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Effect of Coffee Added to a Polyethylene glycol plus Ascorbic acid Solution for Bowel Preparation prior to Colonoscopy

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ABSTRACT

Background & Aims: Conventional bowel cleansers for colonoscopy have an unpleasant taste and a large volume of solution must be ingested. Coffee increases bowel motility and has an intense flavor. The addition of coffee to a polyethylene glycol+ascorbic acid solution reduces the volume of the solution to be consumed without reducing efficacy, improves the taste of the solution and enhances patient comfort.

Methods: Outpatients with clinical indication or people who wanted screening for cancer were considered eligible. Control group (PEGAS group) consumed a 1-L solution of polyethylene glycol+ascorbic acid twice. Study group (COF group) consumed 750 mL of coffee+polyethylene glycol+ascorbic acid twice. Bowel cleansing was rated using the Aronchick, Ottawa scale, polyp detection rate and colonoscopic insertion time. Tolerability, acceptability, preference, and adverse events were investigated by questionnaires.

Results: The COF group had non-inferiority in efficacy (non-inferiority margin, -15 %; lower limit of 95 % confidence interval for difference between success rates, - 4.7 % and –8.4 % from both scales, respectively). Polyp detection rates were 0.48 and 0.60, respectively (P=0.067). Colonoscopic insertion times were 323.6±166.8 s and 330.7±243.6 s, respectively (P=0.831). Significant improvement was observed with respect to ease of drinking (P=0.012), taste (P=0.026) and preference (P=0.046) in the COF group. Adverse events occurred in 52.4 % and 60.4 % in the two groups, respectively (P = 0.251).

Conclusion: The addition of coffee to polyethylene glycol+ascorbic acid solution reduces the required volume for bowel preparation without reduced efficacy and enhances patient comfort in coffee-drinkers.

Key words: coffee – bowel preparation– polyethylene glycol – ascorbic acid.

Abbreviations: ASC: ascorbic acid; PEG: polyethylene glycol; AE: adverse event; PP: per protocol; ITT: intention-to-treat; PICO: sodium picosulfate.

INTRODUCTION

Adequate bowel preparation is essential for effective colonoscopy [1]. Poor compliance with bowel cleansing regimens frequently limits colonoscopy results because most bowel cleansers have unpleasant flavors and/or require the consumption of large volumes of fluid [2]. Previous work reported that drinking a 1-L solution of polyethylene glycol (PEG) and ascorbic acid (ASC) on the evening before colonoscopy, followed by a second 1-L dose on the morning of the procedure, was an effective bowel preparation regimen and slightly easier to drink than PEG alone because of improved taste and reduced consumed fluid volume [3]. However, this preparation method still requires patients to consume large volumes of an unpleasantly tasting fluid.

Coffee has been reported to increase bowel motility, and has an intense, pleasant flavor [4-6]. Thus, mixing coffee with the PEG+ASC solution may reduce the total volume necessary for effective bowel preparation without reduced bowel cleansing efficacy, by enhancing bowel motility and mask the unpleasant taste of the solution, and therefore increase patient comfort and adherence to the solution during bowel preparation. Because coffee is very accessible at low cost world widely, it would be very useful if only mixing coffee can help increasing comfort during preparation for colonoscopy. However, no studies have examined the use of coffee for bowel preparation. In this study, we sought to determine whether mixing coffee with the

PEG+ASC solution can reduce the volume of the solution to be consumed for bowel preparation, without reduced efficacy and improved taste of the solution. Therefore, it could increase patient comfort and adherence to the solution with both the ability of mixing coffee to reduce effective volume to be consumed and improving the taste of the solution.

METHODS

Study design

This was a prospective, single (endoscopist)-blinded, randomized controlled study. It was registered at the Clinical Research Information Service of the Korea National Institute of Health (KCT0000930), and is available on the International Clinical Trials Registry Platform of WHO (http://apps.who.int/trialsearch/Trial2.aspx?Trial ID=KCT0000930).

Ethics

This study was approved by the Institutional Review Board/Ethics Committee of Kangnam Sacred Heart Hospital, Hallym University College of Medicine. Written informed consent was obtained from all participants.

Subjects

Outpatients with general clinical indication or people who wanted to undergo colonoscopy for screening or surveillance for colorectal cancer, aged between 18 and 75 years with spontaneous bowel motility at least three times per week were considered eligible. Exclusion criteria are presented in Table I. Non-coffee drinkers, regardless of the reason, were not considered as subjects.

Randomization and assignment

Participants were assigned to the control or study group using a randomized code list with a block size of four, generated using the 'Random Allocation Program' (ver. 1, by M. Saghaei, M.D., Isfahan University of Medical Sciences, Isfahan, Iran).

Materials and bowel preparation

The participants allocated to the control (PEGAS; PEG + ASC) group received Coolprep (Taejoon Pharmaceutical Co., Ltd.), consisting of two 1 L plastic containers, two pouches of 100.0 g PEG + other ingredients (7.5g sodium sulfate, 2.691g sodium chloride, and 1.015 g potassium chloride) and two pouches of 4.7 g ASC + 5.9 g sodium ascorbate. Subjects were instructed to dissolve the contents of one PEG pouch and one ASC pouch in 1 L of water and to drink the solution within 1h at 10 p.m. on the evening before the scheduled colonoscopy, and then to repeat this procedure within 1h at 6 a.m. on the morning of the scheduled colonoscopy (Supplemental Fig. 1).

Participants allocated to the study (COF: coffee + PEG + ASC) group received two pouches of 5.4 g coffee granules (50 mg of caffeine, roasted and freeze-dried instant coffee, Maxim, Dong Suh Food Co., Ltd.) in addition to Coolprep. Subjects were instructed to dissolve the contents of the three pouches (coffee, PEG, and ASC) in 750 mL water and to drink it in the same manner as participants in the PEGAS group (Supplemental Fig. 1). It was recommended that participants in both groups avoid a high-residue diet for at least three days before the scheduled colonoscopy. Breakfast on the day of the colonoscopy was forbidden.

Masking and colonoscopy

Structured questionnaires regarding the tolerability, acceptability, preference, and subjective adverse events (AEs) of bowel cleansers were completed immediately before the colonoscopy. Colonoscopies were performed between 8:30 a.m. and 12:30 p.m. by endoscopists with experience of more than 5,000 colonoscopies. Patients were kept under conscious sedation, if desired by the examinee with the approval of the clinician. The endoscopists were blinded to the group assignment. Immediately after colonoscopy, the status of bowel preparation, the endoscopic insertion time, and the number and sizes of polyps detected were recorded by the endoscopist. Endoscopists were also required to predict the assigned group of the subject to ascertain whether blinding of the endoscopist was disturbed because the addition of coffee might have affected the color of the luminal fluid.

The primary endpoints included the efficacy of bowel cleansing, polyp detection rate, and colonoscopic insertion time. To evaluate the efficacy of bowel cleansing, the Aronchick Bowel Preparation Scale (ABPS) [7] and the Ottawa Bowel Preparation Scale (OBPS) [8] were used. The polyp detection rate (number of colonoscopies in which at least one polyp was found/the total number of colonoscopies), the more-than-0.5cm-polyp detection rate (number of colonoscopies in which at least one polyp larger than 0.5 cm was found/the total number of colonoscopies), and the colonoscopic insertion time (time of entry of the scope tip through the anal canal - arrival at the cecum) were also used as indicators of bowel cleansing

Tabel I. Excluded patients.

Patients with gastrointestinal and colorectal problems
Acute surgical abdomen, an active state of inflammatory bowel disease, active colon disease (e.g., acute colitis, ileus), acute peptic ulcer, gastric outlet obstruction, or gastroparesis, history of colorectal or gastrointestinal surgery except an appendectomy or hemorrhoid operation.
Patients with cardiac problems
Cardiac arrhythmias, uncontrolled angina, acute myocardial infarction within the last 3 months, congestive heart failure
Patients with a history of any drug influencing bowel motility within a month
e.g., laxatives, antidiarrheal drugs, antispasmodics, prokinetics
Patients with other problems
Ascites, uncontrolled hypertension, renal insufficiency, or electrolyte imbalance
Pregnant or lactating females

efficacy because more effective bowel preparation is associated with a higher polyp detection rate and a shorter colonoscopic insertion time [1, 9].

When using the ABPS, the efficacy of bowel preparation was scored based on a five-point scale from one to five (Supplemental Fig. 2A). Bowel preparation was considered to be "successful" if it was scored as "excellent" or "good." When using the OBPS, a three-point scale from zero to two was used to the general score for fluid in the colon. For scoring each of the three parts of the colon, a five point scale from zero to four was used (Supplemental Fig. 2B). If the colonoscopy was suspended due to poor preparation, the scores for any parts proximal to the insertion site were assigned a score of 4 (very poor). Ultimately, the OBPS score was calculated as the sum of both the general score for fluid and the total score of each of the three segments of the colon, and ranged from zero (best) to 14 (worst). In OBPS, bowel preparation was considered to be "successful" when no segment of the three parts of the colon was scored ≥3.

The secondary endpoints included measures of tolerability, acceptability, preference, and safety. To evaluate the tolerability, acceptability, and preference of both bowel cleansers, patients were surveyed using a structured questionnaire (Supplemental Fig. 3). To assess the safety of the bowel cleansers, participants were asked to indicate which of the following AEs had occurred, if any: nausea or vomiting; insomnia; palpitations or skipped heartbeat; soreness; frequent urine emission; sleep disturbance; abdominal pain; dizziness; diaphoresis; or tremor. Participants were also required to list any other unpleasant experience during bowel preparation. Mucosal inflammation and ulceration were regarded as complications of bowel preparation only in the absence of any other apparent cause, and acute inflammation was identified histologically on tissue obtained by colonoscopic biopsy.

Sample size and statistics

Age, body mass index (BMI), and colonoscopic insertion time were compared using Student's *t*-test. Gender, success or failure of bowel preparation, polyp detection, and answers to questions were analyzed using Pearson's χ^2-test based on the per-protocol (PP) population. Analysis of the completion of consumption of bowel cleanser was based on an intent-to-treat (ITT) population. Differences were considered to be significant at $P< 0.05$.

The sample size for comparison of the efficacies of the bowel cleansers was calculated for a non-inferiority study and, in accordance with previous studies, the success rate for bowel preparation using PEGAS was considered to be ~85%. Thus, a sample size of 112 patients in each arm would have power of 0.80 to detect a difference of 15% at a one-sided significance level of 0.025, allowing for a drop-out rate of 20%.

Non-inferiority of the preparation efficacy of COF vs PEGAS was defined as the lower limit of a one-sided 95% confidence interval (CI) for a difference between the success rates of the two cleansers (rate of COF – rate of PEGAS) greater than 15%. Analysis was based on both the ITT population and the PP population. The judgment as to the blinding of the endoscopist was made using the z-test ($Z=(\hat{p}-p)/\sqrt{(p(1-p)/n)}$; $\hat{p}$=sample proportion, p=hypothesized proportion, n=sample size), and would be considered successful if the two-tailed confidence level was < 0.68 ($|z|\leq 1$).

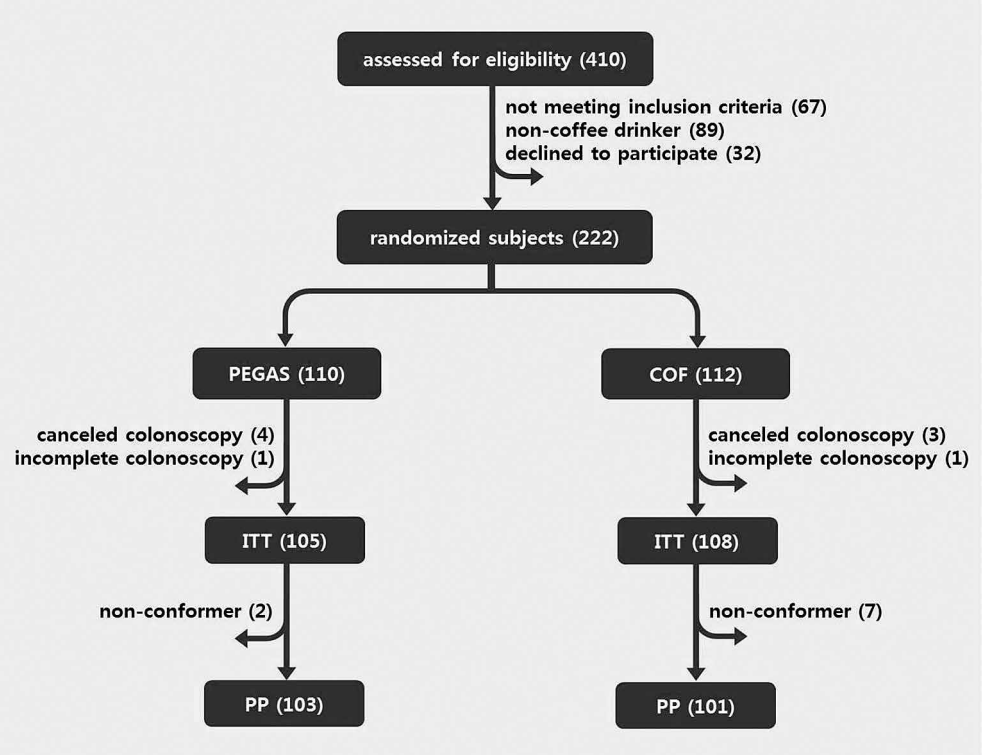

Fig. 1. Subject disposition. Subjects not meeting inclusion criteria included the following: 2 lactating females; 2 subjects with acute peptic ulcer; 3 with ascites; 3 with cardiac arrhythmias; 3 with electrolyte imbalance; 5 with uncontrolled hypertension; 5 with renal insufficiency; 8 with a history of colorectal or gastrointestinal surgery; and 36 with a history of any drug influencing bowel motility within a month.

RESULTS

Eligible participants included patients who underwent colonoscopies at the digestive endoscopy center at Kangnam Sacred Heart Hospital from April 2013 to September 2013. There were 410 subjects assessed for eligibility and 222 subjects were enrolled ultimately. Thirty-two subjects declined to participate in this study, 89 subjects were non-coffee drinkers, and 67subjects were excluded due to various other reasons (Fig. 1).

No significant differences in baseline characteristics were observed between groups (Table II). Four subjects in the PEGAS group and three in the COF group decided not to undergo colonoscopy after consenting to participate. In one subject in the PEGAS group and one in the COF group, colonoscopy was discontinued due to technical difficulties and malignant stricture, respectively. These nine cases (seven canceled colonoscopies and two incomplete examinations) were excluded from the ITT populations. Two subjects in the PEGAS group and seven in the COF group did not conform to the bowel preparation method as instructed and were excluded from the PP populations. Ultimately, the numbers of subjects in the ITT and PP populations were 105 and 103, respectively, for the PEGAS group and 108 and 101, respectively, for the COF group (Fig. 1).

Table II. Demographics and baseline characteristics of the study patients.

	PEGAS group	COF group
Ages, years (range)	55±12.0 (21-75)	53±13.0 (19-75)
Sex		
Male (%)	55 (50.0)	58 (51.8)
Female (%)	55 (50.0)	54 (48.2)
BMI (Kg/m^2) (range)	23.4±3.3 (17.2-34)	23.8±3.1 (18.4-30.4)

The rate of correct prediction of group assignment was 0.52 (107/204) in the PP population. Thus, the blinding of the endoscopist to the group allocation was successful (z = 0.57).

The efficacy of bowel preparation using a total of 1.5 L of COF solution was not inferior to that using a total of 2 L of PEGAS solution because all lower limits of the 97.5%CI for the difference between the success rates of both using ABPS or OBPS calculations for the ITT and PP populations were > –15% (Table III). Based on the ABPS scores, the preparation success rates in the PEGAS and COF groups were 83.5% (86/103) and 77.2% (78/101), respectively (Fig. 2A). Based on the OBPS scores, the preparation success rates were 89.3% (92/103) and 89.1% (90/101), respectively. In the PP population, a significant difference was observed between groups with respect to the overall segmental scores based on the OBPS. However, no significant difference was observed between groups regarding the general scores for fluid in the colon (Fig. 2B).

The polyp detection rates in the PEGAS and COF groups for the PP population were 0.48 (49/103) and 0.60 (61/101), respectively (P=0.067); the more-than-0.5 cm-polyp detection rates were 0.30 (31/103) and 0.36 (36/101), respectively (P=0.402); and the colonoscopic insertion times were 323.6 ± 166.8 s and 330.7 ± 243.6 s, respectively (P=0.831). None of these results differed significantly between groups.

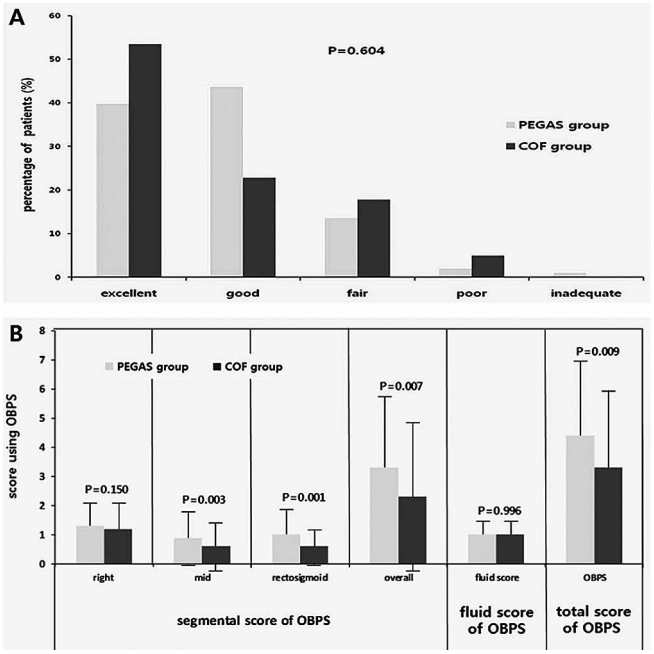

Fig. 2. (A) percentages of patients assigned to each Aronchick bowel preparation scale grade. The proportions of participants achieving successful preparation of both groups were 83.5% and 77.2%, respectively; (B) segmental score, score for fluid and Ottawa bowel preparation scale. The proportions of participants achieving successful preparation of both groups were 89.3% and 89.1%, respectively.

Significant differences were observed between the two cleansers with respect to the ease-of-drinking scores (Fig. 3A) and taste scores (Fig. 3B), whereas there was no significant difference in the proportion of subjects consuming the entire volume of either cleanser as instructed (Fig. 3C). The bowel cleanser preference for future colonoscopy in the COF group was significantly higher than that in the PEGAS group (Fig. 3D).

Adverse events occurred in 54 of 103 (52.4%) subjects in the PEGAS group and in 61 of 101 (60.4%) in the COF group (P=0.251). Two or more AEs occurred in 23 of 103 (22.3%) subjects in the PEGAS group and 20 of 101 (19.8%) in the COF group (Fig. 4A). The incidence of insomnia was significantly higher in the COF group (17/101) than in the PEGAS group (5/103), whereas significantly more subjects in the PEGAS group (20/103) suffered abdominal pain compared to the COF group (6/101). The incidence of nausea or vomiting was higher in the PEGAS group (38/103) than in the COF group (28/101), but the difference was not statistically significant. A case of urinary frequency and a case of transient and spontaneously resolved palpitations occurred in the PEGAS group, and two cases of transient dizziness occurred in the COF group (Fig. 4B). No case of serious AEs disturbing the colonoscopy schedule or requiring specialized treatment occurred. Non-specific colitis or proctitis was identified in 2.9% (3/103) of participants in the PEGAS group and 1.9% (2/101) of participants in the COF group (P=1.000).

DISCUSSION

An excellent bowel cleanser requires three attributes: comfort in administration, excellent cleansing efficacy, and a low incidence of adverse events. Commonly used bowel cleansers for colonoscopy are categorized into three groups: osmotic laxatives,

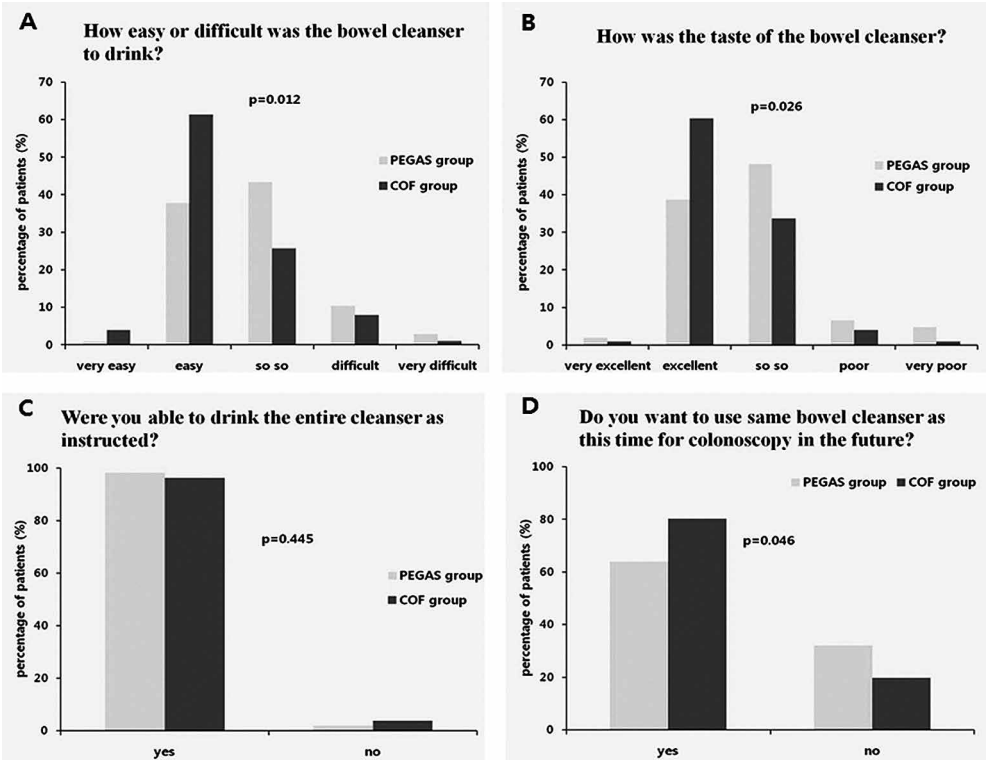

Fig. 3. Evaluation of the two bowel cleansers in terms of tolerability, acceptability, and preference. A) Ease of drinking; B) Taste of cleanser; C) Completeness of drinking (for the ITT population); D) Preference of cleanser for a future study.

such as sodium phosphate; non-absorbable high-molecular-weight polymers, such as PEG; and bowel stimulants, such as sodium picosulfate [2]. In recent years, several modified agents have been evaluated as bowel cleansers. PEG+ASC [10] and sodium picosulfate + magnesium citrate (PICO+Mg) [11] are two examples. When using PEG+ASC, it has been proposed that the residual ASC in the bowel lumen after absorption through the bowel wall may act as an osmotic agent and have a synergistic effect with PEG [3]. A total of 2 L of PEG+ASC showed a bowel-cleansing effect equivalent to that of 4 L of PEG with electrolytes, and better tolerability and acceptability for consumption [3, 10]. However, a relatively large volume must still be consumed and the taste is unpleasant. PICO+Mg has also been reported to have excellent cleansing efficacy and comfortable administration. It requires drinking a smaller amount of the solution (150-250 ml) although more than 1,000 mL of water must also be consumed after drinking the solution [12]. It has also been reported that the incidence of colonic mucosal inflammation is far higher when using PICO+Mg than when using PEG+electrolytes for bowel preparation [13].

Coffee consumption has been reported to increase colonic motor activity and the desire to defecate [4-6]. Rao et al. [4] reported that caffeinated coffee induced more frequent pressure waves and a greater area under the pressure–activity curve (as a result of integrating pressure with respect to seconds: mmHgs) than water in the transverse and descending colon. Sloots et al. [5] reported that rectal tone increased by 45% 30 min after coffee intake. Brown et al. [6] reported that subjects who claimed that coffee induced defecation showed increased motor activity in the distal sigmoid colon and rectum after

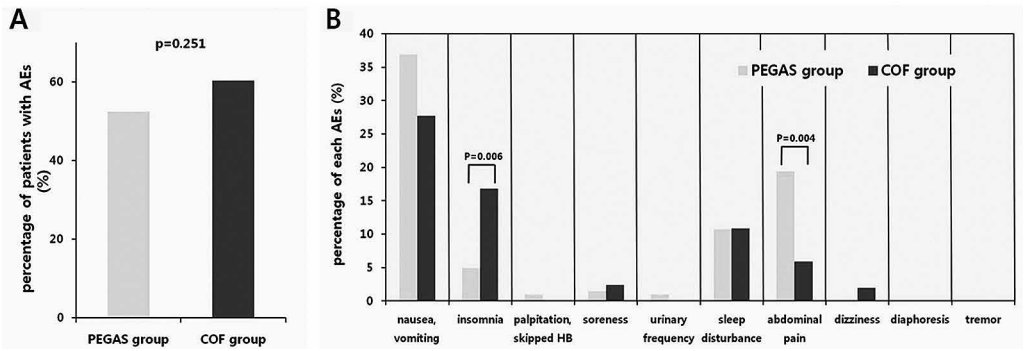

Fig. 4. Incidence of adverse events (AEs). A) Percentages of patients experiencing AEs; B) Percentages of patients with each AE. Nausea and vomiting was the most frequent AE with no significant difference between groups. The incidence of insomnia was significantly higher in the COF group, and that of abdominal pain was significantly higher in the PEGAS group.

coffee intake. Considering these results of previous studies, we hypothesized that adding coffee to a conventional bowel cleanser would reduce the volume to be consumed for bowel cleansing without reduced efficacy. Therefore, we used only 1.5 L water for the coffee, PEG, and ASC mixture regimen (COF group), whereas a 2-L water for the conventional PEG+ASC regimen (PEGAS group) because at least 2 or more liters of PEG+ASC solution were consumed in all previous studies regarding efficacy of bowel preparation using PEG+ASC regimen [3, 10]. As expected, the cleansing efficacy of two 750 mL doses of the coffee-containing solution was not inferior to that of the conventional solution. The effect of coffee enhancing patient comfort is attributed to both the ability to reduce the required volume of the solution to be consumed without reduced efficacy and to improve taste of the solution mixed with coffee. Of course, if the purpose of this study was merely to ascertain that mixing coffee with the solution can improve the taste of the solution, the volume of solution in the treatment group (COF group) should have been equal to that of the control group (PEGAS group). However, the use of different solution volumes between groups is not relevant because this study was designed to ascertain whether an alternative treatment regimen would be more comfortable without reducing cleansing efficacy.

Coffee and its major component, caffeine, can induce various AEs when taken in excess. These include insomnia, cardiac arrhythmias, indigestion, increased urination, increased secretion of gastric acid, and tremor [14, 15]. However, these AEs were expected to be relatively rare in this study, because only coffee drinkers were included and participants of the COF group were required to consume only 5.4 g coffee (approximately 41.3 mg caffeine) at a time. It has been reported that moderate amounts of coffee (50-100 mg caffeine or 5-10 g coffee powder per day) are well tolerated by most elderly people [16]. Nevertheless, the incidence of insomnia in the COF group was significantly higher. Thus, the incidence of insomnia might have been greater than that reported here if we had included subjects from the general population that also included non-coffee drinkers. The incidence of abdominal pain and bloating was significantly higher in the PEGAS group, and that of nausea and vomiting was also higher in the PEGAS group. Because coffee increases colonic motor activity, as do prokinetics, the results regarding abdominal pain/bloating, and nausea/vomiting may be consistent with the report by Mishima et al. showing that significantly fewer uncomfortable abdominal symptoms, such as nausea, vomiting, abdominal pain, and bloating, were observed in patients who received prokinetics, such as itopride hydrochloride or mosapride citrate, prior to oral lavage for colonoscopy compared to a placebo group [17]. The incidences of all other AEs, such as palpitations, skipped heartbeat etc., did not differ significantly between groups. However, the group sizes were calculated only to compare cleansing efficacy in this study. A greater sample size would be required to properly compare AEs between the groups because of the lower incidence of AEs.

This study had several limitations. There may have been bias in filling out the questionnaires regarding ease of drinking, taste, and preference because this was only a single (endoscopist) blinded study; the participants could not be blinded. Also, there may have been the other bias caused by influence from participants' experience of previous bowel preparation for colonoscopy because subgroup analysis for each group with and without previous experience of a colonoscopy was not performed in this study. In addition, only coffee-drinkers were included in an attempt to avoid unpredicted AEs, although the amount used was considerably lower than the known lethal dose of caffeine [14]. Thus, these data cannot be generalized.

CONCLUSION

This study indicates that the addition of coffee to a polyethylene glycol+ascorbic acid solution can reduce the volume required for bowel preparation prior to colonoscopy without reduced efficacy, improve taste of the solution, and enhance patient comfort in coffee-drinkers.

Conflicts of interest. There are no conflicts of interest and no relevant financial relationships.

Authors' contribution: S.J.: drafting the manuscript, concept and design of the study, acquisition, analysis and interpretation of data, statistical analysis, final approvement of the manuscript. H.Y., I.M., S.J2, S.M., S.S.: acquisition, analysis and interpretation of data; J.K.: concept and design of the study, acquisition and interpretation of data, supervision of statistical analyses. M.L.: acquisition, analysis and interpretation of data, data revision.

Supplementary material: To access the supplementary material visit the online version of the *J Gastrointestin Liver Dis* at http://www.jgld.ro/wp/y2016/n1/a10 and http://dx.doi.org/10.15403/jgld.2014.1121.251.cff

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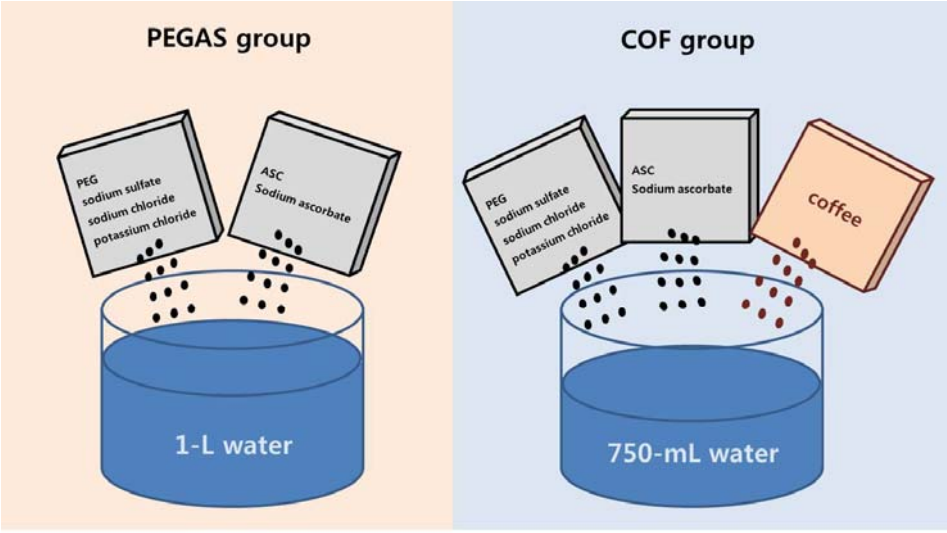
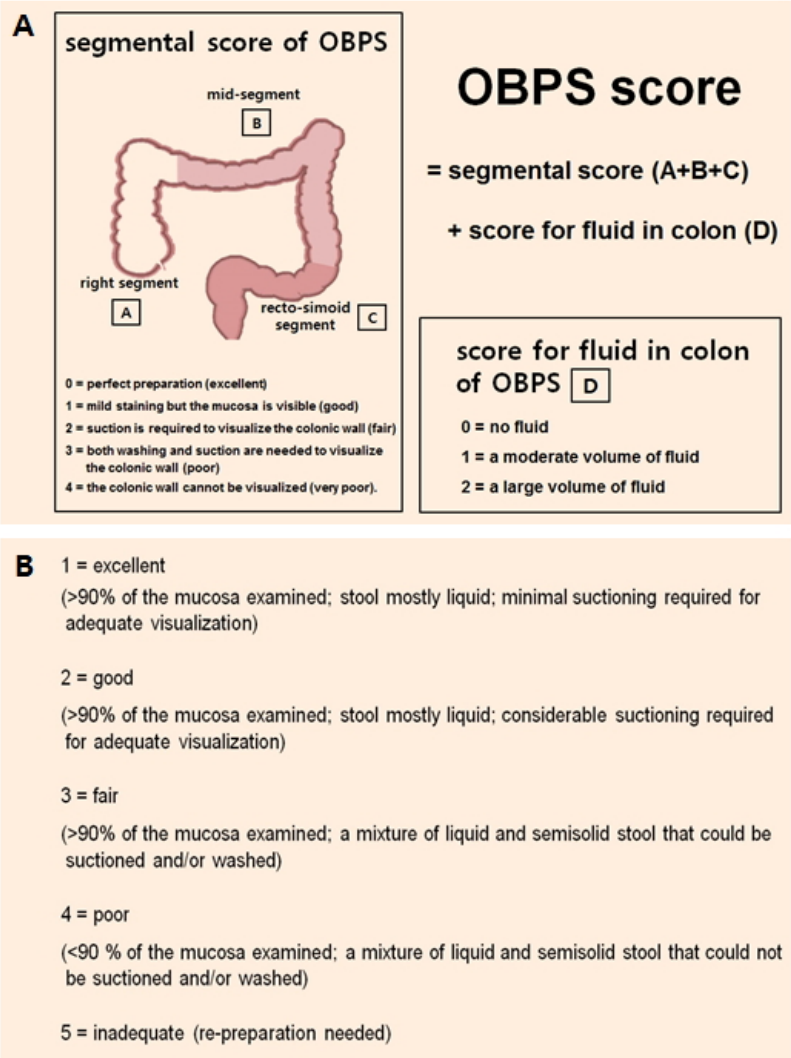
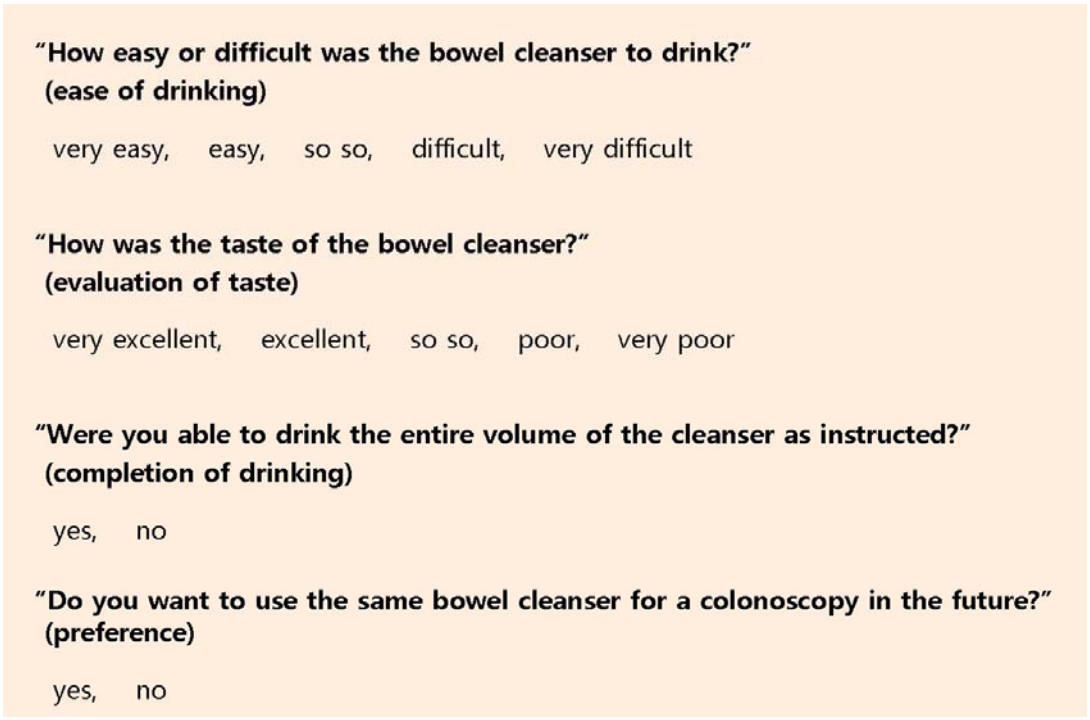


Supplementary Fig. 1. The procedure for colon cleansing followed by the two groups of patients.



Supplementary Fig. 2. The OBPS (Ottawa Bowel Preparation Scale) score.



Supplementary Fig. 3. The questionnaire used to evaluate the tolerability, acceptability, and preference of the bowel cleansers.