Original Article

Effectiveness of 2-liter Split-dose versus 2-liter Non-split-dose Polyethylene Glycol for Bowel Preparation in Colonoscopy

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Background: Adequate bowel cleansing is essential for effective and safe colonoscopy. However, standard 4 liters or low volume 2 liters bowel preparation regimen uses a lot of water that cause pain in patients.

Objective: To compare the degree of colon cleansing using 2-liter split-dosage and 2-liter non-split-dosage and evaluate the outcome from bowel preparation.

Materials and Methods: This study was a single-blind, randomized study, which conducted in tertiary-care institutions. All enrolled patients who underwent colonoscopy were randomized to receive 2-liter split-dose polyethylene glycol [PEG] or 2-liter non-split-dose PEG. The bowel preparation scale and questionnaires were evaluated after the procedure.

Results: One hundred and eighty patients were evaluated in this study, 91 patients received 2-liter split-dose and 89 patients received 2-liter non-split-dose PEG. Boston bowel preparation scale [BBPS] scores were not significantly different in both groups (8.7$\pm$0.6 in 2-liter spilt group vs. 8.6$\pm$0.6 in 2-liter non-split group, p = 0.25). Cecal intubation rate, willingness to repeat colonoscopy and overall satisfaction were also not different in both groups. However, more patients chose 2-liter spilt-dose regimen than 2-liter non-split regimen for the next colonoscopy (66.7% vs. 33.3%, p = 0.003).

Conclusion: Two-liter split-dose PEG was as effective as two-liter non-split-dosage for bowel cleansing in colonoscopy. However, split dose has superior palatability compared to non-split dose.

Keywords: Boston bowel preparation scale, Bowel preparation, Colonoscopy, Non-split-dose, Polyethylene glycol, Split-dose

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Colorectal cancer [CRC] is the second leading cause of cancer-related deaths in the United States[1]. Data from hospital-based cancer registry of the National Cancer Institute of Thailand in 2014[2] reported CRC was the most common form of cancer in male, and the third most common form of cancer in female after breast and cervical cancer. Colonoscopy can prevent CRC by detection and removal of precancerous lesions. The success of colonoscopy links closely to the adequacy of pre-procedural bowel preparation. Unfortunately, up to 20% to 25% of all colonoscopies are reported to have an inadequate bowel preparation[3,4]. Adverse consequences of ineffective bowel preparation include lower adenoma detection rate, longer procedural time, lower cecal intubation rate, increased electrocautery risk, and shorter intervals between examinations[4-7].

Polyethylene glycol [PEG] is a non-absorbable solution that should pass through the bowel without net absorption or secretion. Large volumes (4L) are required to achieve a cathartic effect[8]. Unfortunately,

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5% to 15% of patients cannot intake large volume formula and thus cause insufficient bowel preparation[9,10]. Recent study show high-volume PEG (>3L) and low-volume PEG (<3L) had the same effect in bowel cleanliness[11-15]. However, low-volume PEG (<3L) was still problematic in small patients as the quantity were still too large for small patients which meant they would then need to reschedule their colonoscopy. Splitting dose meant half of the bowel preparation dose is given on the day of colonoscopy. There is a large body of evidence showing superior efficacy of a split dose compared to the traditional regimen[16].

The purpose of study was to evaluate the degree of colon cleansing and other outcome in the patients who undergone elective colonoscopy by comparing low volume (2L) PEG split and low volume (2L) non-split dosage.

Materials and Methods

Patients

This study was a single-blind, prospective, randomized controlled study of adult patients who undergone routine elective colonoscopy which conducted in Phramongkutklao Hospital, Bangkok, Thailand between February 2016 and November 2016. All patients with an appropriate indication for colonoscopy were considered eligible (age 18 to 80 years old, American Society of Anesthesiologists physical status class 1 or 2 with accepted consent form). Exclusion criteria were pregnant or lactating women, significant gastroparesis or gastric outlet obstruction, known or suspected bowel obstruction, history of any gastrointestinal tract surgery, history of inflammatory bowel disease, allergy to PEG, severe chronic renal failure (creatinine clearance <30 mL/min), severe congestive heart failure (New York Heart Association class 3 or 4), compromised swallowing reflex or mental status, patients who morbid obesity (body mass index >40 kg/m^2), history of prolonged laxative and opioid and history of previous failure of adequate bowel preparation for colonoscopy.

Bowel preparation method

PEG used in the present study was Niflec® (Meiji, Japan), which composed of macrogol 4,000 plus electrolytes (sodium sulfate, sodium hydrogen carbonate, sodium chloride and potassium chloride) and is taken by diluting into 2L of plain water. The quantity per interval was 250 mL every 15 minutes. In cases of the non-split dosage, the entire dose was administered in the morning at about 5.00 to 7.00 am of the procedure day. In case of the split dosage, half dose preparation started in the evening of preprocedure day at about 9.00 to 10.00 pm and remaining dose was given in the morning at about 5.00 to 6.00 am on the procedure day.

Dietary advice was given to all patients. Consumption of fruit, legumes, or vegetable were forbidden 3 days prior to the procedure. On the day before colonoscopy patients had a light breakfast and lunch but a semiliquid dinner (clear soup, yoghurt or compote). Solid food was not allowed at the start of the bowel preparation phrase. All patients were instructed to fast from midnight before procedure day but some anti-hypertensive drugs and minimal plain water were permitted.

Randomization and blinding

Patients were enrolled by the medical personnel of the endoscopy unit after assessment of appropriate indications and ruling out any contra indications to the procedure or to the use of PEG solutions. Patients were randomly allocated to receive one of the 2 different bowel preparation regimens (split-dosage vs. non-split-dosage), using a computer generated, and random number list with at permutative block of 4. After a protocol was selected, only endoscopy nurses would have the information on treatment allocation and advice each patient about the regimen of bowel preparation.

Assessment of bowel preparation scoring system

Bowel cleansing from recorded images were assessed by J.I. who were unaware of the preparation method. Boston bowel preparation scale [BBPS] was a selected scale used in our study. BBPS was evaluated in 3 segments (right colon, transverse colon and left colon) with a score of 0 (solid stools) to 3 (no residual staining) for each segment. Adequate bowel preparation was defined as a score of $\geq$2 for each segment. The maximum summation BBPS score for a perfectly clean colon without any residual liquid is 9 and the minimum summation score for an unprepared colon is 0[17].

Colonoscopy and endpoint measurement

In the morning of a colonoscopy, immediately before the procedure, a nurse questioned the patients about their experiences and satisfactions by using a standardized questionnaire. Patients were asked about compliance, tolerance and last stool character. The

endoscopists were not allowed during this process. Colonoscopies were performed by endoscopists who were unaware of the treatment allocation.

Full colonoscopy was defined as the scope reach ileocecal valve and cecum. Failed colonoscopy was defined as endoscope could not reach ileocecal valve and cecum. Overall procedure times was the times between the endoscope enter and withdraw from the anus.

The primary endpoint was the degree of colon cleansing which was evaluated by BBPS. The secondary endpoints were cecal intubation rate, overall procedure times and patient's satisfaction. The patient's satisfaction was evaluated with a 10-cm visual analog scale which 10 means excellent and 0 means very poor.

Any adverse events related to bowel preparation (nausea, vomiting, bloating, abdominal pain, headache, etc) were recorded by the endoscopy nurse, and all participants were monitored for adverse events during colonoscopy.

Sample size calculation and statistical analysis

This study was a non-inferiority design for comparing the degree of colon cleansing using standard 2-liter non-split-dosage and 2-liter split-dosage.According to the previous study in 2010[16], the calculated sample size would be 164 patients with an alpha error of 5%, a power of 99%. Unpaired t-tests and variance analysis were used for multiple comparisons for continuous data. Categorical variables were tested by using corrected Chi-square or 2-sided Fisher exact tests when appropriate. All statistical analyses were performed with SPSS (version 15.0; SPSS Inc., Chicago, IL, USA), and $p<0.05$ was considered significant. Intention-to-treat analysis was performed.

Ethics

Ethical approval for the present study was granted by the institutional review boards of Royal Thai Army Medical Department, Phramongkutklao Hospital, Bangkok, Thailand and conformed to the provisions of the Declaration of Helsinki. This study registered with Thai clinical trial registry (TCTR 20160609005). In addition, all eligible patients were asked to sign written, informed-consent documents.

Results

Study population

A total of 180 patients were included and randomized to the non-spilt-dosage regimen (n = 89) and split-dosage regimen (n = 91). Demographic and clinical features are shown in Table 1. Age, gender, body mass index [BMI], underlying diseases were similar in both groups. The mean age of the patients was 62.5±11.5 years, 51.1% were male and the mean BMI was 23.6±3.5 kg/m^2. Education level of the patients were higher in non-split group. Both groups had similar underlying disease but diabetes mellitus was significantly more common in spilt dosage regimen (11.2% in non-spilt group vs. 25.3% in split group, $p = 0.015$). Some patients had more than one underlying diseases. Indication in colonoscopy was similar in both groups. Colorectal cancer screening was the most common indication. Cecal intubation was not significantly different between the two groups.

Quality of bowel cleansing

The mean summation of BBPS in all segments were similar in both groups (8.7±0.6 in non-spilt group, 8.6±0.6 in spilt group, $p = 0.25$). Scales of 3 were predominantly found in transverse and left side colon, whereas scales of 2 was predominantly found in right side colon as shown in Table 2.

Procedure findings

Mean total procedure time was 35±16 minutes in non-split group, and 43±25 minutes in split group ($p = 0.012$). Findings in colonoscopy were similar in both groups but colonic diverticulosis were significantly found in only the non-split group. The most common finding was colonic polyps. Colonic polyps were detected in 83 of 180 patients (46.1%). Some patients had more than one finding. Others finding in colonoscopy were lipoma in two cases and foreign body in one case.

Failed colonoscopy was found in 4 cases (2.2%, 2 cases in non-split group and 2 cases in split group). Causes of failed colonoscopy were reflex bradycardia in 1 case, nearly obstructive mass in 2 cases and sigmoid redundant with acute angle in 1 case. Patients from 3 of these cases were sent to specialist cardiologist and the colorectal surgeon for proper management. In the last case, the patient was sent to perform virtual colonoscopy and the result was normal. Cecal intubation failed in 11 cases (6.1%, 2 cases in non-split and 7 cases in split group).

Tolerability and satisfaction

Overall satisfaction was excellent in both groups as shown in Table 3. The mean numeric rating

Table 1. Demographic and clinical features

Parameters	Non-split dosage (n = 89)	Split dosage (n = 91)	*p*-value
Age (years), mean ± SD	62.0±11.0	63.0±12.0	0.306
Male sex, n (%)	52 (58.4)	40 (44)	0.052
BMI (kg/m^2), mean ± SD	23.6±3.3	23.5±3.7	0.840
Education, n (%)			0.009
Non-education	3 (3.4)	2 (2.2)	
Below bachelor degree	20 (22.5)	40 (44)	
Bachelor degree and higher	66 (74.2)	49 (53.8)	
Underlying diseases, n (%)	82 (92.1)	77 (84.6)	0.116
Hypertension	52 (58.4)	54 (59.3)	0.901
Dyslipidemia	41 (46.1)	46 (50.5)	0.547
Diabetes mellitus	10 (11.2)	23 (25.3)	0.015
Others$^+$	10 (11.2)	6 (6.6)	0.274
Indication for colonoscopy, n (%)			
Colorectal cancer screening	63 (70.8)	66 (72.5)	0.890
Iron deficiency anemia	12 (13.5)	14 (15.4)	0.358
Diarrhea	6 (6.7)	4 (4.4)	0.263
Others^{++}	8 (9.9)	7 (7.7)	0.452
Total procedure time (min), mean ± SD	35±16	43.0±25.0	0.012
Cecal intubation, n (%)	87 (97.8)	84 (92.3)	0.663
Colonoscopic findings, n (%)			
Normal	21 (23.6)	18 (19.8)	0.533
Colonic polyp(s)	42 (47.2)	41 (45.1)	0.769
Colonic diverticulosis	27 (30.3)	42 (46.2)	0.028
Ulcer(s)	2 (2.2)	7 (7.7)	0.169
Tumor	3 (3.4)	3 (3.3)	1.000
Hemorrhoids	19 (21.3)	18 (19.8)	0.854
Others*	1 (1.1)	2 (2.2)	1.000

BMI = body mass index; SD = standard deviation

$^+$ Other underlying diseases include chronic viral hepatitis, chronic kidney disease, previous ischemic stroke and allergic rhinitis.

$^{++}$ Other indications include weight loss, chronic abdominal pain and abnormal radiological examination.

* Other findings include lipoma and foreign body.

scale score of satisfaction was 9.5 (standard deviation, 1) in both groups which 10 means excellent and 0 means very poor. One hundred and seventy one of 180 (95%) patients were willing to repeat colonoscopy in the future if needed. When we ask for a favorable regimen, most of the patient (120 of 180, 66.7%) selected split-dosage regimen as a future regimen. Only one patient in non-split group reported nausea and bloating. Serious adverse event was not reported in our study.

Discussion

Colonoscopy is one of the most important tools to prevent colorectal cancer. Effectiveness of colonoscopy depends on the cleanliness of bowel preparation. The current guideline recommends 4-litre split-dose PEG (2L or 3L on the night before and 2L or 1L the day of procedure, respectively) for bowel preparation[18-21].

Corporaal et al reported low volume PEG (2L on the day of procedure) was as effective as 4L of PEG[22] but cleanliness in the right colon was less frequently satisfactory with 2L PEG than with 4L PEG. However, 2L of PEG was better tolerated by small patients, especially in Asians.

This study showed that bowel cleanliness in 2-litre spilt-dose PEG (1L on the night before and 1L the day of procedure) was not different from 2-litre non-split PEG. Moreover, cecal intubation rate and adenoma detection rate were not different between groups. This result was similar to the study of Marmo et al which showed that degree of colon cleansing in spilt low volume PEG was superior to non-spilt low

Table 2. Quality of bowel cleansing in different regimens

	Non-split dosage (n = 89)	Split dosage (n = 91)	*p*-value
Summation of BBPS score, mean ± SD	8.7±0.6	8.6±0.6	0.250
BBPS score at each segment, n (%)			
Right side colon			0.573
1	2 (2.2)	2 (2.2)	
2	24 (27)	28 (30.8)	
3	63 (70.8)	61 (67)	
Transverse colon			0.048
1	2 (2.2)	0	
2	0	4 (4.4)	
3	87 (97.8)	87 (95.6)	
Left side colon			0.805
1	0	0	
2	6 (6.7)	7 (7.7)	
3	83 (93.3)	84 (92.3)	

BBPS = Boston bowel preparation scale; SD = standard deviation

Table 3. Tolerability and satisfaction in different regimens

	Non-split dosage (n = 89)	Split dosage (n = 91)	*p*-value
Overall satisfaction[+], mean ± SD	10±1	9±1	0.171
Willing to repeat colonoscopy if needed, n (%)	85 (95.5)	86 (94.5)	1.000
Favorable regimen, n (%)			0.003
Non-split dosage	39 (43.8)	21 (23.1)	
Split dosage	50 (56.2)	70 (76.9)	

SD = standard deviation
[+] 10 point scales, 0 means very poor and 10 means excellent

volume[16]. However, in that study, low volume PEG patients were encouraged to drink at least 1L of additional clear fluid.

In the present study, the right colon tended to be dirtier than transverse and left colon but all segments of the colon were also adequately cleaned (BBPS ≥2). Total procedure time was longer in split group. This is due to numbers of polyps that were higher than the non-split group, so it took times for polypectomy. However, there was no difference in adenoma detection rate.

This study had several strengths. First, we used BBPS to access quality of bowel cleansing. BBPS has been validated by studies as the best scoring system and was recommended by US multi-society task force on colorectal cancer. Score of 5 or higher was associated with only a 2% rate of repeat colonoscopy owing to inadequate preparation. Second, we evaluated level of education for each groups. Patients' education level is very important for bowel cleansing. However, it did not affect the bowel cleansing score as we closely advised the patients as well as giving them the information sheets and contact number in case they had a problem with bowel preparation. The patients in our study were very cooperative regardless of their level of education and so their education level has no impact on the results. Third, we used only PEG without any additional agents (e.g. ascorbic acid or bisacodyl) that may cause some adverse side effects. So there were no side effect in this study.

This study had some limitations. First, population consisted of only Thais and low BMI patients which do not reflect the patients in western countries. Second, population were selected by more

strict criteria that do not reflect the patient in real world. Third, this study was a single-center study.

Conclusion

The efficacy of low volume (2L) PEG was good. There is no serious adverse side effects in colon cleanliness for colonoscopy and the effect from non-split dosage and split dosage were the same. However, most patients favored split dose regimen. We suggested larger scale studies and perform in western countries for further evaluation.

What is already known on this topic?

The 2-liter non-split dose PEG was widely used for bowel preparation regimen in Thailand. This study showed that bowel cleanliness in that regimen was good.

What this study adds?

The 2-liter split-dose PEG was as effective as 2-liter non-split-dosage for bowel cleansing in colonoscopy.

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Potential conflicts of interest

None.

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin 2012; 62: 10-29.
2. Information and Technology Division National Cancer Institute (NCI), Thailand. Hospital-based cancer registry annual report 2014. Bangkok: NCI; 2016.
3. Froehlich F, Wietlisbach V, Gonvers JJ, Burnand B, Vader JP. Impact of colonic cleansing on quality and diagnostic yield of colonoscopy: the European Panel of Appropriateness of Gastro-intestinal Endoscopy European multicenter study. Gastrointest Endosc 2005; 61: 378-84.
4. Harewood GC, Sharma VK, de Garmo P. Impact of colonoscopy preparation quality on detection of suspected colonic neoplasia. Gastrointest Endosc 2003; 58: 76-9.
5. Bond JHJr, Levitt MD. Factors affecting the concentration of combustible gases in the colon during colonoscopy. Gastroenterology 1975; 68: 1445-8.
6. Rex DK, Imperiale TF, Latinovich DR, Bratcher LL. Impact of bowel preparation on efficiency and cost of colonoscopy. Am J Gastroenterol 2002; 97: 1696-700.
7. Senore C, Ederle A, Fantin A, Andreoni B, Bisanti L, Grazzini G, et al. Acceptability and side-effects of colonoscopy and sigmoidoscopy in a screening setting. J Med Screen 2011; 18: 128-34.
8. Di Palma JA, Brady CE 3rd, Stewart DL, Karlin DA, McKinney MK, Clement DJ, et al. Comparison of colon cleansing methods in preparation for colonoscopy. Gastroenterology 1984; 86: 856-60.
9. Golub RW, Kerner BA, Wise WEJr, Meesig DM, Hartmann RF, Khanduja KS, et al. Colonoscopic bowel preparations—which one? A blinded, prospective, randomized trial. Dis Colon Rectum 1995; 38: 594-9.
10. Marshall JB, Pineda JJ, Barthel JS, King PD. Prospective, randomized trial comparing sodium phosphate solution with polyethylene glycol-electrolyte lavage for colonoscopy preparation. Gastrointest Endosc 1993; 39: 631-4.
11. Abut E, Guveli H, Yasar B, Bolukbas C, Bolukbas FF, Ince AT, et al. Administration of olive oil followed by a low volume of polyethylene glycol-electrolyte lavage solution improves patient satisfaction with right-side colonic cleansing over administration of the conventional volume of polyethylene glycol-electrolyte lavage solution for colonoscopy preparation. Gastrointest Endosc 2009; 70: 515-21.
12. Di Palma JA, Wolff BG, Meagher A, Cleveland M. Comparison of reduced volume versus four liters sulfate-free electrolyte lavage solutions for colonoscopy colon cleansing. Am J Gastroenterol 2003; 98: 2187-91.
13. Jansen SV, Goedhard JG, Winkens B, van Deursen CT. Preparation before colonoscopy: a randomized controlled trial comparing different regimes. Eur J Gastroenterol Hepatol 2011; 23: 897-902.
14. Mathus-Vliegen EM, van der Vliet K. Safety, patient's tolerance, and efficacy of a 2-liter vitamin C-enriched macrogol bowel preparation: a randomized, endoscopist-blinded prospective comparison with a 4-liter macrogol solution. Dis Colon Rectum 2013; 56: 1002-12.
15. Park SS, Sinn DH, Kim YH, Lim YJ, Sun Y, Lee JH,

et al. 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: 1319-26.
16. Marmo R, Rotondano G, Riccio G, Marone A, Bianco MA, Stroppa I, et al. 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: 313-20.
17. Lai EJ, Calderwood AH, Doros G, Fix OK, Jacobson BC. The Boston bowel preparation scale: a valid and reliable instrument for colonoscopy-oriented research. Gastrointest Endosc 2009; 69: 620-5.
18. Hassan C, Bretthauer M, Kaminski MF, Polkowski M, Rembacken B, Saunders B, et al. Bowel preparation for colonoscopy: European Society of Gastrointestinal Endoscopy (ESGE) guideline. Endoscopy 2013; 45: 142-50.
19. Lieberman DA, Rex DK, Winawer SJ, Giardiello FM, Johnson DA, Levin TR. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2012; 143: 844-57.
20. Rex DK, Johnson DA, Anderson JC, Schoenfeld PS, Burke CA, Inadomi JM. American College of Gastroenterology guidelines for colorectal cancer screening 2009 [corrected]. Am J Gastroenterol 2009; 104: 739-50.
21. Wexner SD, Beck DE, Baron TH, Fanelli RD, Hyman N, Shen B, et al. A consensus document on bowel preparation before colonoscopy: prepared by a task force from the American Society of Colon and Rectal Surgeons (ASCRS), the American Society for Gastrointestinal Endoscopy (ASGE), and the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES). Gastrointest Endosc 2006; 63: 894-909.
22. 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: 1380-6.