3-L Split-dose is Superior to 2-L Polyethylene Glycol in Bowel Cleansing in Chinese Population

A Multicenter Randomized, Controlled Trial

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Abstract: Large volume (4 L) of polyethylene glycol (PEG) solution would ensure a better quality of bowel cleansing but might be poorly tolerated. Due to the smaller body size, lower body weight, and different diet habits, the large volume of 4-L PEG might be poorly tolerated by the Chinese population. In view of this, a balance should be made between the volume and effectiveness. This study aimed to compare the effectiveness, compliance, and safety between 3-L split-dose and 2-L PEG in Chinese population.

Consecutive patients scheduled for colonoscopy were recruited from 5 tertiary medical centers in South China between April and July, 2014. Patients were prospectively randomized into 2 groups: 3-L split-dose PEG (3L-group) and 2L PEG (2L-group). The primary endpoint was bowel cleansing and was defined according to Ottawa Bowel Preparation Scale (OBPS). The safety and compliance were also evaluated.

A total of 318 patients were included in the analysis. The mean total OBPS score was significantly higher in 2L-group than in 3L-group (4.4 ± 2.7 vs 2.9 ± 2.4 , P < 0.001). Both the intention-to-treat and perprotocol analysis found that rates of successful and excellent bowel preparation were much higher in 3L-group (89.9% and 78.0%) than 2L-group (79.2% and 48.4%), respectively (P < 0.001). The average cecum intubation time was significantly shorter in 3L-group (8.2 ± 3.7 min) than in 2L-group (10.3 ± 4.2 min) (P = 0.04). Adenoma detection rate in right colon was slightly higher in 3L-group than in 2L-group (17.6% vs 12.6%, P = 0.21). The safety and compliance including the taste, smell, and dosage of PEG were similar between 2 groups (P > 0.05).

3-L split-dose PEG is superior to 2-L PEG by better bowel cleansing, improved safety and compliance, shorter cecum intubation time,

SZ and ML contributed equally to the work

The authors declared no conflicts of interest.

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and potentially higher adenoma detection rate in rightward colon in Chinese population.

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Abbreviations: PEG = polyethylene glycol, OBPS = Ottawa Bowel Preparation Scale, CRC = colorectal cancer, IBD = inflammatory bowel disease, GI = gastrointestinal, ESGE = European Society of Gastrointestinal Endoscopy, CKD = chronic kidney disease, ADR = adenoma detection rate.

INTRODUCTION

C olorectal cancer (CRC) is one of the most common cancers worldwide.¹⁻³ Advanced CRC results in poor prognosis. Early detection and timely treatment improve patients' outcome. Colonoscopy has become a standard and valuable tool in screening colorectal polyps and CRC. Detection and removal of colonic polyps greatly reduce the risk of CRC.⁴ In addition, colonoscopy can also be used to detect early inflammatory bowel disease (IBD) and to monitor the disease progression.⁵ It has great advantage as a noninvasive tool and has not been surpassed despite a number of techniques that are developed in the last 2 decades.

Proper bowel cleansing is a crucial aspect directly correlated with the diagnostic performance and the complication rate of a colonoscopy. An ideal bowel cleansing solution should be safe, effective, and well tolerated by the patients.⁶ Nowadays, polyethylene glycol (PEG) is recommended as the first-line bowel preparation agent and it has achieved great success in clinical practice.⁷ However, the volume of PEG solution most suitable for patients in different populations is still debatable. European Society of Gastrointestinal Endoscopy recommends a split regimen of 4-L PEG solution for routine bowel cleansing in Western countries.⁷ In contrast, in the past 2 decades, 2-L PEG alone without any supplement is routinely used in China. In the recent Chinese consensus on bowel preparation before endoscopy, PEG alone is recommended in clinical practice.8 However, from the experience of ours and other gastrointestinal (GI) doctors in China, the widely used 2-L PEG in bowel preparation is not satisfactory, especially for screening the lesions in the rightward colon. Brown solid or liquid residuals are often found at this site, masking potential lesions. It also causes discomfort to the patients and increases the risk of complication due to the difficulty in intubation. We have previously reported that CRC in South China has experienced a rightward shift in the site distribution in the past 2 decades.⁹ Therefore, it is important to achieve an adequate bowel preparation in the whole large intestine to reduce the miss rate of potential lesions.

Previous studies including a recent meta-analysis reported that 4-L split-dose (2+2L or 3+1L) PEG was superior to

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other bowel preparation methods, but great heterogeneity existed among the included studies.^{10,11} Currently, no study has been conducted in Chinese. Due to the smaller body size, lower body weight, and different diet habits, the large volume of -4L PEG might be poorly tolerated by the Chinese population. In view of this, a balance should be made between the volume and effectiveness. We therefore proposed to reduce the volume of 4-L PEG to 3 L. We hypothesized that 3-L split-dose (1+2L) PEG bowel preparation regimen would be superior to 2 L in bowel preparation. To test our hypothesis, we performed a prospective, multicenter, randomized controlled trial to compare the effectiveness, tolerability, and safety between 3-L split-dose and 2-L PEG in a Chinese cohort in South China.

PATIENTS AND METHODS

Patients and Study Design

This is a prospective, multicenter, single-blinded, randomized, controlled trial. Consecutive patients who were scheduled for colonoscopy were recruited from outpatient clinics and inpatient wards of 5 tertiary medical centers in South China between April and July, 2014. All patients were between age of 18 and 75 years. Exclusion criteria included suspected GI perforation or obstruction, history of GI resection, moderate or massive active GI bleeding (>100 mL/day), chronic kidney disease (CKD, Stage 2-5), chronic heart failure (New York Heart Association Class II-IV), pregnancy, severe IBD with stricturing or penetrating disease, severe constipation (<2 bowel movements per week), and major psychiatric illness. Patients were randomly assigned to receive 2-L PEG (2L-group) or 3-L split-dose (1+2L) PEG (3L-group) for their bowel preparation according to a computer-generated randomization table. Figure 1 shows patient recruitment and randomization. Demographic characteristics, body mass index (BMI), major complaints, and previous medical history were collected using the questionnaire on the day before colonoscopy. The study protocol was approved by the Human Ethics Committee of Endoscopy Society of Guangdong Province in South China and was conducted according to Declaration of Helsinki. The procedure was strictly conducted and monitored, and was guided by the Chairman of Endoscopy Society of Guangdong Province (Prof. Minhu Chen and Prof. Yi Cui). Written informed consent was given by all patients.

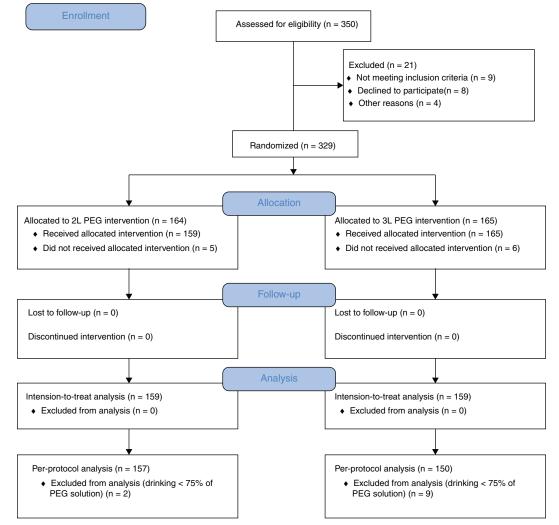


FIGURE 1. Patients' recruitment and randomization.

Bowel Preparation

Colonoscopy was performed by experienced GI endoscopists (3 endoscopists in each study center) who performed >500 colonoscopies per year and who were blinded to the bowel preparation regimens that the patients received. The bowel preparation regimens were 3-L split-dose or 2 L of PEG4000 (Pfizer Italia S.R.L.). All patients were limited to low-residue foods the day before colonoscopy. Patients randomized to the 2L-group received 2 bags of PEG and were instructed to drink the whole dosage at a rate of 250 mL every 10 to 15 minutes 4 to 6 h before colonoscopy. Patients randomized to the 3L-group received 3 bags of PEG and were instructed to drink 1 L at 21:00 in the evening before the day of colonoscopy, and to drink the remaining 2 L 4 to 6 h before colonoscopy. PEG solution was contained in graduated bottles and the volume ingested was recorded by the patients themselves.

Primary Endpoint: Colon Cleansing

The primary endpoint of the study was the overall quality of bowel preparation. Preparation effectiveness was evaluated by the blinded endoscopists according to the Ottawa bowel preparation scale (OBPS).^{12,13} This scale assesses cleanliness and fluid volume, separately. Cleanliness was assessed for the right colon (cecum, ascending), mid-colon (transverse, descending), and the rectosigmoid colon separately (Figure 2). Each colon section was rated from 0 to 4 score (0 score = perfect, no liquid; 1 score = minimal clear liquid, no suction; 2 score = suction required to see mucosa; 3 score = semi-solid residue, required washing and suction; 4 score = solid stool, not washable). Global fluid quantity was rated from 0 to 2 for the whole colon (0 score = minimal, no suction; 1 score = moderate, need some

suction; 2 score = large, need a lot of suction). Total score was obtained by adding the cleanliness scores of the 3 segments and the fluid score, ranging from 0 (perfect colon cleansing) to 14 score (solid stool in each colon segment and lots of fluid). A total score <7 was considered successful bowel cleansing¹⁴ and a total score ≤ 4 as excellent bowel cleasing.¹⁵ To minimize interobserver variability, in our preliminary study, all the endoscopists were trained to use OBPS. They were asked to review colonoscopy videos of 15 patients and evaluate the bowel preparation effectiveness using OBPS. Afterwards, they discussed the OBPS score of each patient and reached a consensus.

Secondary Endpoints

Secondary endpoints of the study included patients' tolerability on the taste, smell, and dosage of PEG, sleep disturbance, and adverse events related to the PEG. Patients were required to complete a questionnaire before the colonoscopy. Tolerability on the perceived taste and smell were assessed using a 4-point scale (very good = 1, good = 2, tolerable = 3, intolerable = 4). Tolerability on the dosage was measured according to a scale based on the consumption of the PEG: 1 = optimal (100% of the prescribed solution), 2 = good (\geq 75% of the prescribed solution), 3 = poor (<75% of the prescribed solution).^{16,17} Adverse events such as abdominal pain, bloating, vomiting, and nausea were recorded. Sleep disturbance referred to <70% of their usual sleep duration during the bowel preparation.

Statistical Analysis

This study was designed to assess the superiority of 3-L split-dose PEG regimen compared with 2-L PEG regimen in

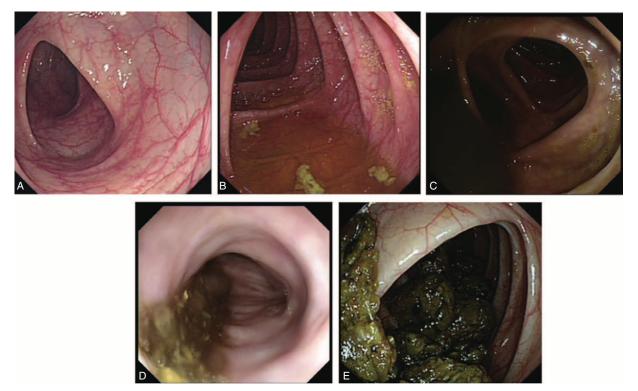


FIGURE 2. Ottawa bowel preparation scale. The cleanliness of each colon section was individually rated from 0 to 4. (A) 0 score = perfect, no liquid; (B) 1 score = minimal clear liquid, no suction; (C) 2 score = suction required to see mucosa; (D) 3 score = semi-solid residue, required washing and suction; (E) 4 score = solid stool, not washable.

bowel cleansing. Our primary endpoint was the successful bowel cleansing rate defined as a total OBPS score <7. Sample size was calculated using the following formula: $\frac{(Z_{a\alpha}+Z_{\beta})^2[P_{C}*(1-P_{C})+P_{T}(1-P_{T})]}{(P_{T}-P_{C})^2}$ According to previous studies, we assumed that the proportion of patients achieving successful bowel preparation was 85% for the 3-L PEG regimen group and 70% for the 2-L PEG regimen group, respectively.¹⁵ Allowing a drop-out rate of 10%, a sample size of 300 patients (150 per group) would achieve 85% power to detect a significant difference between the 2 groups with a significance level (alpha) of 0.05.

Statistical analyses were performed using the SPSS for Windows version 19.0 (IBM Corp, Armonk, NY, USA). Continuous variables were reported as means \pm SD or median (interquartile range) and categorical variables as numbers and percentages. Continuous variables were compared between the 2 groups using *t* test and categorical variables using Pearson's χ^2 test. Analyses on the primary endpoints (the rates of successful and excellent bowel cleansing) were performed on both intention -to-treat (ITT) and per-protocol (PP) (patients who had ingested at least 75% of the prescribed PEG solution) cohorts. All other analyses were performed on ITT cohort. All hypotheses were 2-tailed and a *P* value <0.05 was considered statistically significant.

RESULTS

Demographic and Clinical Characteristics

A total of 350 patients were screened for eligibility for the study (Figure 1). Twenty-one patients did not meet the inclusion criteria because of comorbidity or GI surgery (n = 9), refusal to participate (n = 8), and insufficient compliance (n = 4), and 11 patients canceled colonoscopy before the procedure due to personal reason. The remaining 318 patients (159 patients in each group) were enrolled in this study for ITT analysis.

Table 1 shows the demographic and clinical characteristics of the study cohort. Male to female ratio, age, body weight, and BMI were comparable between the 2 groups. The most common indications for colonoscopy were abdominal pain or discomfort, diarrhea, health checkup, constipation, and hematochezia, with no significant difference between the 2 groups (P = 0.76). Other complaints included anemia, weight loss and altered fecal characteristics. The percentage of patients with a history of constipation did not differ between the 2 group (P = 1.0). Polyps were the most frequent positive findings under colonoscopy in both groups. The total adenoma detection rate (ADR) in colorectum was 25.8% in 2-L group, and 27.7% in 3-L group, without significant difference between them (P = 0.723). ADR in right colon was slightly higher in 3L-group than in 2L-group (17.6% vs 12.6%, $\chi^2 = 1.57$, P = 0.21). A total of 158 patients

TABLE 1. Demographic and Clinical Characteristics

Variables	2L-group (n = 159)	3L-group (n = 159)	Р
Sex, n (%)			
Male	90 (56.6)	79 (49.7)	0.22
Female	69 (43.4)	80 (50.3)	
Age, years, median (IQR)	47 (37–58)	47 (39-60)	0.27
Body weight, kg, median (IQR)	60 (53-65)	61 (55–68)	0.15
Body mass index, kg/m ² , median (IQR)	22.0 (20.6-23.5)	22.3 (20.7–23.6)	0.23
Indication for colonoscopy, n (%)	· · · · ·		0.76
Rectal bleeding	17 (10.7)	11 (6.9)	
Constipation	15 (9.4)	19 (11.9)	
Diarrhea	23 (14.5)	22 (13.9)	
Abdominal pain	47 (29.6)	50 (31.4)	
Health checkup	23 (14.4)	24 (15.1)	
Others	34 (21.4)	33 (20.8)	
Prior colonoscopy, n (%)			0.17
Yes	70 (44.0)	58 (36.5)	
No	89 (56.0)	101 (63.5)	
History of constipation, n (%)			1.0
Yes	40 (25.2)	40 (25.2)	
No	119 (74.8)	119 (74.8)	
Anesthesia, n (%)			0.65
Yes	79 (49.7)	83 (52.2)	
No	80 (50.3)	76 (47.8)	
Diagnosis of colonoscopy, n (%)			0.82
Tumor	4 (2.5)	4 (2.5)	
Inflammatory bowel disease	8 (5.0)	8 (5.0)	
Chronic enteritis	14 (8.8)	8 (5.0)	
Polyps	50 (31.4)	52 (32.7)	
Other	7 (4.5)	5 (3.1)	
Normal	76 (47.8)	82 (51.7)	

IQR = interquartile range.

had a negative finding under colonoscopy (49.7%), with no significant difference between the 2 groups (P = 0.50).

Efficacy of Bowel Preparation

The mean \pm SD duration between the last intake of the solution and colonoscopy in the 3L- and 2L-group was 5.0 ± 1.4 and 4.6 ± 1.4 h, respectively. The percentage of patients achieving a clean without any fecal residual bowel preparation was significantly higher in the 3L-group than in the 2L-group (83% vs 69.9%, P = 0.01) (Table 2). Total OBPS score for 318 patients was significantly higher in the 2L-group than in the 3L-group (mean \pm SD: 4.4 \pm 2.7 vs 2.9 \pm 2.4, P < 0.001). OBPS cleanliness scores for right colon, mid-colon, and rectogsigmoid were all significantly higher in the 2L-group. Average fluid score was 40% significantly higher in the 2Lgroup (mean \pm SD: 0.7 \pm 0.7 vs 0.5 \pm 0.6, P < 0.001). In ITT analysis, the percentage of successful bowel preparation, indicated by total OBPS score <7, were significantly higher in 3Lgroup (89.9%) than in 2L-group (79.2%) ($\chi^2 = 6.97, P = 0.008$). The percentage of excellent bowel preparation, indicated by total OBPS score ≤ 4 was also significantly higher in patients in 3L-group (78.0%) than in 2L-group (48.4%) ($\chi^2 = 29.87$, P < 0.001). Similar results were found in PP analyses. Successful cecal intubation was achieved in all the patients in both groups. The average cecum intubation time was significantly shorter in 3L-group $(8.2 \pm 3.7 \text{ min})$ than in 2L-group $(10.3 \pm 4.2 \text{ min})$ (P = 0.04). No significant difference in average total OBPS score was found between male and female patients in either 2L-group (4.2 vs 4.7, P = 0.27) or 3L-group (2.7 vs 3.1, P = 0.22). Similarly, there were no significant differences between patients with BMI $<24 \text{ kg/m}^2$ and BMI \geq 24 kg/m² in either 2L-group (4.3 vs. 4.7, P=0.31) or 3L-group (2.8 vs. 3.1, P = 0.37).

Patients' tolerability, compliance, and safety

TABLE 2 Bowel Preparation Quality

All patients could endure the taste of the solution (Table 3). The smell of the solution was rated acceptable (1-3 points) by most of the patients (92.5%). The majority of patients in both groups could ingest more than 75% of the amount of solution

DISCUSSION

adverse event. However, the percentage of patients having

disturbance of sleep was significantly higher in the 3L-group

than in 2L-group (51.6% vs 38.4%, P = 0.02).

The quality of bowel cleansing is vital to a successful colonoscopy. A poor bowel cleansing would prolong the procedure time, increase the risk of bowel penetration, shorten the interval of colonoscopy screening, and increase the miss rate of polyps or early CRC lesions.¹⁸ This would result in increased costs to the family and society. Strategies for bowel preparation are the subject of investigation and there is still a pursuit of optimal regime. Recent findings from meta-analysis or clinical trial showed that PEG, introduced in 1980, remains a good option for bowel cleansing. In most of the colonoscopy centers, PEG is the first-line bowel cleansing regimen in clinical practice. Due to its mechanical lavage, a higher volume of solution will usually achieve a better bowel cleansing. It is confirmed by a recent meta-analysis comparing 4-L split-doses PEG and other bowel cleansing methods. Analysis showed that 4-L split-dose PEG had a much better bowel cleansing efficacy than others.^{7,10} However, the tolerability of such a large volume is questionable, especially for patients with smaller body size such as the Asians. It has been reported that BMI was an independent factor associated with bowel preparation efficacy.¹⁹ More intensive bowel preparation solution is recommended to patients with higher BMI. In view of this, we designed this randomized controlled clinical trial to compare the effectiveness, tolerability, compliance, and safety in bowel cleansing between the 3-L split-dose and 2-L PEG in Chinese.

Variables	2L-group (n = 159)	3L-group (n = 159)	Р
Fecal character before colonoscopy, n (%)			
Very clean, no residual	111 (69.8)	132 (83.0)	0.01
Minimal fecal residual	43 (27.0)	26 (16.4)	
Lots of fecal residual	5 (3.2)	1 (0.6)	
OBPS total score, mean (SD)	4.4 (2.7)	2.9 (2.4)	< 0.001
Cleanliness score			
Right colon	1.5 ± 1.0	1.0 ± 1.0	< 0.001
Mid-colon	1.2 ± 0.9	1.1 ± 0.9	< 0.001
Rectosigmoid colon	0.8 ± 0.8	0.7 ± 0.7	< 0.001
Fluid score	0.7 ± 0.7	0.5 ± 0.6	< 0.001
Intention-to-treat analysis			
Successful bowel cleansing, n (%)	126 (79.2%)	143 (89.9%)	0.008
Excellent bowel cleansing, n (%)	77 (48.4%)	124 (78.0%)	< 0.001
Per-protocol analysis			
Successful bowel cleansing, n (%)	123 (78.3%)	138 (92.0%)	< 0.001
Excellent bowel cleansing, n (%)	80 (51.0%)	115 (76.7%)	< 0.001

Variables	2L-group (n = 159)	3L-group (n = 159)	Р
Taste, n (%)			0.43
Very good	6 (3.8)	2 (1.3)	
Good	51 (32.1)	54 (34.0)	
Average	69 (43.3)	64 (40.2)	
Poor	33 (20.8)	39 (24.5)	
Smell, n (%)			0.19
Very good	7 (4.4)	2 (1.3)	
Good	52 (32.7)	58 (36.4)	
Average	85 (53.5)	90 (56.6)	
poor	15 (9.4)	9 (5.7)	
Dosage, n (%)			0.06
Easy to repeat	82 (51.6)	62 (39.0)	
Acceptable	56 (35.2)	75 (47.2)	
Too much	21 (13.2)	22 (13.8)	
Adverse event, n (%)			
Bloating	49 (30.8)	53 (33.3)	0.63
Nausea	36 (22.6)	41 (25.8)	0.51
Headache	13 (8.2)	16 (10.1)	0.56
Dizziness	8 (5.0)	13 (8.2)	0.26
Vomiting	7 (4.4)	9 (5.7)	0.61
Abdominal cramps	6 (3.8)	8 (5.0)	0.59
Disturbance on sleep, n (%)	· · ·		0.02
Yes	61 (38.4)	82 (51.6)	
No	98 (61.6)	77 (48.4)	

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IABLE 3.	Patients'	Compliance	to the	Polyeth	ylene Glycol

Our results confirmed our hypothesis that 3-L split dose PEG was more effective than 2-L PEG in bowel preparation. Rate of successful bowel preparation was significantly higher in 3L-group (89.8%) than in 2L-group (79.2%). Rate of excellent bowel preparation was also higher by 1.6-folds in patients in 3Lgroup than in 2L-group. The successful rate was comparable with that reported in 4-L split-dose in whites.^{10,20-22} Compared with 2L-group, 3L-group had a better quality of bowel cleansing according to the Ottawa scoring system. In sub-analysis by site, the mean OBPS score in right, mid, and rectosigmoid colon was all much higher in 2L-group than in 3L-group. Due to the better bowel cleansing, the cecum intubation time was shorter in 3Lgroup than in 2L-group. Solid or brown liquid residual are often found in the rightward colon, resulting in a higher miss rate of small lesions at this site, especially some early CRC or advanced polyp. Previous studies found that poor bowel preparation was associated with lower detection rate of proximal adenoma.^{23,24} In a large population-based study, significantly more right-sided CRC cases were found in prior negative colonoscopy cohort than the general population during a 10year interval of colonoscopy. The authors concluded that this might be partly attributable to the inadequate bowel cleansing that affects the right colon more than the rest of the colorectum.²⁵ ADR in the whole colorectum was similar in these 2 groups, which was consistent with previous studies.^{26–28} Compared with other sites, the mean OBPS was much higher in 2Lgroup than in 3L-group in right colon. ADR in right colon was also higher by 5% in the 3L-group, albeit not statistical significant. In addition, lower volume of PEG solution with an unsatisfactory bowel cleansing might shorten the interval to repeat colonoscopy, which would impose psychological and economic burden to the patients. Together with the rightward shift on the location of CRC as reported in China and in Western countries,⁴ the significantly improved bowel cleansing in the whole colon especially in the right colon proved that 3-L splitdose PEG regimen has the potential to reduce miss rate of precancerous lesions and should be recommended as standard regimen in Chinese.

It was reported that the quality of bowel cleansing was associated with the interval between the last dose of solution and the procedure. A short interval may be insufficient for bowel content to discharge completely, whereas a long interval may lead to excessive secretion of the bowel.²⁹ An interval of 5 to 8 h was found optimal for adequate bowel cleansing.²⁹ In this study, this interval was about 5 h in both the groups and the majority of the patients had adequate bowel cleansing. Therefore, this interval should also be recommended for clinical practice.

In addition to the quality of bowel cleansing, patients' tolerability, compliance, and adverse events are also important issues. Although higher volume of PEG solution would achieve a better quality of bowel cleansing, patients would be less tolerated by it. In this study, >90% of patients in both groups could ingest >75% of the amount of solution, suggesting that the 3-L solution was as well-tolerated as 2-L solution. The symptoms related to PEG ingestion such as bloating, nausea, vomiting, abdominal cramps, headache, and dizziness were not common and percentage of these adverse events were similar to that reported by previous studies.^{9,21,22,30} No significant difference on percentage of adverse events was found between 2L and 3L-group. However, sleep disturbance was more common in the 3L-group than in 2L-group. This was probably attributed to the schedule of PEG ingestion the day before colonoscopy, which resulted in bowel movements after drinking 1-L PEG and disturbed the sleep quality in some patients.

There were several limitations in this study. First, we did not compare the effectiveness between 3-L split-dose PEG and 2-L PEG with supplement. A clinical trial addressing this issue

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is currently ongoing in our center. It might provide more evidence for the optimal regimen in bowel cleansing. Second, BMI might influence the efficacy of bowel cleansing. Although the baseline of the 2 groups in this study was comparable, further study should address whether personalized volume of PEG based on individual's BMI would be superior. Last, the sample size may not be large enough. Further study involving larger sample would confirm the effectiveness, safety, and compliance in Chinese population.

In conclusion, this randomized controlled trial found that 3-L split-dose PEG regimen is superior to 2-L PEG regimen in achieving a better quality of bowel preparation in Chinese. It could shorten the cecal intubation time and has the potential to increase the detection rate of adenoma in the proximal colon. It is also as well-tolerated and safe as 2-L PEG regimen with good compliance. We recommend the 3-L split-dose PEG the standard regimen in clinical setting for Chinese patients.

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REFERENCES

- Bray F, Ren JS, Masuyer E, et al. Global estimates of cancer prevalence for 27 sites in the adult population in 2008. *Int J Cancer*. 2013;132:1133–1145.
- van Leersum NJ, Janssen-Heijnen ML, Wouters MW, et al. Increasing prevalence of comorbidity in patients with colorectal cancer in the South of the Netherlands 1995–2010. *Int J Cancer*. 2013;132:2157–2163.
- Maringe C, Mangtani P, Rachet B, et al. Cancer incidence in South Asian migrants to England, 1986–2004: unraveling ethnic from socioeconomic differentials. *Int J Cancer*. 2013;132:1886–1894.
- Brenner H, Chang-Claude J, Jansen L, et al. Colorectal cancers occurring after colonoscopy with polyp detection: sites of polyps and sites of cancers. *Int J Cancer.* 2013;133:1672–1679.
- Lei P, Gu F, Hong L, et al. Pediatric colonoscopy in South china: a 12-year experience in a tertiary center. *PLoS One*. 2014;9:e95933.
- Martens P, Bisschops R. Bowel preparation for colonoscopy: efficacy, tolerability and safety. *Acta Gastroenterol Belg.* 2014;77:249–255.
- Hassan C, Bretthauer M, Kaminski MF, et al. Bowel preparation for colonoscopy: European Society of Gastrointestinal Endoscopy (ESGE) guideline. *Endoscopy*. 2013;45:142–150.
- Chinese Society for Gastrointestinal Endoscopy. Chinese consensus on bowel preparation before endoscopy. *Chinese J Pract Intern Med.* 2013;33:705–707.
- Zhang S, Cui Y, Weng Z, et al. Changes on the Disease Pattern of Primary Colorectal Cancers in Southern China: a retrospective Study of 20 years. *Int J Colorectal Dis.* 2009;24:943–949.
- Enestvedt BK, Tofani C, Laine LA, et al. 4-Liter split-dose polyethylene glycol is superior to other bowel preparations, based on systematic review and meta-analysis. *Clin Gastroenterol Hepatol.* 2012;10:1225–1231.
- 11. Kilgore TW, Abdinoor AA, Szary NM, et al. Bowel preparation with split-dose polyethylene glycol before colonoscopy: a meta-analysis

of randomized controlled trials. *Gastrointest Endosc.* 2011;73:1240–1245.

- Gupta T, Mandot A, Desai D, et al. Comparison of two schedules (previous evening versus same morning) of bowel preparation for colonoscopy. *Endoscopy*. 2007;39:706–709.
- Kim HJ, Kim TO, Shin BC, et al. 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.
- de Leone A, Tamayo D, Fiori G, et al. Same-day 2-L PEG-citratesimethicone plus bisacodyl vs split 4-L PEG: Bowel cleansing for late-morning colonoscopy. World J Gastrointest Endosc. 2013;5:433–439.
- Brahmania M, Ou G, Bressler B, et al. 2 L versus 4 L of PEG3350 b electrolytes for outpatient colonic preparation: a randomized, controlled trial. *Gastrointest Endosc.* 2014;79:408–416.
- Moon CM, Park DI, Choe YG, et al. Randomized trial of 2-L polyethylene glycol + ascorbic acid versus 4-L polyethylene glycol as bowel cleansing for colonoscopy in an optimal setting. J Gastroenterol Hepatol. 2014;29:1223–1228.
- Repici A, Cestari R, Annese V, et al. Randomised clinical trial: lowvolume bowel preparation for colonoscopy-a comparison between two different PEG-based formulations. *Aliment Pharmacol Ther*. 2012;36:717–724.
- Hillyer GC, Basch CH, Lebwohl B, et al. Shortened surveillance intervals following suboptimal bowel preparation for colonoscopy: results of a national survey. *Int J Colorectal Dis.* 2013;28:73–81.
- Fayad NF, Kahi CJ, Abd El-Jawad KH, et al. Association between body mass index and quality of split bowel preparation. *Clin Gastroenterol Hepatol.* 2013;11:1478–1485.
- Corporaal S, Kleibeuker JH, Koornstra JJ. Low-volume PEG plus ascorbic acid versus high-volume PEG as bowel preparation for colonoscopy. *Scand J Gastroenterol.* 2010;45:1380–1386.
- Xie Q, Chen L, Zhao F, et al. A meta-analysis of randomized controlled trials of low- volume polyethylene glycol plus ascorbic acid versus standard-volume polyethylene glycol solution as bowel preparations for colonoscopy. *PLoS One.* 2014;9:e99092.
- Parente FR, Repici A, Crosta C, et al. Overall acceptability and efficacy of commonly used bowel preparations for colonoscopy in Italian clinical practice. A multicentre prospective study. *Dig Liver Dis.* 2014;46:795–802.
- de Wijkerslooth TR, Stoop EM, Bossuyt PM, et al. Differences in proximal serrated polyp detection among endoscopists are associated with variability in withdrawal time. *Gastrointest Endosc*. 2013;77:617–623.
- 24. Anderson JC, Butterly LF, Robinson CM, et al. Impact of fair bowel preparation quality on adenoma and serrated polyp detection: data from the New Hampshire Colonoscopy Registry by using a standardized preparation-quality rating. *Gastrointest Endosc*. 2014;80:463–470.
- Singh H, Turner D, Xue L, et al. Risk of developing colorectal cancer following a negative colonoscopy examination: evidence for a 10-year interval between colonoscopies. *JAMA*. 2006;295:2366– 2373.
- 26. Sabbagh LC, Reveiz L, Aponte D, et al. Narrow-band imaging does not improve detection of colorectal polyps when compared to conventional colonoscopy: a randomized controlled trial and metaanalysis of published studies. *BMC Gastroenterol.* 2011;11:100.
- Kumbhari V, Behary J, Hui JM. Prevalence of adenomas and sessile serrated adenomas in Chinese compared with Caucasians. J Gastroenterol Hepatol. 2013;28:608–612.

- Yang MH, Rampal S, Sung J, et al. The prevalence of colorectal adenomas in asymptomatic Korean men and women. *Cancer Epidemiol Biomarkers Prev.* 2014;23:499–507.
- 29. Seo EH, Kim TO, Park MJ, et al. Optimal preparationto-colonoscopy interval in split-dose PEG bowel preparation determines satisfactory bowel preparation quality: an

observational prospective study. *Gastrointest Endosc.* 2012; 75:583–590.

 Park DI, Park SH, Lee SK, et al. Efficacy of prepackaged, low residual test meals with 4L polyethylene glycol versus a clear liquid diet with 4L polyethylene glycol bowel preparation: a randomized trial. J Gastroenterol Hepatol. 2009;24:988–991.