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Phase II Randomized Controlled Trial of Combined Oral laxatives Medication for BOWel PREPARation (COMBO-PREP study)

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Abstract: The combination of different laxatives at reduced volumes may benefit patients by enhancing efficacy for bowel cleansing and increasing tolerability. However, evidence regarding combined preparations is scarce. This study evaluated whether the combined preparations are associated with enhanced efficacy and tolerability.

This randomized phase II study had a single-blind, parallel-arm design.

Between December 2013 and September 2014, consecutive patients aged between 20 and 65 years and who required diagnostic colonoscopies were considered for inclusion. Patients were randomly allocated into 4 arms: sodium picosulfate and magnesium citrate (PMC) and polyethylene glycol (PEG) with ascorbic acid in a day-prior (PMC-PEG-DP), PMC and oral sodium phosphate (NaP) in a day-prior (PMC-NaP-DP), PMC and PEG with ascorbic acid in a split-dose (PMC-PEG-SD), and PMC and oral NaP in a split-dose (PMC-NaP-SD). Primary endpoint was the Aronchick scale, and Ottawa scale results by colon segment, patients' adverse gastrointestinal symptoms, and willingness to reuse the same agents were also recorded. Successful bowel preparation was defined as an "excellent" or "good" score on the Aronchick scale.

A total of 236 patients were randomized and 229 patients received the planned colonoscopy. The rates of successful bowel preparation in the PMC-PEG-DP, PMC-NaP-DP, PMC-PEG-SD, and PMC-NaP-SD were 82.5%, 64.4%, 100%, and 100%, respectively. Excluding the failed PMC-NaP-DP group, all groups showed satisfactory rates of successful bowel preparation, and the mean Ottawa scores were

significantly better in the PMC-PEG-SD and PMC-NaP-SD groups than in the PMC-PEG-DP group ($P < 0.0001$). The PMC-PEG-DP, PMC-NaP-DP, PMC-PEG-SD, and PMC-NaP-SD groups were similar in terms of rates of adverse gastrointestinal symptoms reported on a 5-point scale ($P = 0.40$) and willingness to reuse the same combined preparations ($P = 0.55$).

PMC-PEG in a day-prior or split-dose and PMC-NaP in a split-dose were efficient and tolerable bowel preparations for colonoscopy.

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Abbreviations: CI = Confidence interval, DP = day-prior regimen, ESGE = European Society of Gastrointestinal Endoscopy, GI = gastrointestinal, NaP = sodium phosphate, PEG = polyethylene glycol, PMC = sodium picosulfate plus magnesium citrate, SD = split-dose regimen.

INTRODUCTION

The need for adequate colon cleansing has intensified as a consequence of increases in screening and therapeutic colonoscopies over recent years.¹ The quality of bowel preparation affects diagnostic accuracy and therapeutic safety.² Inadequate bowel cleansing can lead to missed lesions, unnecessarily prolonged examination times, additional patient discomforts, and increased complications during therapeutic procedures.

The ideal agent for bowel preparation should be both effective and tolerable.^{3,4} Adequate preparations for colonoscopy should cleanse the colon without remnant fecal material, should be easy to digest, and should not cause any adverse events. In addition, minimizing patient discomfort is critical for colonoscopy acceptance.

There have been extensive attempts to identify ideal bowel preparations,^{2,5-13} and various colon cleansing agents have been evaluated in terms of efficacy, safety, and tolerability—including polyethylene glycol (PEG), sodium picosulfate and magnesium citrate (PMC), and sodium phosphate (NaP). On the basis of previous studies, the practical guidelines of the European Society of Gastrointestinal Endoscopy (ESGE) recommend a split-dose regimen of 4 L of PEG for colonoscopic preparation and propose split-dose regimens of 2-L PEG along with ascorbic acid or of PMC as alternatives.¹⁴

PEG solution is a safe and highly effective colon cleansing agent.^{14,15} Because PEG passes through colon without absorption or secretion, it could minimize fluid shifts and electrolyte imbalance. However, the use of large volumes (4 L) to achieve a purgative effect could cause patient discomfort, including abdominal bloating, pain, and nausea and vomiting. In turn, patient discomfort could lead to low compliance. PMC is a low-volume agent with an acceptable taste and is mainly composed of sodium picosulfate (stimulant laxative) and magnesium

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citrate (osmotic laxative). PMC has been reported to be at least as effective as other cleansing products and to be better tolerated than large-volume PEG.^{16–18} Oral NaP preparations have been preferred by clinicians and shown to have superior efficacy than PEG preparations.^{19–21} Nonetheless, the ESGE has advised against routine use of NaP for bowel preparation because of safety concerns.¹⁴

Because each agent has its own drawbacks, there have been attempts to combine regimens and thereby achieve better efficacy while also minimizing side effects.^{22,23} Combination regimens of different preparations at reduced volumes could benefit patients by enhancing the quality of bowel cleansing and improving compliance. However, there has been limited evidence regarding the utility of combined regimens and their clinical use for bowel cleansing. The purpose of this study was to evaluate the efficacy and tolerability of PMC combined with PEG along with ascorbic acid and PMC combined with oral NaP in day-prior and split-dose regimens for bowel preparation.

METHODS

Study Design

This randomized phase II selection study had a single-center, single-blind, parallel-arm design. The study was reviewed and approved by our Institutional Review Board (NCCCTS-13-691, Approval date: September 16, 2013) and the trial was registered at www.clinicaltrials.gov (NCT01919255).

Study Population

The study was conducted in the outpatient clinics of the National Cancer Center, Republic of Korea, between December 2013 and September 2014. Consecutive patients who were between the ages of 20 and 65 years and who required diagnostic colonoscopies were considered for inclusion. They were approached by their endoscopists to obtain informed consent. Patients were excluded if they had general contraindications of bowel preparations, such as active colitis; gastrointestinal (GI) bleeding; bowel obstruction; toxic megacolon; severe cardiac, hepatic, or renal impairment; known allergies to the preparation agents, or clinically significant electrolyte imbalances. The study also excluded pregnant and breast-feeding women, as well as subjects with a history of colorectal surgery or abdominal surgery within 6 months.

Study Medications

Picolight (Pharmbio Korea, Seoul, Korea) consists of 10 mg sodium picosulfate hydrate, 3.5 g magnesium oxide, and 12 g citric acid. In solution, sodium picosulfate acts as a stimulant laxative and magnesium oxide combined with citric acid as an osmotic laxative. Coolprep (TaeJoon Pharmaceuticals, Seoul, Korea) is 2 L of PEG-based laxative with ascorbic acid (100 g PEG 3350, 1.015 g potassium chloride, 5.9 g sodium ascorbate, 2.691 g sodium chloride, 7.5 g sodium sulfate anhydrous, and 4.7 g ascorbic acid). Clicolon (Korea-Pharma Pharm, Inc., Seoul, Korea) is an oral NaP drug containing 398 mg dibasic sodium phosphate anhydrous and 1102 mg monobasic sodium phosphate monohydrate.

Randomization and Masking

An independent statistician used a computer-generated random numbers table to randomize study preparation agents such that the distribution of patients into the 4 groups was equal (1 : 1 : 1 : 1). Subjects were assigned into 1 of 4 groups: PMC and

PEG with ascorbic acid in a day-prior regimen (PMC-PEG-DP), PMC and oral NaP in a day-prior regimen (PMC-NaP-DP), PMC and PEG with ascorbic acid in a split-dose regimen (PMC-PEG-SD), and PMC and oral NaP in a split-dose regimen (PMC-NaP-SD). A total of 6 endoscopists performed colonoscopies and were blinded to group allocation. All participating endoscopists had participated in a pre-study consensus meeting to decrease inter-observer variations in bowel cleansing scores. All colonoscopies were performed between 8:30 AM and 1:00 PM.

Preparation Regimens

Written instructions for bowel preparation were provided to the subjects after informed consent had been obtained. Each subject was instructed to consume a semi-solid diet the day before colonoscopy, with the last meal taken at 4:00 PM. The subjects were further instructed to take 2 tablets of bisacodyl at 5:00 PM.

Patients in day-prior groups took all preparations between 5:00 PM and 8:00 PM on the day before the colonoscopy. Subjects in the PMC-PEG-DP group received a packet of Picolight and 4 sachets of Coolprep. One packet of Picolight was dissolved in 150 mL of water and consumed at 5:00 PM, followed by 1 L of water. After 3 hours, patients were to dissolve the 4 sachets of Coolprep in 1 L of water and drink this preparation over 1 hour with an additional 500 mL of water. Subjects in the PMC-NaP-DP group were asked to consume Picolight following the instructions described above and were instructed to take 16 tablets of Clicolon instead of Coolprep. They were asked to take 4 tablets every 15 minutes, beginning at 8:00 PM.

Patients in split-dose groups were asked to follow the same preparation instructions as day-prior groups, except that they were asked to consume each preparation at 7:00 PM on the day before their colonoscopy and at 5:00 AM on the day of their colonoscopy.

Primary Endpoint

The primary endpoint was the rate of successful bowel preparation as evaluated according to the Aronchick scoring system.²⁴ At the end of the colonoscopy, blinded investigators evaluated overall cleansing of the colon according to the Aronchick scoring system. The Aronchick scale has been described in a previous study,¹² and can be briefly summarized as follows: “poor” indicates semi-solid stool that could not be suctioned or washed away, and less than 90% of surfaces seen; “fair” indicates some semi-solid stool that could be suctioned or washed away, but greater than 90% of surfaces seen; “good” indicates a large volume of clear liquid on 5% to 25% of the colon surfaces, but greater than 90% of surfaces seen; and “excellent” indicates a small volume of clear liquid or greater than 95% of surfaces seen. Successful bowel preparation was defined as an “excellent” or “good” score on the Aronchick scale, and the success rate was defined as the percentage of patients who showed successful bowel preparations in each group.

Secondary Endpoints

In addition, preparation efficacy was evaluated according to the Ottawa preparation score by rating colon segments in a range of 0 (excellent) to 4 (inadequate). The overall amount of fluid was scored from 0 to 2. The total scores summed with the individual parameters were compared between the 4 groups.²⁵

The completeness of the bowel preparation protocol, tolerability, and the patient’s willingness to reuse the same

preparation agents for the next colonoscopy were also evaluated as secondary endpoints. Before the colonoscopies, the study subjects completed questionnaires regarding the tolerability of the preparation and GI adverse events, which were rated on 5-point scales as follows: 1 = “none”; 2 = “mild”; 3 = “bothersome”; 4 = “distressing”; and 5 = “severely distressing”. Scores of 4 or 5 were documented as the presence of adverse GI symptoms.

Statistical Analysis

Simon’s optimal 2-stage method was employed for each preparation method.^{26,27} This method allowed the evaluation of each preparation as in a single-arm, 2-stage, phase II design, while also allowing the selection of methods that presented the best success rate. For the evaluation of primary endpoint according to the Aronchick score, the success rate of the bowel preparation was expected to be 80% (p_1) based on previous studies, and a success rate below 60% (p_0) was assumed to represent preparation failure. With a type I error rate of 5% and 90% power, 19 patients per arm were considered necessary for the first stage of the trial. In the interim analysis, it was determined whether more than 13 of the subjects had successful preparations in each arm. If each arm of the study satisfied this criterion, the study was allowed to proceed to the next stage, in which we sought to enroll an additional 34 subjects per arm. We considered the preparation to have statistically significant efficacy if more than 38 (71.6%) subjects received successful preparations. To account for an expected dropout rate of 10%, 59 subjects were enrolled in each arm. A direct comparison of the success rates of the preparation methods was

not the primary concern of this selection design. However, this comparison was performed as a secondary analysis that was limited to preparations showing efficacy significantly greater than 60% (p_0).

The χ^2 test was used for 4-group comparisons of categorical variables, including Aronchick bowel preparation score, and the rate of successful preparation and adverse GI symptoms. One-way analysis of variance was used for 4-group comparisons of continuous variables, but the Kruskal–Wallis test was used when we could not assume the normality of data distribution. Data on age, Ottawa preparation score, cecal intubation time, and GI symptom ratings according to severity were analyzed by using the Kruskal–Wallis test, and posthoc comparisons were performed on the basis of the Ottawa preparation score and cecal intubation time based on Tukey multiple comparison test using ranks. All statistical analyses were performed using SPSS 14.0 for Windows (SPSS Inc., Chicago, Illinois) and *P* values less than 0.05 were considered to be statistically significant.

RESULTS

Baseline Variables

Between December 2013 and September 2014, 250 consecutive patients were considered for inclusion in the trial, and a total of 236 of these patients were randomized (Figure 1). In the interim analysis, which was performed after enrolling 19 subjects in each arm, more than 13 subjects showed successful preparations in all groups. As described in the Methods section, this interim success rate allowed each arm of the study to proceed to the next stage, in which 40 more subjects were

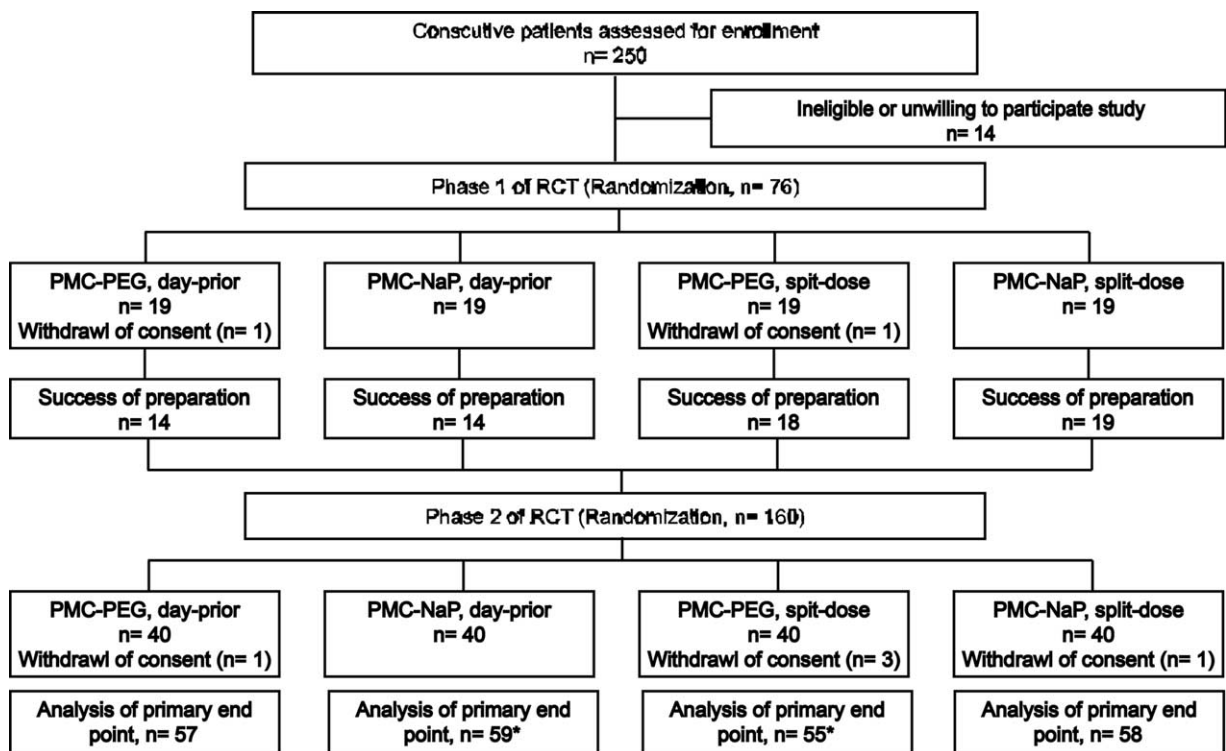


FIGURE 1. CONSORT flow chart. NaP = sodium phosphate; PEG = polyethylene glycol; PMC = sodium picosulfate and magnesium citrate; RCT = randomized controlled study. *One patient in the PMC-NaP, day-prior group took 3 tablets of Cicolon instead of 4 tablets, and the other in the PMC-PEG, split-dose group took the study preparation in a reversed order.

TABLE 1. Patient Characteristics and Detection of Colonic Neoplasms

	PMC-PEG, Day-Prior (n = 57)	PMC-NaP, Day-Prior (n = 59)	PMC-PEG, Split-Dose (n = 55)	PMC-NaP, Split-Dose (n = 58)	P*
Age, median (IQR), y	53 (48–57.5)	54 (50–59)	55 (50–59)	53 (46–57)	0.387
Female sex, n (%)	31 (54.4%)	28 (47.5%)	27 (49.1%)	34 (58.6%)	0.613
BMI, mean ± SD, kg/m ²	23.9 ± 3.2	23.2 ± 2.9	23.5 ± 2.6	23.8 ± 3.1	0.603
Polyp detection, n (%)	29 (50.8%)	32 (54.2%)	18 (32.7%)	28 (48.3%)	0.106
Adenoma detection, n (%)	25 (43.9%)	24 (40.7%)	14 (25.5%)	21 (36.2%)	0.198
Cancer detection, n	2	0	0	0	

BMI = body mass index, IQR = interquartile range, NaP = sodium phosphate, PEG = polyethylene glycol, PMC = sodium picosulfate and magnesium citrate, SD = standard deviation.

*The P value was calculated between the 4 groups.

enrolled per group. Two hundred twenty-nine of the 236 patients (97.0%) received the planned screening colonoscopy and the remaining 7 patients withdrew their consent. The results of the 229 patients were included in the intention-to-treat analysis.

The 4 groups were well balanced with regard to sex, age, and body mass index (Table 1). The 4 groups did not differ significantly in terms of the adenoma and polyp detection rate, as summarized in Table 1. Cancers were detected in 2 patients belonging to the PMC-PEG-DP group.

Bowel Preparation Quality

Successful bowel preparation was defined by excellent or good results on the Aronchick scale (primary endpoint), and was

seen in 82.5% (95% confidence interval [95% CI], 69.6–90.8) of PMC-PEG-DP subjects, 64.4% (95% CI, 50.8–76.1) of PMC-NaP-DP subjects, 100% (95% CI, 91.9–100) of PMC-PEG-SD subjects, and 100% (95% CI, 92.3–100) of PMC-NaP-SD subjects (Table 2, Figure 2). The PMC-NaP-DP group was regarded as preparation failure, because the lower margin of 95% CI in PMC-NaP-DP group was lower than 60% (p₀). In the PMC-PEG-SD and PMC-NaP-SD groups, 52.7% and 50% of patients had “excellent” preparations, respectively, whereas 3.5% and 6.8% of patients in the PMC-PEG-DP and PMC-NaP-DP groups had “excellent” preparations, respectively (Table 2). For 2 patients in the PMC-PEG-DP group and 2 patients in the PMC-NaP-DP group, the status of the bowel preparation was considered to be inadequate and re-preparation was needed.

TABLE 2. Degree of Bowel Preparation and Cecal Intubation Time According to 4 Different Combinations of Agents

	PMC-PEG, Day-Prior (n = 57)	PMC-NaP, Day-Prior (n = 59)	PMC-PEG, Split-Dose (n = 55)	PMC-NaP, Split-Dose (n = 58)	P*
Success of preparation [†] , n (%)	47 (82.5%)	38 (64.4%)	55 (100.0%)	58 (100.0%)	<0.0001
Aronchick bowel preparation score, n (%)					
Excellent	2 (3.5%)	4 (6.8%)	29 (52.7%)	29 (50.0%)	<0.0001
Good	45 (79.0%)	34 (57.6%)	26 (47.3%)	29 (50.0%)	
Fair	6 (10.5%)	19 (32.2%)	0	0	
Poor	2 (3.5%)	0	0	0	
Inadequate	2 (3.5%)	2 (3.4%)	0	0	
Ottawa preparation score, median (IQR) [‡]					
Total score	6 (5–7.5)	6 (4–8)	4 (2–5)	4.5 (3–6)	<0.0001
a		a	b	b	
Right colon	2 (2–3)	2 (2–3)	1 (1–2)	2 (1–2)	<0.0001
a		a	b	b	
Mid-colon	2 (1–2)	2 (1–3)	1 (1–1)	1 (1–1)	<0.0001
a		a	b	b	
Left colon	1 (1–2)	2 (1–3)	1 (1–2)	1 (1–2)	0.003
a, b		a	b	b	
Overall fluid	1 (0.5–1)	1 (0–1)	0 (0–1)	1 (0–1)	0.022
a		a, b	b	a, b	
Cecal intubation time, median (IQR) [‡] , min	4 (2–5)	4 (3–5)	4 (2–5)	3 (2–4)	0.014
a, b		b	a, b	a	

IQR = interquartile range, NaP = sodium phosphate, PEG = polyethylene glycol, PMC = sodium picosulfate and magnesium citrate.

*The P value was calculated between the 4 groups.

[†]“Success of preparation” refers to excellent or good on the Aronchick scale.

[‡]The results of posthoc comparisons were demonstrated as letters, a and b, and the same letters indicate nonsignificant difference between groups based on Tukey multiple comparison test using ranks.

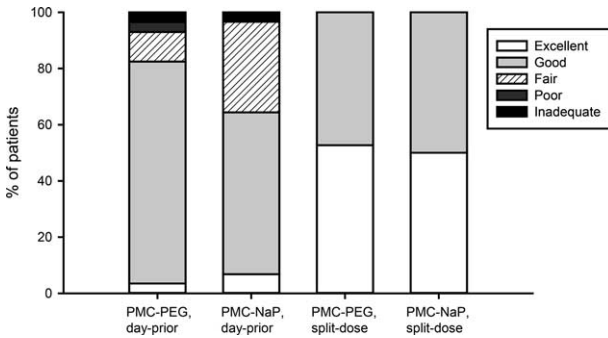


FIGURE 2. Aronchick bowel preparation score according to 4 different combinations of agents for bowel preparation before colonoscopy. NaP = sodium phosphate; PEG = polyethylene glycol; PMC = sodium picosulfate and magnesium citrate.

Investigators also reported Ottawa preparation scores (Table 2). The PMC-PEG-SD and PMC-PEG-SD group showed lower total Ottawa preparation score ($P < 0.0001$), less frequent residual stool in the right- and mid-colon than did the PMC-PEG-DP and PMC-NaP-DP groups ($P < 0.0001$, $P < 0.0001$, respectively), and less frequent residual stool in left colon than the PMC-PEG-DP group ($P = 0.003$). Regarding the residual overall fluid, the PMC-PEG-SD group demonstrated less cases of residual fluid than the PMC-PEG-DP group, and no significant difference was observed between the PMC-NaP-DP, PMC-PEG-SD, and PMC-NaP-SD groups.

The median cecal intubation time in the PMC-NaP-SD group was significantly shorter than in the PMC-NaP-DP group, and posthoc comparisons between the other 3 groups except the PMC-NaP-DP group did not show a statistically significant difference in the cecal intubation time (Table 2).

Tolerance and Compliance

All subjects in the PMC-PEG-DP and PMC-NaP-SD groups completed the preparation per protocol, as compared with 98.3% (58/59) of subjects in the PMC-NaP-DP group and 98.2% (54/55) of subjects in the PMC-PEG-SD group (Table 3; $P = 0.99$). One patient in the PMC-NaP-DP group took 3 tablets of Clicolon instead of 4 tablets, and 1 patient in the PMC-PEG-SD group took the study preparation in a reversed order. The quality of bowel preparation was “excellent” for both patients, as assessed on the Aronchick scale.

Adverse GI symptoms were reported by subjects on a 5-point scale, as shown in Table 3 and Figure 3. Vomiting scores differed significantly between the PMC-NaP-DP and PMC-PEG-SD groups ($P = 0.03$). Otherwise, no significant differences between the 4 combinations of preparation agents were detected in terms of symptoms of abdominal distension, pain, nausea, vomiting, or abdominal discomfort (Figure 3; $P = 0.40$). For all of the 4 preparation protocols, the average value of each symptom score ranged from 1 (none) to 2 (mild).

The number of patients who were willing to reuse the same preparation regimen did not differ significantly between the groups (Table 3; $P = 0.55$).

DISCUSSION

The ideal bowel-cleansing agent should be effective, safe, and tolerable. Given the tremendous increases in the use of colonoscopic examinations, the importance of identifying ideal bowel-cleansing agents has grown as well. Extensive studies of the 3 most commonly used agents—PEG, PMC, and NaP—have revealed that they each have their own advantages and weak points. For example, PEG has suboptimal tolerability, while PMC and NaP can present safety issues. Although it may be possible to overcome these limitations by combining agents, there has been relatively little evidence regarding combinations. More than a few studies have focused on combinations of a bowel-cleansing agent with a laxative, such as ascorbic acid,

TABLE 3. The Survey of Patients’ Satisfaction and Adverse Effects According to 4 Different Combinations of Agents

	PMC-PEG, Day-Prior (n = 57)	PMC-NaP, Day-Prior (n = 59)	PMC-PEG, Split-Dose (n = 55)	PMC-NaP, Split-Dose (n = 58)	<i>P</i> *
Completeness of bowel preparation protocol, n (%)	57 (100.0 %)	58 (98.3 %)	54 (98.2 %)	58 (100.0 %)	0.998
Adverse GI symptoms†, n (%)	6 (10.5 %)	2 (3.4 %)	5 (9.1 %)	3 (5.2 %)	0.401
Distension	1 (1.8 %)	1 (1.7 %)	1 (1.8 %)	2 (3.4 %)	
Pain	0	0	1 (1.8 %)	0	
Nausea	3 (5.3 %)	1 (1.7 %)	2 (3.6 %)	1 (1.7 %)	
Vomiting	5 (8.8 %)	1 (1.7 %)	5 (9.1 %)	1 (1.7 %)	
Discomfort	3 (5.3 %)	1 (1.7 %)	3 (5.5 %)	1 (1.7 %)	
Symptom ratings (1–5) by severity, median (IQR)					
Distension	1 (1–2)	2 (1–3)	1 (1–2)	1 (1–2)	0.509
Pain	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–2)	0.612
Nausea	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–2)	0.282
Vomiting	1 (1–2.5)	1 (1–2)	2 (1–2)	1 (1–2)	0.22
Discomfort	2 (1–2)	2 (1–3)	2 (1–2)	2 (1–2.3)	0.652
Willing to reuse, n (%)	53 (93.0 %)	56 (94.9 %)	51 (92.7 %)	51 (87.9 %)	0.546

GI = gastrointestinal, IQR = interquartile range, NaP = sodium phosphate, PEG = polyethylene glycol, PMC = sodium picosulfate and magnesium citrate.

* The *P* value was calculated between the 4 groups.

† “Adverse GI symptoms” refer to 4 or 5 on score of symptom rating by severity.

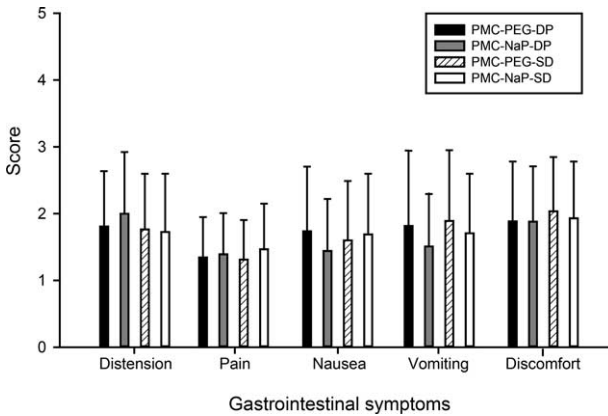


FIGURE 3. Adverse gastrointestinal symptoms after administration of 4 different combinations of agents for bowel preparation before colonoscopy. DP = day-prior regimen; NaP = sodium phosphate; PEG = polyethylene glycol; PMC = sodium picosulfate and magnesium citrate; SD = split-dose regimen.

senna, or bisacodyl.^{13,28–30} To date, however, few studies have investigated combinations of 2 different bowel-cleansing agents.^{22,31} Our hypothesis was that the combination of 2 different regimens at half dosage could augment the strength of each regimen while also reducing side effects. In this prospective, randomized, single-blind, phase II study, we evaluated the efficacy, tolerability, and side effects of 4 different combination regimens: PMC-PEG-DP, PMC-PEG-SD, PMC-NaP-DP, and PMC-NaP-SD. To the best of our knowledge, this is the first study to investigate the clinical potential of these combination regimens for bowel cleansing.

We found that the combined regimens PMC-PEG-DP, PMC-PEG-SD, and PMC-NaP-SD provided efficacious bowel preparation in all segments of the whole colon, showing success rates that exceeded 80% on the basis of Aronchick bowel preparation scores. Indeed, bowel preparations were excellent or good in all patients who had taken the PMC-PEG-SD or PMC-NaP-SD regimens. Because single-agent regimens of PEG, PMC, and NaP showed approximately 60% to 90% success rates for bowel cleansing in previous large series,^{8,10,13,17,32,33} our results indirectly suggest that the combination regimens are at least comparable to these single-agent regimens, and may even offer superior efficacy. This conclusion may be surprising, considering that our regimens combined agents at half dosages. Although 2-L PEG with ascorbic acid has been included as a valid alternative to 4-L PEG in the ESGE guideline, several studies have noted the relatively low quality of right colon preparation as a drawback of 2-L PEG with ascorbic acid.^{23,31} Accordingly, we were concerned that using agents at half dosages could possibly result in suboptimal bowel preparation; however, excellent results were achieved in all segments of the colon, including the right colon. It is likely that the combination of PMC and PEG or NaP might be synergistic, potentially conferring better efficacy for bowel preparation than any of the individual agents.

In the present study, the 2 combined, split-dose regimens showed significantly higher success rates and lower Ottawa scores than the corresponding day-prior regimens, indicating that the split-dose regimens have better efficacy. Several large series and associated meta-analyses have established that split-dose regimens are more efficacious than nonsplit-dose regimens for bowel preparation, regardless of type and dose.^{17,34,35} It has been

suggested that short time intervals between the last dose of the purge and the beginning of the procedure could raise the quality of bowel cleansing. As demonstrated in the present study, this approach can be also applied for combination regimens.

It is also noteworthy that all but 2 patients (99.1%) completed the instructed bowel preparation protocol properly, and approximately 90% of patients expressed willingness to reuse the same preparation regimens. These findings show excellent tolerability and high satisfaction with the combinations of regimens that were investigated in the current study. The efficacy of 4-L PEG has been verified in previous studies, and it is recommended as a standard regimen by ESGE. However, 4-L PEG has low tolerability because of the large volume that is employed, an issue that has been noted as its main drawback.¹⁴ Two-liter PEG regimens with ascorbic acid, PMC, and NaP are known to have better patient tolerability than 4-L PEG.^{6,7,12} The results of the present study suggest that increased tolerability might be achieved through the combined use of these agents at half dosages.

Safety is also a crucial issue when evaluating the clinical value of bowel-cleansing agents. In the current study, approximately 7% of patients suffered from some kind of adverse GI symptom, and the number of patients who experienced adverse GI symptoms was similar across the 4 groups ($P = 0.401$). However, the mean severity score did not exceed 2 (mild) for any category of GI symptoms or combination regimen. These findings are also comparable to results of previous studies that have examined single-agent regimens.^{16,20,21,33}

The NaP tablet (CLICOLON tablets; South Korea Pharma Co., Seoul, Korea) used in this study is an improved version of the residue-free NaP tablet (Osmoprep™; Salix Pharmaceuticals, Inc., Morrisville, NC, USA) with the same active ingredients, the efficacy and safety of which for a colonoscopic preparation has been demonstrated in a clinical trial.³⁶ According to the FDA drug safety communication in 2014, using more than 1 dose of NaP drugs in 24 hours can cause rare but serious damage to the kidney and heart, so these drugs should be used only as recommended on the label, especially in patients at a higher risk for adverse events. We used the 32-tablet CLICOLON tablets in half (16 tablets) of the recommended dose, and excluded the subjects who were at a high risk of acute phosphate nephropathy with advanced age or with renal disease or hypertension, using renal medications. Serious adverse events such as acute renal failure were not reported in this study.

Our study has several limitations. First, this is a phase II study. Therefore, we could not perform a direct comparison between the results of combined regimens and conventional single-agent regimens. Instead, the superiority or comparability of combined regimens could be only assessed indirectly by comparing our findings with those of other studies. We are planning a phase III study to evaluate whether a combined regimen is associated with greater efficacy and tolerability than the conventional regimen. Second, objective safety variables were not assessed in this study. We only collected self-reported, subjective questionnaire responses regarding the presence of adverse GI symptoms. Additional data on vital signs and laboratory tests should be collected pre- and postbowel preparation, to allow the objective evaluation of physical changes.

In conclusion, this prospective randomized phase II study demonstrated that PMC combined with half doses of either PEG with ascorbic acid or oral NaP provided efficacious bowel cleansing for colonoscopies, except for a day-prior regimen of PMC combined with NaP. Use of PMC-PEG or PMC-NaP in split-dose regimens provided the most efficacious cleansings

for all segments of the colon. The combined regimens also resulted in minimal adverse symptoms and most of the patients indicated willingness to reuse the same combined preparations for later colonoscopies. Further study is needed to compare the combined regimens that we have validated with the standard single preparations.

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