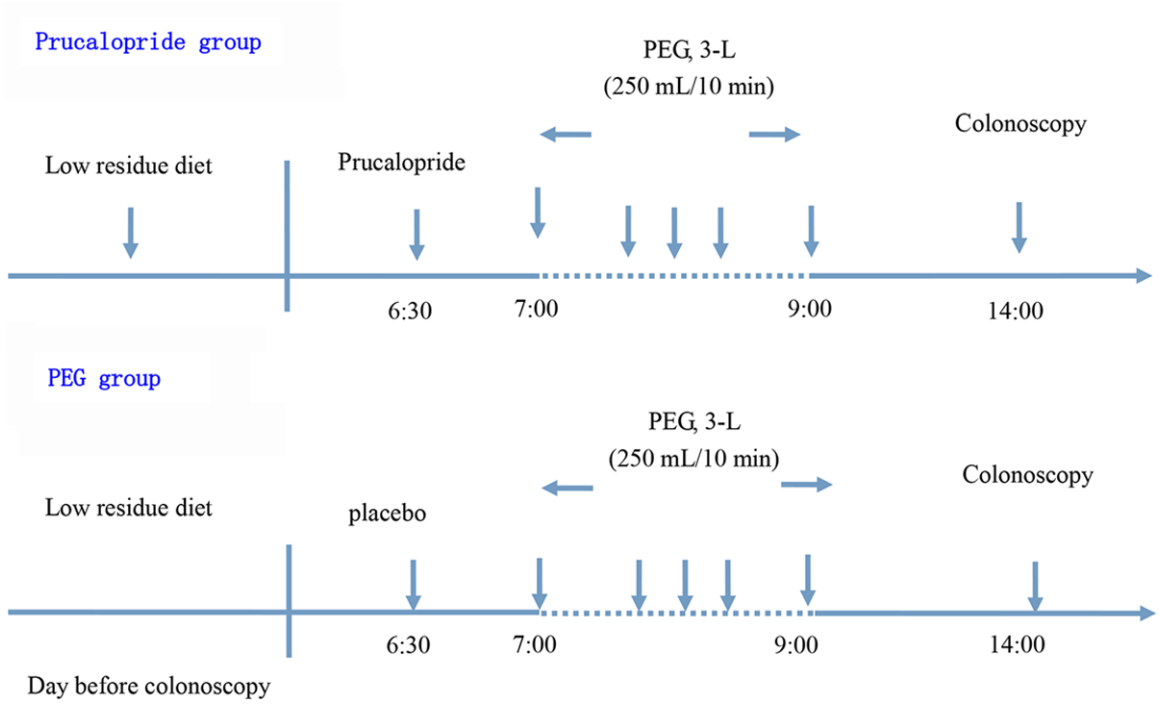

Figure 1. Schematic representation of protocol for the colon cleansing experiments. One prucalopride tablet or placebo tablet were administered orally with water at 6:30 am. After 30 min, both the groups were instructed to drink PEG-electrolyte solution (3 L) 0.25 L every 10 min. Colonoscopies were performed from 14:00.

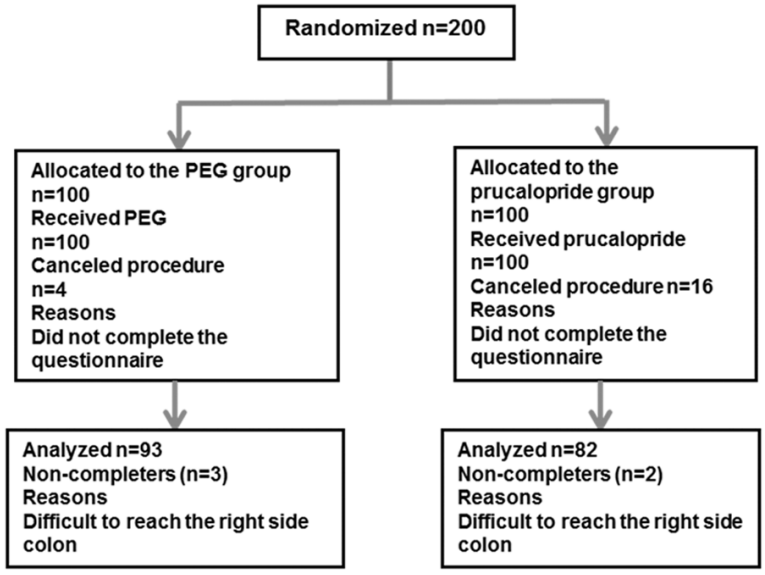

Figure 2. Flow diagram of patient recruitment and summary of treatment outcomes. A total of 200 patients were randomly assigned to two groups. Seven patients in the PEG group and eighteen patients in the prucalopride group did not undergo colonoscopy due to did not complete the questionnaire (n=4 in the PEG group, n=16 in the prucalopride group) and difficult to reach the right side colon (n=3 in the PEG group, n=2 in the prucalopride group). They withdrew from the study. Therefore, 175 patients were included in the final analyses (93 in the PEG group and 82 in the prucalopride group). PEG: Polyethylene glycol, n, sample size.

[25]. A third expert reviewer graded and scored the recorded images later, if the decision was discordant, and this evaluation was used in the final analysis.

Patients completed the questionnaire (including patients demographics, side effects of two colon preparations, time for first defecation, frequency of defecation, and willingness to repeat the same regimen or not) [15] before undergoing colonoscopy. The questionnaire was translated and modified into Chinese to make patients easy to understand. The patients submitted the form to the nursing staff, who recorded the colon abnormalities reported by endoscopists.

The primary end point of this study was cleansing efficacy

Table 3. Ottawa scores, proportions of "good prep" in different locations of the colon and Ottawa scores, proportions of "inadequate prep", "excellent prep" of the whole colon were compared in two groups

Ottawa scale variable	PEG (n=93)	Prucalopride (n=82)	*P* value
Right colon			
Mean score (SD)	2.37 (0.60)	2.24 (0.88)	0.295
Good prep (score <2) (n, %)	4 (4.3)	14 (17.1)	0.006
Middle colon			
Mean score (SD)	1.84 (0.63)	1.74 (0.93)	0.44
Good prep (score <2) (n, %)	23 (24.7)	24 (29.3)	0.499
Left colon			
Mean score (SD)	1.36 (0.79)	1.20 (0.96)	0.23
Good prep (score <2) (n, %)	54 (58.1)	53 (64.6)	0.374
Overall fluid quantity			
Mean score (SD)	0.41 (0.52)	0.34 (0.48)	0.38
Good prep (score <1) (n, %)	58 (62.4)	54 (65.9)	0.631
Mean total score (SD)	5.96 (1.61)	5.54 (2.32)	0.16
Inadequate prep (≥8) (n, %)	12 (12.9)	14 (17.1)	0.439
Excellent prep (≤4) (n, %)	13 (14.0)	27 (32.9)	0.003

PEG, Polyethylene glycol; SD, standard deviation; prep, preparation.

in the prucalopride and PEG groups. Secondary endpoints included differences in patients' acceptability and tolerance of solutions, time for first defecation, frequency of defecation, and willingness to repeat the bowel preparation in future if required. The number of polyps detected was assessed, polyp detection rate and adenoma detection rate (ADR) were calculated, and time interval between the last dose of bowel preparation and the start of colonoscopy, *i.e.*, the reparation-to-colonoscopy (PC) interval was noted.

Statistical analysis

As per one study [26], the sample size was calculated using the Lehr's formula. The demographic, colonoscopic, and patient questionnaire data were compared across the two groups to examine any significant differences between the groups. The Ottawa scale including the total score, overall fluid quantity, mean age, time for first defecation, frequency of defecation, and elapsed time from last fluid intake to colonoscopy were then compared between the two groups using the Student's *t* test. The Ottawa scale was also measured in categories in which a "good preparation (prep)" was considered to be an individual component score of <2 (for right, middle, and left colon) or <1 (for overall fluid quantity), an "inadequate prep" was considered to be an individual total score of ≥8, and an "excellent prep" was considered to be an individual total score of ≤4. The x^2 test with a 2×2 contingency table was used to measure the association between a "good prep", "inadequate prep", "excellent prep", and the type of bowel preparation regimen used. Many of the demographic, colonoscopic, and patient questionnaire data were measured in proportions, and 2×2 tables with either x^2 statistics or Fisher's exact tests were used to assess the degree of association and statistical significance where applicable. The criterion for statistical significance was $P<0.05$.

Results

Basic data

Between February and May 2015, 200 patients initially consented to participate in this study. However, 25 patients were subsequently excluded for various reasons (**Figure 2**). The data for the primary outcome measures were obtained for the remaining 175 participants. These 175 patients were evenly distributed between the PEG group (n=93) and the prucalopride group (n=82). No significant differences were observed between the two groups in the basic data, including demographic data, indications for colonoscopy, and previous history of colonoscopy (**Table 2**).

Bowel cleansing efficacy and colonoscopy data

The bowel cleansing efficacy was measured using the Ottawa scale. Means and proportions were calculated. Differences in the mean scores of each individual component, the sum of these components, and overall fluid quantity between the two groups were not significant (**Table 3**). A "good prep" as defined previously was observed more often in the prucalopride group than in the PEG group in the right colon (P=0.006). An "inadequate prep" was not sig-

Table 4. The time interval between the last PEG intake and the start of colonoscopy and endoscopic findings in two groups

Variable	PEG	Prucalopride	*P* value
No of patients n	93	82	
Elapsed time from last fluid intake to colonoscopy (min, mean ± SD)	384.4±72.2	383.6±62.0	0.936
Endoscopic findings (n, %)			
Cancer	5 (5.4)	3 (3.7)	0.857
Polyps	25 (26.9)	20 (24.4)	0.626
Adenoma	11 (11.8)	8 (9.8)	0.651
Inflammation	3 (3.2)	4 (4.9)	0.865
Ulcer colitis	4 (4.3)	1 (1.2)	0.443
Coron disease	0	1 (1.2)	0.469
Ascending colon lipoma	0	1 (1.2)	0.469

PEG, Polyethylene glycol; SD, standard deviation.

Table 5. Results of side effects, willingness to repeat, time to first defecation and frequency of defecation were compared in two groups

Patient questionnaire variable	PEG	Prucalopride	*P* value
Side effects (n, %)			
Nausea	41 (44.1)	33 (39.8)	0.608
Vomiting	20 (21.5)	8 (9.6)	0.034
Abdominal pain	11 (11.8)	17 (20.5)	0.109
Bloating	13 (14.0)	10 (12.2)	0.728
Circulatory reactions	2 (2.2)	3 (3.6)	0.886
Headache	0	2 (2.4)	0.218
Willingness to repeat the same regimen *(n, %)*	78 (83.9)	72 (87.8)	0.458
Time to first defecation (min, mean ± SD)	57.2±44.1	25.7±19.7	0.000
Frequency of defecation (times, median ± s.d)	8.0±3.2	9.3±3.5	0.008

PEG, Polyethylene glycol; SD, standard deviation.

nificant between the two groups. An "excellent prep" was observed more often in the prucalopride group than in the PEG group (P=0.003).

Studies [27] found that the quality of bowel preparation was influenced by the time interval between the last PEG intake and the start of colonoscopy. In the current study, the elapsed time from the last fluid intake to colonoscopy was not significantly different between the two groups (P=0.936).

Colonoscopic data (polyp detection rate, adenoma detection rate, and other abnormal findings of colon) also showed no significant difference between the groups (**Table 4**).

Patient questionnaire data

The frequency of vomiting was significantly lower in the prucalopride group than in the PEG group (P=0.03). The frequency of defecation was significantly higher in the prucalopride group than in the PEG group (P=0.008). The time of first defecation was significantly shorter in the prucalopride group than in the PEG group (P<0.001). Frequencies of symptoms such as nausea, bloating, abdominal pain, headache, circulatory reactions, and willingness to repeat the same regimen were similar in both the groups (**Table 5**).

Discussion

Colonoscopy is widely considered to be the gold standard for the detection of colorectal polyps and cancer. To achieve the optimal visualization of the mucosa, good bowel preparation is essential. Unfortunately, no such bowel preparation exists. Today, split-dose 4-L PEG with electrolytes is a better method for colon preparation compared with other bowel preparation

regimens [13]. However, it also needs a large volume of fluid, and it turns a same-day scheme to a 2-day procedure. Prucalopride is a selective, high-affinity, 5-HT_4 agonist with gastrointestinal prokinetic properties. The high affinity and selectivity for 5-HT_4 differentiates prucalopride from former generation compounds, and minimizes the potential for target-unrelated side effects [17]. The stimulation of the 5-HT_4 receptor induces the facilitation of cholinergic and noncholinergic excitatory neurotransmission, and hence prucalopride has potential for the treatment of disorders associated with small and/or large bowel dysfunction, including constipation, postoperative ileus, and pseudo-obstruction [28]. The safety and efficacy of prucalopride in CC has been investigated in an extensive development program [29, 30]. The recommended dose of the drug in adults in most countries is 2 mg daily [31, 32]. However, whether prucalopride would have additive beneficial effects on bowel cleansing before colonoscopy in humans is unclear.

In the bowel preparation of colonoscopy, right colon cleansing is considered to be important because the cleansing can be difficult and polyps located in the right colon may be easily missed. Sessile serrated polyps are more commonly located in the right colon and are likely even more vulnerable to underdetection than adenomas in persons with suboptimal preparations [33]. Hong et al [34] showed that risk of missed colon lesions increased in patients with poor/inadequate bowel preparation compared with patients with excellent bowel preparation. In this study, although the mean scores of each individual component, the sum of these components and overall fluid quantity was lower in the prucalopride group than in the PEG group, but the difference was not statistically significant. A "good prep" and an "excellent prep" as defined previously were observed more often in the prucalopride group than in the PEG group in the right colon (P=0.006) and in the whole colon (P=0.003), respectively.

The time between bowel preparation and start of colonoscopy is also important in determining bowel preparation quality. A shorter interval between the last dose of bowel preparation and colonoscopy procedure is associated with improved bowel preparation quality [26]. To maximize preparation quality, colonoscopy should be performed within -5 h of the last dose of preparation. Every hour by which the interval is extended is associated with a 10% decrease in adequate bowel preparation [26]. An interval of more than 5 h from the last purgative dose allows new small intestinal effluent to coat the right colonic mucosa, which impairs mucosal visualization [33]. Because of significant worsening in bowel preparation quality, consideration should be given to not performing colonoscopies with a preparation-to-colonoscopy interval greater than 7 h [35]. In this study, the lapsed time from the last fluid intake to colonoscopy is (mean ± SD) 384.4±72.2 and 383.6±62.0 min in the PEG group and the prucalopride group, respectively. No statistical difference was observed in the two groups (P=0.936). Studies found that through reducing residual fluid in the colon, mosapride and itopride improved efficacy in patients [15, 16]. In this study, although the overall fluid quantity in the Ottawa scale was lower in the prucalopride group than in the PEG group, the difference was not statistically significant. The lapsed time from the last fluid intake to colonoscopy was too long, allowing new small intestinal effluent to colon may be associated with these.

The ADR is currently the most important measure of colonoscopy quality [36]. In an asymptomatic screening population, an ADR of ≥25% in men and of ≥15% in women over 50 years old has been proposed in the American screening guidelines [36]. In both the groups in this study, adenoma detection rates were lower than the average standards for colonoscopy screening, which were ≥25% for men and ≥15% for women 50 years of age or more. These results may be explained as follows: (1) The time between bowel preparation and the start of colonoscopy exceeding 6 h allows new small intestinal effluent to colon and coats the colon surface, which impairs mucosal visualization. (2) Colonoscopic withdrawal times and withdrawal technique may influence ADR. In China, endoscopists need to do too much work, which make them pursuit of speed at the expense of efficiency.

Although many preparations and regimens are available, patient compliance with bowel cleansing can be a significant issue [37]. Reduced tolerability of bowel preparations is associated with high volume, bad taste, and increased abdominal symptoms, particularly vomiting [38]. There was evidence that frequen-

cies of vomiting are significantly lower in the prucalopride group than in the PEG group (P=0.034). The time of first defecation was shorter in the prucalopride group than in the PEG group (P=0.00). More frequent bowel movement was observed in the prucalopride group than in the PEG group (P=0.008). The findings of this study were same with other studies [17, 18]. These findings may be due to prokinetic effects of prucalopride.

One of the limitations of this study was that the quality of preparation was assessed at the time of insertion of the colonoscope before any cleansing maneuvers. Cleaning up is part of colonoscopy and is necessary to one degree or another in most examinations, even if in many cases this simply means washing down bubbles and mucus. In clinical practice, retained fluid and much of the semisolid debris in the colon can be removed by intraprocedural cleansing. The quality of the bowel preparation should be judged after the cleaning process has occurred since only that level of cleansing reflects on the adequacy of mucosal inspection [39]. The other limitation is that the patients took a fixed dose of prokinetics at a fixed time. Further studies need to be performed to analyze the influence of different administration time of prokinetics and their optimal dose on colon preparation.

In summary, this study showed that prucalopride results in less vomiting, improves the quality of bowel preparation for colonoscopy in the right colon, and for the whole colon the excellent prep is more. Thus, it is concluded that prucalopride may be an effective and safe adjunct to PEG that leads to improved quality of bowel preparation.

Disclosure of conflict of interest

None.

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References

[1] Jemal A, Bray F, Center MM, Ferlay J, Ward E and Forman D. Global cancer statistics. CA Cancer J Clin 2011; 61: 69-90.

[2] Nettles JL and Linscheid RL. Sternoclavicular dislocations. J Trauma 1968; 8: 158-164.

[3] Li B, Shi XY, Liao DX, Cao BR, Luo CH and Cheng SJ. Advanced colorectal adenoma related gene expression signature may predict prognostic for colorectal cancer patients with adenoma-carcinoma sequence. Int J Clin Exp Med 2015; 8: 4883-4898.

[4] Rex DK, Johnson DA, Anderson JC, Schoenfeld PS, Burke CA and Inadomi JM. American College of Gastroenterology guidelines for colorectal cancer screening 2009 [corrected]. Am J Gastroenterol 2009; 104: 739-750.

[5] Froehlich F, Wietlisbach V, Gonvers JJ, Burnand B and Vader JP. Impact of colonic cleansing on quality and diagnostic yield of colonoscopy: the European Panel of Appropriateness of Gastrointestinal Endoscopy European multicenter study. Gastrointest Endosc 2005; 61: 378-384.

[6] Marmo R, Rotondano G, Riccio G, Marone A, Bianco MA, Stroppa I, Caruso A, Pandolfo N, Sansone S, Gregorio E, D'Alvano G, Procaccio N, Capo P, Marmo C and Cipolletta L. Effective bowel cleansing before colonoscopy: a randomized study of split-dosage versus non-split dosage regimens of high-volume versus low-volume polyethylene glycol solutions. Gastrointest Endosc 2010; 72: 313-320.

[7] Sharma VK, Chockalingham SK, Ugheoke EA, Kapur A, Ling PH, Vasudeva R and Howden CW. Prospective, randomized, controlled comparison of the use of polyethylene glycol electrolyte lavage solution in four-liter versus two-liter volumes and pretreatment with either magnesium citrate or bisacodyl for colonoscopy preparation. Gastrointest Endosc 1998; 47: 167-171.

[8] Adams WJ, Meagher AP, Lubowski DZ and King DW. Bisacodyl reduces the volume of polyethylene glycol solution required for bowel preparation. Dis Colon Rectum 1994; 37: 229-233; discussion 233-224.

[9] Di Palma JA, Rodriguez R, McGowan J and Cleveland M. A randomized clinical study evaluating the safety and efficacy of a new, reduced-volume, oral sulfate colon-cleansing preparation for colonoscopy. Am J Gastroenterol 2009; 104: 2275-2284.

[10] Huppertz-Hauss G, Bretthauer M, Sauar J, Paulsen J, Kjellevold O, Majak B and Hoff G. Polyethylene glycol versus sodium phosphate in bowel cleansing for colonoscopy: a randomized trial. Endoscopy 2005; 37: 537-541.

[11] Kao D, Lalor E, Sandha G, Fedorak RN, van der Knoop B, Doornweerd S, van Kooten H, Schreuders E, Midodzi W and Veldhuyzen van Zanten S. A randomized controlled trial of four precolonoscopy bowel cleansing regimens. Can J Gastroenterol 2011; 25: 657-662.

[12] Park SS, Sinn DH, Kim YH, Lim YJ, Sun Y, Lee JH, Kim JY, Chang DK, Son HJ, Rhee PL, Rhee JC and Kim JJ. Efficacy and tolerability of split-dose magnesium citrate: low-volume (2 liters) polyethylene glycol vs. single- or split-dose polyethylene glycol bowel preparation for morning colonoscopy. Am J Gastroenterol 2010; 105: 1319-1326.

[13] Johnson DA, Barkun AN, Cohen LB, Dominitz JA, Kaltenbach T, Martel M, Robertson DJ, Boland CR, Giardello FM, Lieberman DA, Levin TR and Rex DK. Optimizing adequacy of bowel cleansing for colonoscopy: recommendations from the U.S. multi-society task force on colorectal cancer. Gastrointest Endosc 2014; 80: 543-562.

[14] Chinese Medical Association of Gastroenterology, Chinese Journal of Digestive Endoscopy related bowel preparation guidelines. Chin J Dig Endosc 2013; 30.

[15] Tajika M, Niwa Y, Bhatia V, Kawai H, Kondo S, Sawaki A, Mizuno N, Hara K, Hijioka S, Matsumoto K, Kobayashi Y, Saeki A, Akabane A, Komori K and Yamao K. Efficacy of mosapride citrate with polyethylene glycol solution for colonoscopy preparation. World J Gastroenterol 2012; 18: 2517-2525.

[16] Kim HJ, Kim TO, Shin BC, Woo JG, Seo EH, Joo HR, Heo NY, Park J, Park SH, Yang SY, Moon YS, Shin JY and Lee NY. Efficacy of prokinetics with a split-dose of polyethylene glycol in bowel preparation for morning colonoscopy: a randomized controlled trial. Digestion 2012; 86: 194-200.

[17] Briejer MR, Bosmans JP, Van Daele P, Jurzak M, Heylen L, Leysen JE, Prins NH and Schuurkes JA. The in vitro pharmacological profile of prucalopride, a novel enterokinetic compound. Eur J Pharmacol 2001; 423: 71-83.

[18] Quigley EM, Vandeplassche L, Kerstens R and Ausma J. Clinical trial: the efficacy, impact on quality of life, and safety and tolerability of prucalopride in severe chronic constipation--a 12-week, randomized, double-blind, placebo-controlled study. Aliment Pharmacol Ther 2009; 29: 315-328.

[19] Annex 1: Summary of product characteristics. Available 1. URL:http://www.ema.europa.eu/docs/en_GB/document_library/ EPAR_-_Product_Information/human/001012/WC500053998.pdf (Accessed 5 December, 2013). Italy: Janssen Cilag S.P.A; 2011.

[20] Emmanuel A, Cools M, Vandeplassche L and Kerstens R. Prucalopride improves bowel function and colonic transit time in patients with chronic constipation: an integrated analysis. Am J Gastroenterol 2014; 109: 887-894.

[21] Nennstiel S, Bajbouj M, Schmid RM and Becker V. Prucalopride reduces the number of reflux episodes and improves subjective symptoms in gastroesophageal reflux disease: a case series. J Med Case Rep 2014; 8: 34.

[22] Ke M, Zou D, Yuan Y, Li Y, Lin L, Hao J, Hou X and Kim HJ. Prucalopride in the treatment of chronic constipation in patients from the Asia-Pacific region: a randomized, double-blind, placebo-controlled study. Neurogastroenterol Motil 2012; 24: 999-e541.

[23] Rostom A and Jolicoeur E. Validation of a new scale for the assessment of bowel preparation quality. Gastrointest Endosc 2004; 59: 482-486.

[24] Sharara AI, Harb AH, Sarkis FS, Chalhoub JM, Badreddine R, Mourad FH, Othman M and Masri O. Split-dose menthol-enhanced PEG vs PEG-ascorbic acid for colonoscopy preparation. World J Gastroenterol 2015; 21: 1938-1944.

[25] Shah H, Desai D, Samant H, Davavala S, Joshi A, Gupta T and Abraham P. Comparison of split-dosing vs non-split (morning) dosing regimen for assessment of quality of bowel preparation for colonoscopy. World J Gastrointest Endosc 2014; 6: 606-611.

[26] Varughese S, Kumar AR, George A and Castro FJ. Morning-only one-gallon polyethylene glycol improves bowel cleansing for afternoon colonoscopies: a randomized endoscopist-blinded prospective study. Am J Gastroenterol 2010; 105: 2368-2374.

[27] Eun CS, Han DS, Hyun YS, Bae JH, Park HS, Kim TY, Jeon YC and Sohn JH. The timing of bowel preparation is more important than the timing of colonoscopy in determining the quality of bowel cleansing. Dig Dis Sci 2011; 56: 539-544.

[28] De Schryver AM, Andriesse GI, Samsom M, Smout AJ, Gooszen HG and Akkermans LM. The effects of the specific 5HT(4) receptor agonist, prucalopride, on colonic motility in healthy volunteers. Aliment Pharmacol Ther 2002; 16: 603-612.

[29] Camilleri M and Deiteren A. Prucalopride for constipation. Expert Opin Pharmacother 2010; 11: 451-461.

[30] Camilleri M, Beyens G, Kerstens R, Robinson P and Vandeplassche L. Safety assessment of prucalopride in elderly patients with constipation: a double-blind, placebo-controlled study. Neurogastroenterol Motil 2009; 21: 1256-e1117.

[31] Resolor, prucalopride. European Public Assessment Report (EPAR) Product Information. Updated 11/11/ 2011. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/

human/001012/WC500053998.pdf (accessed 5 Dec 2011).
[32] Australian Public Assessment Report for prucalopride. Therapeutic Goods Administration (TGA), Australian Government Department of Health and Ageing. November 2011. Available at: http://www.tga.gov.au/pdf/auspar/auspar-resotrans.pdf (accessed 5 Dec 2011).
[33] Seo EH, Kim TO, Park MJ, Joo HR, Heo NY, Park J, Park SH, Yang SY and Moon YS. Optimal preparation-to-colonoscopy interval in split-dose PEG bowel preparation determines satisfactory bowel preparation quality: an observational prospective study. Gastrointest Endosc 2012; 75: 583-590.
[34] Hong SN, Sung IK, Kim JH, Choe WH, Kim BK, Ko SY, Lee JH, Seol DC, Ahn SY, Lee SY, Park HS and Shim CS. The effect of the bowel preparation status on the risk of missing polyp and adenoma during screening colonoscopy: a tandem colonoscopic study. Clin Endosc 2012; 45: 404-411.
[35] Sweetser S and Baron TH. Optimizing bowel cleansing for colonoscopy. Mayo Clin Proc 2015; 90: 520-526.
[36] Rex DK, Petrini JL, Baron TH, Chak A, Cohen J, Deal SE, Hoffman B, Jacobson BC, Mergener K, Petersen BT, Safdi MA, Faigel DO and Pike IM. Quality indicators for colonoscopy. Gastrointest Endosc 2006; 63: S16-28.
[37] The prep is worse than the procedure. Split dosing and some new liquids may make bowel cleansing needed for colonoscopy a bit easier and perhaps more palatable. Harv Health Lett 2010; 35: 6-7.
[38] Dykes C and Cash BD. Key safety issues of bowel preparations for colonoscopy and importance of adequate hydration. Gastroenterol Nurs 2008; 31: 30-35; quiz 36-37.
[39] Rex DK. Optimal bowel preparation--a practical guide for clinicians. Nat Rev Gastroenterol Hepatol 2014; 11: 419-425.