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Comparison of the Efficacy and Safety of Sodium Phosphate Tablets and Polyethylene Glycol Solution for Bowel Cleansing in Healthy Korean Adults

Seung-Hwa Lee,[1] Duck-Joo Lee,[1] Kwang-Min Kim,[1] Sang-Wook Seo,[1] Joon-Koo Kang,[2] Eun-Hye Lee,[3] and Dong-Ryul Lee[4]

[1]Health Promotion Center, Ajou University School of Medicine, Suwon;
[2]Department of Gastroenterology, Ajou University School of Medicine, Suwon;
[3]Department of Anesthesiology, Seoul National University College of Medicine, Seoul;
[4]Health Promotion Center, Wonkwang University College of Medicine, Gunpo, Korea.

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Corresponding author: Dr. Duck-Joo Lee,
Health Promotion Center,
Ajou University School of Medicine,
164 World cup-ro, Yeongtong-gu,
Suwon 443-380, Korea.
Tel: 82-31-219-7164, Fax: 82-31-219-5561
E-mail: djleemd@medicus.co.kr

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Purpose: Bowel cleansing is generally regarded as time-consuming and unpleasant among patients. Patients commonly state that bowel preparation provokes more discomfort than the actual colonoscopic examination. The purpose of this study was to compare two regimens of sodium phosphate (NaP) tablets versus polyethylene glycol (PEG) solution for bowel preparation in healthy Korean adults. **Materials and Methods:** This was a single center, prospective, open-label, investigator-blinded, randomized, controlled-pilot study. A total of 62 healthy Korean subjects were randomly assigned to two groups (NaP vs. PEG). Efficacy, safety, and patient-related outcomes, as well as procedural parameters, were evaluated. **Results:** Although there were no significant differences in total Ottawa bowel quality score, fluid scores and the rate of adequate bowel preparation were significantly better in the NaP group than the PEG group. Additionally, the NaP group showed better results regarding patient tolerance, satisfaction, preference, and rate of adverse events than the PEG group. Significant fluctuations in specific serum electrolytes were common and of a greater magnitude in the NaP group than the PEG group. However, these abnormalities were transient and did not result in serious complications and side effects. **Conclusion:** In this study, NaP tablets were shown to be an effective, well-tolerated, and acceptable regimen for bowel preparation. Also, our study suggests that NaP tablets may be safe and can be used as a bowel cleansing agent in healthy adults undergoing elective colonoscopy. Further multicenter, large scale studies are needed to confirm these findings.

Key Words: Sodium phosphate tablet, polyethylene glycol, bowel preparation, safety, efficacy

INTRODUCTION

Colonoscopy is accepted as an effective and powerful method for the diagnosis of

large bowel disorders, including colorectal cancer (CRC) and polyps.[1] Compared to examination tools, such as fecal occult blood test and immunochemical test, double contrast barium enema, computed tomographic colonography (e.g., virtual colonoscopy), and colon-capsule endoscopy, colonoscopy is the only method that allows for biopsy and/or removal of pathologic lesions with cancerous potential.[2-4] In developed Western countries, such as the United Kingdom and United States, CRC screening, in which coloscopy plays a key role, has effectively reduced the mortality and incidence of malignant neoplasm, in combination with other evaluation strategies.[5-9]

An adequate level of bowel preparation is essential for a successful and complete examination of the entire colorectal mucosa and for safeguarding against missing pathologic lesions during colonoscopy. Inadequate bowel preparation prolongs the procedural time (e.g., intubation time, withdrawal time, total procedure time), reduces the colonoscopy completion rate (e.g., cecal intubation rate, terminal ileal intubation rate), and increases the risk of complications (e.g., iatrogenic perforation, abdominal and anal pain, flatulence).[10-12] Also, it can increase the likelihood of missing lesions, even though endoscopists are skillful and spend an enough withdrawal (observation) time to be recommended by the guidelines of gastroenterological societies of various countries.[13,14]

Despite advances in endoscopic equipment, techniques, and sedation, which have resulted in improved tolerability of the colonoscopic procedures, bowel preparation remains a time-consuming and uncomfortable part of undergoing colonoscopy. This may result in reduced patient acceptance of colonoscopy in CRC screening programs. Although a variety of bowel preparation agents can be used, polyethylene glycol (PEG)-based and sodium phosphate (NaP)-based regimens have been widely used for bowel cleansing prior to colonoscopy.[15] For many years, the PEG regimen was regarded as the gold standard for bowel cleansing because of its proven safety and efficacy. However, the need to ingest a large volume, as well as the unpleasant smell and taste, of PEG frequently led to poor patient compliance, resulting in inadequate bowel preparation. In this respect, NaP regimens have been sought by clinicians and patients as an alternative method for bowel preparation, due to its low volume and good efficacy. However, there are potential risks associated with NaP regimens, such as electrolyte imbalance and irreversible renal dysfunction, including acute phosphate nephropathy, because it acts as an osmotic laxative.

Many studies have been conducted to compare the two aforementioned agents.[16-19] However, to date, most of these studies have focused on the bowel cleansing efficacy and patient compliance; only a few studies have compared the safety (including laboratory data) of the two regimens, especially tablet-type formulation NaP. The aim of this study was to compare the efficacy, safety, patient-related outcomes, and procedural parameters of NaP tablets versus standard 4-liters PEG solution for bowel preparation in healthy Korean adults undergoing colonoscopy.

MATERIALS AND METHODS

This was a single center, prospective, open-label, investigator-blinded, randomized controlled, pilot study. The entire protocol and study design are presented in Fig. 1.

Ethics statement

The study protocol was conducted in accordance with the Declaration of Helsinki and its amendments, and is consistent with the guidelines of Good Clinical Practice. The study was approved by the Institutional Review Board of Ajou University Hospital (Suwon, Korea). It was registered with the Clini-

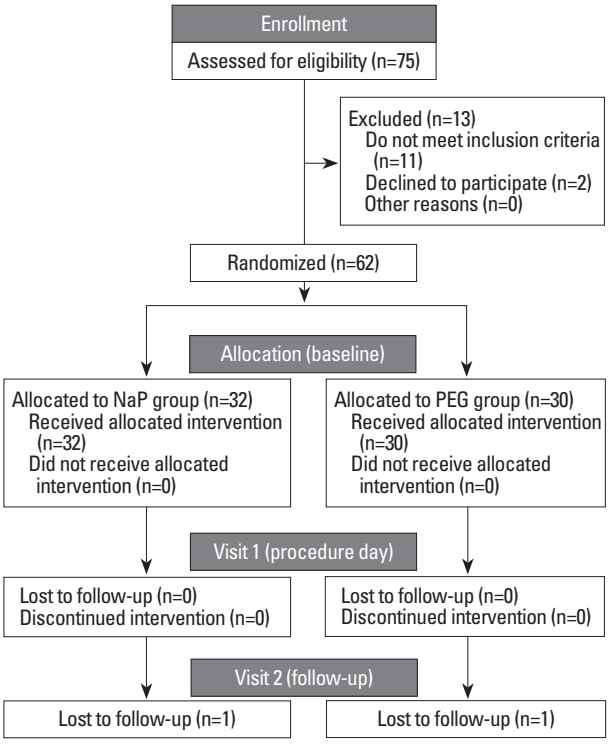

Fig. 1. Consolidated Standards of Reporting Trials (CONSORT) flow chart detailing the conduct of the study. Visit 1 (the day of colonoscopy and post-preparation); Visit 2 (1 week follow-up after colonoscopy). NaP, sodium phosphate; PEG, polyethylene glycol.

cal Research Information Service (identifier: KCT0000868), the national clinical trial registry of Korea in World Health Organization International Clinical Trials Registry Platform. Written informed consent was obtained from all of the patients before enrollment in the study.

Study population

Patients were enrolled from August 2013 to October 2013. In total, 62 Korean adults were enrolled in the study among an initial 75 patients. Patients were considered eligible if they were between 20 and 60 years old, scheduled for elective outpatient colonoscopy at our hospital, able to swallow tablets without any difficulty, competent to provide written informed consent, and able to effectively communicate with study investigators. However, patients with the following conditions were excluded: 1) acute or chronic renal insufficiency; 2) cardiovascular and cerebrovascular disease, including congestive heart failure, myocardial infarction, unstable angina pectoris, uncontrolled hypertension, cerebral hemorrhage, and stroke; 3) serious hepatobiliary disease, including liver cirrhosis and active-stage viral hepatitis; 4) ascites; 5) major psychiatric illness; 6) known electrolyte imbalance, such as hypo/hyper-natremia, hypo/hyper-kalemia, hypo/hyper-calcemia, hypo/hyper-magnesemia, and hypo/hyper-phosphatemia; 7) history of large bowel surgery (partial or total colorectal resection); 8) paralytic and/or mechanical ileus; 9) suggestive bowel obstruction; 10) inflammatory bowel disease; or 11) known allergies or contraindication to the drugs used in the study.

Randomization and assignment

Eligible participants who fulfilled all of the inclusion criteria and met none of the exclusion criteria were randomly assigned to one of the two groups (NaP vs. PEG) according to a computer-generated randomization sequence with a block size of four.

All of the enrolled patients in both groups were instructed to avoid foods that contain a lot of fiber, such as vegetables, seaweed, mushrooms, and fruits, for the last few days before colonoscopy and to ingest a soft diet on the day before colonoscopy. Up to 10 days before the scheduled colonoscopic examination, patients in each group received one of the following bowel preparation agents as appropriate: 1) All participants of the NaP group were asked to take a total of 32 NaP tablets in divided doses (20 tablets divided into four tablets every 15 minutes with 240 mL of clear liquid in the evening prior to colonoscopy and the remaining 12 tablets taken in the same way on the next morning, 3–5 hours prior to colonoscopy). One NaP tablet (Clicolon, Korea-Pharma Pharm Inc., Seoul, Korea) used in the study contained 1102 mg of monobasic sodium phosphate monohydrate (NaH_2PO_4) and 398 mg of dibasic sodium phosphate anhydrous ($NaHPO_4$). 2) All of the participants in the PEG group were asked to take a total of 4-liters of PEG solution in divided doses (3 liters of PEG solution as 250 mL of PEG every 25 minutes in the evening prior to colonoscopy and the remaining 1 liter taken in the same way on the next morning, 3–5 hours before colonoscopy). PEG (Colonlyte-F, Taejoon Pharm Inc., Seoul, Korea) used in the study contained 420 g of polyethylene glycol 3350, 5.72 g of sodium bicarbonate ($NaHCO_3$), 11.2 g of sodium chloride (NaCl), and 1.48 g of potassium chloride (KCl). All of the subjects in each group were given written instructions for the bowel preparation to which they were assigned.

Blinding

The enrollment and assignment of all subjects was performed by a clinical research coordinator not involved in the study. All of the investigators who were involved in the study were blinded to group allocation. The colonoscopists, who directly performed colonoscopy and/or evaluated the quality of bowel preparation, were also blinded. Study materials were kept at a location that could only be accessed by a study nurse or pharmacy personnel to ensure that the study medication (NaP tablets and PEG solution) remained blinded. Additionally, the study nurse instructed the patient not to discuss the study medication or any response to the study medication with the colonoscopist during colonoscopic examination.

Colonoscopic examination

As procedure-related parameters can be affected by the colonoscopist's level of experience and skill, as well as by the endoscopic equipment (especially the scope), all of the procedures were performed by a single experienced colonoscopist with over 8 years of experience more than 5000 performed colonoscopies to date, using an identical-type colonoscope (Olympus CF-H260-L, Olympus Optical Co., Ltd., Tokyo, Japan). Additionally, all colonoscopic examinations were performed without sedation in our study because sedation can influence colonoscopic outcomes. An antispasmodic agent, cimetropium bromide (Algiron, Green-Cross Pharm Inc., Yongin, Korea), was intravenously given immediately before the procedure to prevent colonic wall spasms.

All of the colonoscopies were started with the subject in the left lateral decubitus position. If the colonoscope could not be advanced during the procedure, one of the assistant nurses applied external abdominal compression at the discretion of the colonoscopist, as needed. If the abdominal compression was not sufficient for allowing the advancement of the scope, the subject's position was changed from the initial left lateral decubitus to the supine position and back again.

Measurements

Lifestyle and anthropometric data

At enrollment, we collected patient information on age, gender, current smoking habits (experience of smoking regularly during the past 12 months), alcohol consumption (≥70 g/week or ≥10 g/day), exercise (at least once a week on a regular basis), experience of previous colonoscopy, history of abdominopelvic surgery, weight, height, and body mass index (BMI, kg/m^2; calculated as weight divided by height squared).

Colonoscopic parameters

During and after the colonoscopy, data were collected for procedure-related outcomes, such as cecal intubation time (CIT), cecal intubation rate (CIR), terminal ileal intubation time (TIIT), terminal ileal intubation rate (TIIR), and total procedure time (TPT), as well as polyp detection rate (PDR). All colonoscopy-related times were recorded by an assistant nurse using the stopwatch function on the endoscopy equipment. Cecal intubation was considered successful based on the visualization of colonoscopic landmarks (i.e., the ileocecal valve and appendiceal orifice), and CIT was defined as the time required from the introduction of colonoscope to reach the base of the cecum. After the cecum was identified and still photographs of cecal landmarks were taken, ileal intubation was attempted. The TIIT was defined as the time required for the colonoscope end to be maneuvered from the cecum to the intubation of the terminal ileum.[20] Intubation of the terminal ileum was confirmed by photographic documentation of apparent villi in the terminal ileum by water-filling or using the narrow-band imaging method.[21] Cases where the terminal ileum could not be intubated were not included in the analysis of TIIT. Withdrawal time (WT) was calculated by subtracting the TIIT or CIT (unsuccessful cases of terminal ileum intubation) from the TPT. Detailed examination was performed during withdrawal of the colonoscope. During the examination, all detected polyps were removed by either cold biopsy or snare polypectomy according to their size and shape, and then the specimens were sent for pathological analysis. PDR was defined as the proportion of procedures in which at least one polyp was seen. All of the biopsies and polypectomies were performed during withdrawal in order to avoid the effect of intubation time. Adenomas were diagnosed by pathological evaluation of retrieved lesions. Thus, adenoma detection rate (ADR) was defined as the proportion of procedures in which at least one adenoma was documented by the pathology report.

Evaluation of bowel preparation quality

The bowel cleansing quality in participants was evaluated by two blinded investigators (the colonoscopist performing the procedure and the colonoscopist observing the procedure) using the Ottawa Bowel Preparation Quality Scale (OBPQS). In cases of discrepancy, these two investigators worked on reaching a consensus after the colonoscopic examination. Prior to commencement of the study, a calibration exercise was conducted to ensure that the participating colonoscopists understood and agreed on the rating of bowel-preparation quality using the OBPQS.

The OBPQS has been shown to be a valid and reliable tool for assessing bowel cleansing. It uses ratings from 0 to 4 (5-point scale: 0, excellent; 1, good; 2, fair; 3, poor; 4, inadequate) for assessment of the right colon (cecum, ascending), the mid colon (transverse, descending), and the rectosigmoid colon (sigmoid, rectum). Also, it includes an additional score (3-point scale: 0, small; 1, moderate; 2, large) for the fluid quantity of the entire colon.[22] These four individual scores are added, and therefore, the total OBPQS score ranges from 0 to 14. Adequate bowel preparation was defined as a total OBPQS score of ≤4, while inadequate bowel preparation was defined as a score of more than 5.[23]

Patient questionnaire with regards to assigned bowel cleansing agents

After the colonoscopy, all of the participants completed a nurse-administered questionnaire to assess their experience with the assigned bowel preparation regimen in another room in the absence of the investigators involved in the study. The questionnaire evaluated the following: the amount of bowel preparation agent ingested; tolerability and taste (4-point Likert scale); satisfaction [10-cm (VAS)]; willingness to repeat the regimen; and adverse events (nausea, vomiting, abdominal discomfort, and bloating). Patient compliance was classified according to three grades based on the percentage of

ingested solution or tablets: 1) complete, intake of all of the solution or tablets; 2) good, intake of at least 75% of the solution or tablets; or 3) poor, intake of <75% of the solution or tablets.

Laboratory tests between both groups and follow-up

In order to evaluate the safety of each bowel preparation agents, especially NaP tablets, laboratory tests were conducted three times in all of the participants: 1) baseline (the day of enrollment and allocation); 2) visit 1 (the day of the colonoscopy and post-preparation); and 3) visit 2 (1 week follow-up after colonoscopy). Blood samples were taken from the antecubital vein of subjects and measured using an automatic analyzer (Toshiba TBA 200FR, Toshiba Medical Systems Co. Ltd., Tokyo, Japan). The quantity levels of protein and blood in urine were assessed using Uropaper (US-3100R, Eiken Chemical, Tokyo, Japan). Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) study equation as an indicator of renal function: eGFR (milliliter per minute per 1.73 m^2)=186.3×(serum creatinine)$^{-1.154}$×(age)$^{-0.203}$ (×0.742 if the subject was female).

Statistical analysis

Continuous variables were expressed as means±standard deviation, whereas categorical variables were presented as numbers and percentages. For differences between both groups, continuous variables were analyzed appropriately using the independent t-test, and categorical variables were analyzed using the chi-square test or the Fisher-Freeman-Halton extension of Fisher's probability test. The paired t-test or Wilcoxon signed-rank test was used to evaluate the differences in laboratory tests between baseline, visit 1 (post-preparation), and visit 2 (1 week follow-up) in each group, as appropriate. Since we designed this trial as a randomized-pilot study, a formal sample size calculation was not performed. All *p*-values less than 0.05 were considered statistically significant. All statistical analyses were performed using SPSS version 13.0 software (SPSS Inc., Chicago, IL, USA) for Windows.

RESULTS

Baseline characteristics of all enrolled patients in the two groups

A summary of the baseline characteristics of all patients is shown in Table 1. The mean age was 40.5±10.6 years (range 23–58), and the study population predominantly consisted of men (64.5%). Overall, 22.6% of patients were smokers,

Table 1. Baseline Characteristics of the Participants

Characteristic	All patients (N=62)	NaP group (N=32)	PEG group (N=30)	*p* value
Age (yrs)	40.5±10.6	40.4±10.7	40.6±10.6	0.944*
20–29, N (%)	13 (21.0)	7 (21.9)	6 (20.0)	0.877†
30–39, N (%)	18 (29.0)	10 (31.3)	8 (26.7)	
40–49, N (%)	10 (16.1)	4 (12.5)	6 (20.0)	
≥50, N (%)	21 (33.9)	11 (34.4)	10 (33.3)	
Gender, N (%)				0.382†
Male	40 (64.5)	19 (59.4)	21 (70.0)	
Female	22 (35.5)	13 (40.6)	9 (30.0)	
Height (cm)	166.9±8.2	166.1±8.2	167.7±8.2	0.449*
Weight (kg)	67.2±12.8	66.5±11.5	67.8±14.3	0.682*
Waist circumference (cm)	83.2±10.3	83.1±9.2	83.3±11.5	0.944*
BMI (kg/m^2)	24.0±3.3	24.0±2.9	24.0±3.7	0.996*
Experience of PC, N (%)	12 (19.4)	6 (18.8)	6 (20.0)	0.901†
Surgical history, N (%)	9 (14.5)	6 (18.8)	3 (10.0)	0.328‡
Current smoker, N (%)	14 (22.6)	7 (21.9)	7 (23.3)	0.891†
Alcohol user, N (%)	39 (62.9)	21 (65.6)	18 (80.0)	0.647†
Exercise, N (%)	37 (59.7)	18 (56.3)	19 (63.3)	0.570†

NaP, sodium phosphate; PEG, polyethylene glycol; N, number; BMI, body mass index; PC, previous colonoscopy.
All data are expressed as mean±standard deviation or number (percentage), as appropriate.
**p*-value was calculated using the independent t-test.
†*p*-value was calculated using the chi-square test.
‡*p*-value was calculated using the Fisher-Freeman-Halton extension of Fisher's probability test.

62.9% were alcohol users, and 59.7% exercised regularly. The mean BMI was 24.0±3.3 kg/m^2 (range 17.3–33.8). Among all of the participants, 19.4% had undergone colonoscopy once previously, and 14.5% had undergone abdominopelvic surgeries: simple appendectomy (n=6; 4 males and 2 females) and cesarean section without complications (n=3, all females). No significant differences in baseline characteristics were observed between the two groups.

Comparison of bowel preparation quality and procedure-related parameters between the two groups

Clinical outcomes according to bowel cleansing regimens are shown in Table 2. There were no significant differences in the total OBPQS score between the two groups, although the score was better in the NaP tablet group than the PEG group (4.3 vs. 5.4, p=0.071). However, fluid scores were significantly better in the NaP group than the PEG group upon detailed analysis of individual OBPQS scores (0.1 vs. 0.6, p<0.001) (Fig. 2A). In addition, an adequate level of bowel preparation was more commonly observed in the NaP group than in the PEG group (62.5% vs. 33.3%, p=0.022) (Fig. 2B). There were no statistically significant differences in the procedural parameters, such as CIR, CIT, TIIR, TIIT, WT, TPT, PDR, and ADR, between the two groups. Also, no serious complications such as perforation or severe bleeding occurred during the colonoscopic examinations.

Comparison of patient tolerance, satisfaction, preference, and adverse events between the two groups

Data from the patients' questionnaires regarding the bowel preparation regimen (NaP vs. PEG) are shown in Table 3. The total amount of bowel cleansing agents ingested in the NaP group and the PEG group was 31.91±0.39 tablets and 3.85±0.44 liters, respectively. Although the difference in the percentage of patient compliance between the two groups was not statistically significant (p=0.800), the percentage of complete compliance was higher in the NaP group than the PEG group (93.8% vs. 86.7%) (Fig. 3A). When the patients were asked about their overall impression of taking the bowel cleansing agents, the percentage of patients who indicated that the preparation was "very easy" or "easy" to take was significantly higher in the NaP group than the PEG group (12.5+71.9% vs. 3.3+23.3%, p<0.001) (Fig. 3B). With respect to the taste of bowel cleansing agents, a great-

Table 2. Bowel Preparation Quality and Procedure-Related Parameters

Variables	All patients (N=62)	NaP group (N=32)	PEG group (N=30)	p value
OBPQS (scores)				
Right colon	1.9±0.9	1.8±1.1	1.9±0.6	0.796*
Mid colon	1.2±0.9	1.1±1.0	1.2±0.7	0.640*
Rectosigmoid colon	1.5±0.7	1.3±0.7	1.7±0.7	0.052*
Overall fluid	0.4±0.6	0.1±0.3	0.6±0.7	<0.001*
Total score	4.9±2.3	4.3±2.5	5.4±1.9	0.071*
Bowel cleansing, N (%)				0.022†
Adequate	30 (48.4)	20 (62.5)	10 (33.3)	
Inadequate	32 (51.6)	12 (37.5)	20 (66.7)	
CIR, N (%)	62 (100)	32 (100)	30 (100)	1.000‡
CIT (secs)	299.1±154.4	312.8±181.9	284.4±119.6	0.472*
TIIR, N (%)	60 (96.8)	31 (96.9)	29 (96.7)	1.000‡
TIIT (secs)	30.1±18.9	30.9±20.5	29.4±17.2	0.753*
WT (secs)	750.7±164.8	729.9±153.8	772.9±175.6	0.308*
TPT (secs)	1079.0±225.5	1072.8.8±249.1	1085.7±201.3	0.823*
PDR, N (%)	18 (29.0)	11 (34.4)	7 (23.3)	0.338†
ADR, N (%)	10 (16.1)	5 (15.6)	5 (16.7)	0.911‡

NaP, sodium phosphate; PEG, polyethylene glycol; N, number; OBPQS, Ottawa Bowel Preparation Quality Scale; CIR, cecal intubation rate; CIT, cecal intubation time; TIIR, terminal ileal intubation rate; TIIT, terminal ileal intubation time; WT, withdrawal time; TPT, total procedure time; PDR, polyp detection rate; ADR, adenoma detection rate.

All data are expressed as mean±standard deviation or number (percentage), as appropriate. The OBPQS was calculated by adding 0 to 4 points for each colon segment and 0 to 2 points for total fluid quantity in the entire colon. The scale has a range from 0 to 14. Adequate level of bowel cleansing was defined as a total OBPQS score of ≤4.

*p-value was calculated using the independent t-test.

†p-value was calculated using the chi-square test.

‡p-value was calculated using the Fisher-Freeman-Halton extension of Fisher's probability test.

er proportion of patients in the NaP group were satisfied with the taste of the bowel preparation agent, compared with that of patients in the PEG (Fig. 3C). Additionally, the satisfaction level of the bowel-cleansing regimen was higher in the NaP group than in the PEG group (8.5 vs. 5.5, $p<0.001$) (Fig. 3D). There was a statistically significant difference in the willingness to repeat the same regimen in the future between both groups (93.8% vs. 30.0%, $p<0.001$) (Fig. 3E).

The most common adverse events were nausea, vomiting,

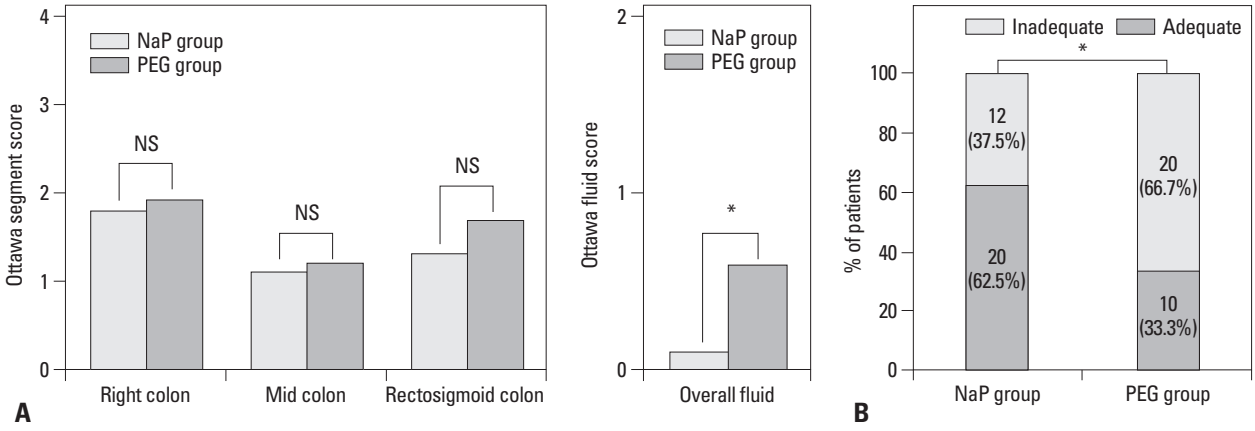

Fig. 2. Comparison of bowel cleansing efficacy between the NaP tablet group and the PEG solution group. (A) Sub-analysis of Ottawa scale score (cleansing of each colon segment, 5-point scale; total amount of remnant fluids in the entire colon, 3-point scale). (B) Percentage of patients with adequate level of bowel preparation. Adequate level of bowel preparation was defined as a total Ottawa score of ≤4. *$p<0.05$. NaP, sodium phosphate; PEG, polyethylene glycol; NS, not significant.

Table 3. Comparison of Patient-Related Outcomes in Both Groups

Variables	NaP group (N=32)	PEG group (N=30)	*p* value
Patient compliance, N (%)			0.800‡
Complete	30 (93.8)	26 (86.7)	
Good	2 (6.3)	3 (10.0)	
Poor	0 (0)	1 (3.3)	
What was the overall impression how difficult it was to take the study regimen? N (%)			<0.001‡
Very easy	4 (12.5)	1 (3.3)	
Easy	23 (71.9)	7 (23.3)	
Difficult	4 (12.5)	13 (43.3)	
Very difficult	1 (3.1)	9 (30.0)	
How did the study preparation taste? N (%)			0.004‡
Very good	5 (15.6)	0 (0)	
Good	22 (68.8)	15 (50.0)	
Bad	5 (15.6)	13 (43.3)	
Very bad	0 (0)	2 (6.7)	
Satisfaction level (10-cm VAS)	8.5±1.2	5.5±2.3	<0.001*
Number of patients who would repeat the preparation in future, N (%)	30 (93.8)	9 (30.0)	<0.001†
Adverse events, N (%)			
Nausea	8 (25.0)	15 (50.0)	0.042†
Vomiting	4 (12.5)	13 (43.3)	0.007†
Abdominal pain	3 (9.4)	2 (6.7)	1.000‡
Bloating/distension	12 (37.5)	11 (36.7)	0.946†

NaP, sodium phosphate; PEG, polyethylene glycol; N, number; cm, centimeter; VAS, visual analogue scale.
All data are expressed as in mean±standard deviation or number (percentage), as appropriate.
*p-value was calculated using the independent t-test.
†p-value was calculated using the chi-square test.
‡p-value was calculated using the Fisher-Freeman-Halton extension of Fisher's probability test.

abdominal pain, and bloating/distension in both groups. No significant differences in abdominal pain and bloating were observed between the two groups among these adverse events. However, nausea and vomiting were relatively more frequent in the PEG group than the NaP group (50.0% vs. 25.0%, p=0.042; 43.3% vs. 12.5%, p=0.007) (Fig. 3F).

Comparison of laboratory data between the two groups

Table 4 and 5 demonstrate the analysis of laboratory tests in both groups (NaP vs. PEG) during the study periods. Before bowel preparation (enrollment and allocation), most of the baseline laboratory test results were within normal limits, and there were no statistically significant differences between the

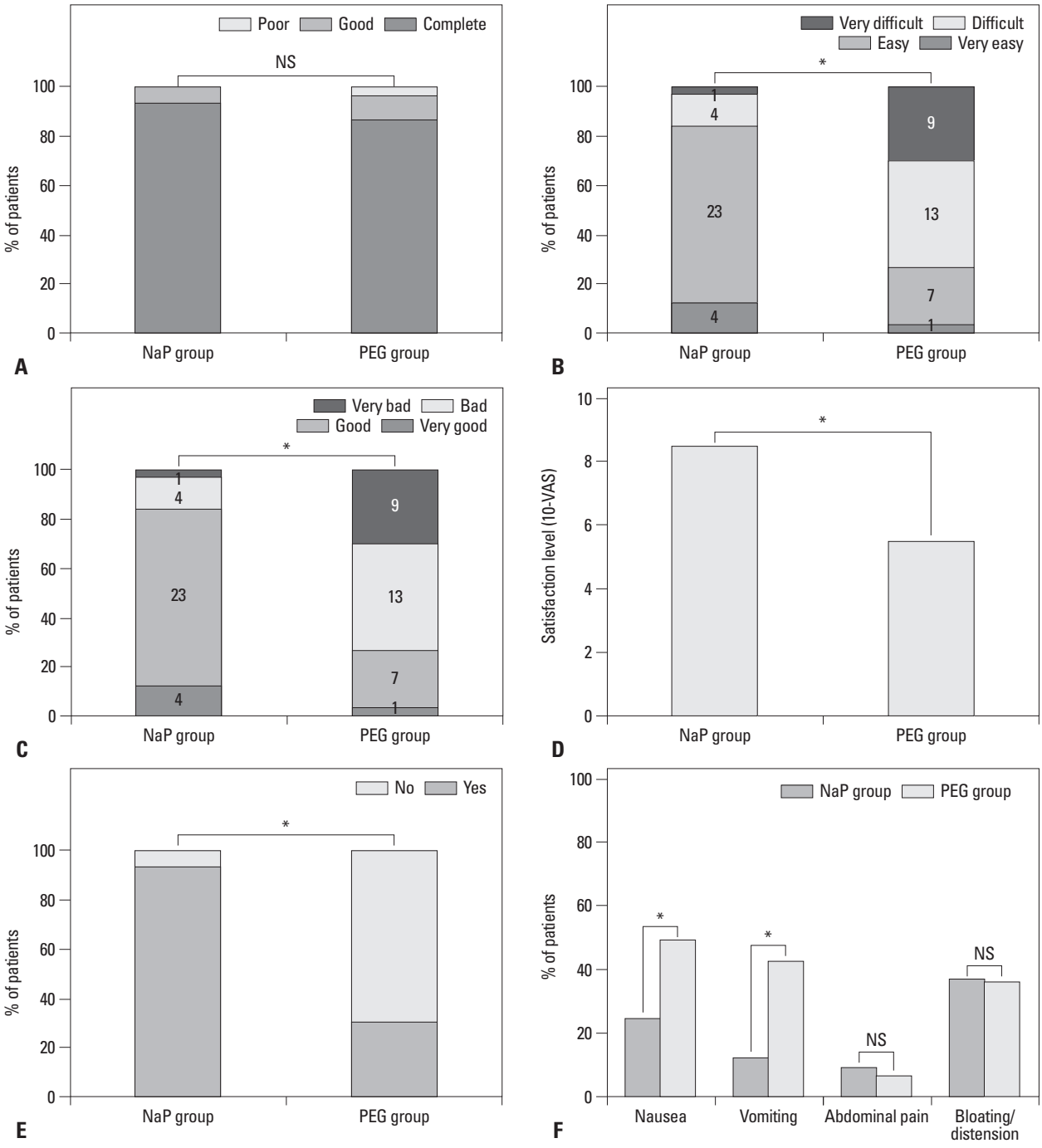

Fig. 3. Comparison of patient-related outcomes between the NaP group and the PEG group. (A) Patient compliance. i) Complete: intake of the whole solution or tablets; ii) Good: intake of at least 75% of the solution or tablets; iii) Poor: intake of <75% of the solution or tablets. (B) Patient acceptance of the assigned bowel cleansing agent (what was the overall impression how difficult it was it to take the study regimen?). (C) Taste, (D) Satisfaction, (E) Preference (patients who would repeat the preparation in future). (F) Adverse events in both groups. *p<0.05. NaP, sodium phosphate; PEG, polyethylene glycol; NS, not significant; VAS, visual analogue scale.

Table 4. Mean Change from Baseline and Effects of Cleansing Procedures on Laboratory Test Results

Laboratory variables	Reference ranges	NaP group					PEG group				
		Baseline	Mean or percentage change				Baseline	Mean or percentage change			
			1st visit	*p* value	2nd visit	*p* value		1st visit	*p* value	2nd visit	*p* value
WBC ($\times10^3/\mu L$)	4.0–11.0	6.69±1.45	0.29	0.155*	-0.21	0.424*	6.87±1.60	-0.15	0.465*	-0.28	0.147*
Hb. (g/dL)	12.5–17.5	14.13±1.65	-0.90	0.267*	-0.16	0.205*	14.24±0.86	0.08	0.547*	-0.19	0.424*
Hct. (%)	37.0–51.6	42.51±4.86	-0.35	0.091*	-0.44	0.217*	43.08±2.86	0.11	0.892*	-1.14	0.208*
Plt. ($\times10^3/\mu L$)	134–387	225.66±46.97	-0.16	0.258*	6.11	0.315*	242.77±58.16	-4.24	0.537*	-0.36	0.505*
FPG (mg/dL)	70–110	94.28±6.12	-3.15	0.072*	-0.47	0.860*	93.43±7.60	1.24	0.482*	0.36	0.905*
BUN (mg/dL)	8–25	12.98±3.35	-1.03	0.086*	0.29	0.555*	12.62±3.76	-1.25	0.076*	0.78	0.316*
Cr. (mg/dL)	0.5–1.4	1.05±0.15	0.03	0.133*	0.00	0.839*	1.07±0.16	0.02	0.211*	0.01	0.663*
eGFR (mL/min per 1.73 m^2)	≥60	75.26±8.40	-1.61	0.243*	0.35	0.623*	76.66±14.24	-0.98	0.321*	-0.91	0.676*
Na (mEq/L)	135–145	139.97±1.53	-0.06	0.862*	0.61	0.211*	140.70±1.51	0.30	0.256*	0.60	0.147*
K (mEq/L)	3.5–5.5	4.32±0.32	-0.66	<0.001*	0.02	0.798*	4.18±0.25	-0.21	0.004*	0.04	0.522*
Cl (mEq/L)	98–107	101.97±2.16	-0.53	0.074*	0.71	0.060*	102.70±1.60	-0.60	0.095*	0.02	0.933*
TCO_2 (mEq/L)	24–31	26.81±1.47	-1.72	<0.001*	0.16	0.721*	26.57±1.85	-18.4	<0.001*	0.22	1.000*
Total Ca (mg/dL)	8.2–10.2	9.52±0.43	-0.45	<0.001*	0.04	0.505*	9.59±0.40	-0.01	0.963*	-0.02	0.686*
IP (mg/dL)	2.7–4.5	3.61±0.39	1.58	<0.001*	0.18	0.082*	3.60±0.46	0.13	0.180*	-0.17	0.264*
Mg (mg/dL)	1.8–2.8	2.28±0.20	-0.16	<0.001*	-0.03	0.090*	2.21±0.16	-0.12	0.002*	-0.02	0.864*
Uric acid (mg/dL)	4.5–8.2	5.38±1.41	0.22	0.062*	-0.07	0.922*	5.69±1.26	0.24	0.094*	0.07	0.567*
AST (IU/L)	8–41	24.47±9.25	1.62	0.093*	-0.05	0.916*	22.03±6.16	0.94	0.228*	1.11	0.120*
ALT (IU/L)	5–40	26.72±19.18	2.44	0.158*	0.31	0.821*	23.07±12.41	0.13	0.898*	1.52	0.345*
Alb. (g/dL)	3.5–5.3	4.68±0.22	-0.05	0.083*	-0.05	0.210*	4.73±0.27	-0.08	0.084*	-0.03	0.201*
Urine protein	Negative			0.102†		0.317†			0.130†		1.000†
i) Negative		28 (87.5)	26 (81.3)		29 (93.5)		27 (90.0)	23 (76.7)		26 (89.7)	
ii) Trace		4 (12.5)	4 (12.5)		2 (6.5)		3 (10.0)	5 (16.7)		3 (10.3)	
iii) ≥1+(1+, 2+, 3+)		0 (0)	2 (6.3)		0 (0)		0 (0)	2 (6.7)		0 (0)	
Urine blood	Negative			1.000†		0.317†			0.564†		1.000†
i) Negative		28 (87.5)	29 (90.6)		29 (93.5)		28 (93.3)	28 (93.3)		27 (93.1)	
ii) Trace		4 (12.5)	2 (6.3)		2 (6.5)		2 (6.7)	1 (3.3)		2 (6.9)	
iii) ≥1+(1+, 2+, 3+)		0 (0)	1 (3.1)		0 (0)		0 (0)	1 (3.3)		0 (0)	

NaP, sodium phosphate; PEG, polyethylene glycol; WBC, white blood cells count; Hb., hemoglobin, Hct., hematocrit; Plt., platelet; FPG, fasting plasma glucose; BUN, blood urea nitrogen; Cr., creatinine; eGFR, estimated glomerular filtration rate; Na, sodium; K, potassium; Cl, chloride; TCO_2, total carbon dioxide; Ca, calcium; IP, inorganic phosphorus; Mg, magnesium; AST, aspartate transaminase; ALT, alanine transaminase; Alb., albumin.
All data are expressed as mean±standard deviation or number (percentage), as appropriate.
* *p*-value was calculated using the paired t-test.
† *p*-value was calculated using the Wilcoxon signed rank test. Laboratory tests were conducted three times in all of the participants: i) baseline (the day of enrollment and allocation); ii) visit 1 (the day of colonoscopy and post-preparation); iii) visit 2 (1 week follow-up after colonoscopy). eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) study equation: eGFR (milliliter per minute per 1.73 m^2)=186.3×(serum creatinine)$^{-1.154}$×(age)$^{-0.203}$ (×0.742 if the individual was female).

Table 5. Comparison of Laboratory Tests Results between Both Groups from Baseline to Visit 1 and Visit 2

Laboratory variables	Reference range	Baseline			Visit 1			Visit 2		
		NaP (n=32)	PEG (n=30)	*p* value	NaP (n=32)	PEG (n=30)	*p* value	NaP (n=31)	PEG (n=29)	*p* value
WBC ($\times10^3/\mu L$)	4.0–11.0	6.69±1.45	6.87±1.60	0.651*	6.98±1.39	6.72±1.51	0.675*	6.48±1.34	6.59±1.66	0.780*
Hb. (g/dL)	12.5–17.5	14.13±1.65	14.24±0.86	0.744*	14.04±1.70	14.32±1.00	0.437*	13.97±1.61	14.05±1.27	0.817*
Hct. (%)	37.0–51.6	42.51±4.86	43.08±2.86	0.578*	42.16±4.71	43.15±3.49	0.337*	42.07±4.58	41.94±3.81	0.908*
Plt. ($\times10^3/\mu L$)	134–387	225.66±46.97	242.77±58.16	0.206*	222.50±42.83	238.53±51.74	0.188*	231.77±50.77	242.41±54.05	0.435*
FPG (mg/dL)	70–110	94.28±6.12	93.43±7.60	0.629*	91.13±8.56	94.67±9.99	0.138*	93.81±10.90	93.79±11.19	0.996*
BUN (mg/dL)	8–25	12.98±3.35	12.62±3.76	0.694*	11.95±3.26	11.37±2.42	0.432*	13.27±3.19	13.40±3.39	0.877*
Cr. (mg/dL)	0.5–1.4	1.05±0.15	1.07±0.16	0.604*	1.08±0.17	1.09±0.17	0.843*	1.05±0.17	1.08±0.16	0.508*
eGFR (mL/min per 1.73 m^2)	≥60	75.26±8.40	76.66±14.24	0.644*	73.65±9.62	75.68±14.09	0.843*	75.61±11.10	75.75±13.25	0.965*
Na (mEq/L)	135–145	139.97±1.53	140.70±1.51	0.064*	139.91±1.80	140.40±1.33	0.227*	140.58±2.42	140.10±1.57	0.372*
K (mEq/L)	3.5–5.5	4.32±0.32	4.18±0.25	0.069*	3.66±0.39	3.97±0.31	0.001*	4.34±0.35	4.22±0.31	0.158*
Cl (mEq/L)	98–107	101.97±2.16	102.70±1.60	0.138*	101.44±2.03	102.10±2.20	0.223*	102.68±2.17	102.72±2.33	0.936*
TCO_2 (mEq/L)	24–31	26.81±1.47	26.57±1.85	0.563*	25.09±1.92	24.73±2.33	0.508*	26.97±2.15	26.79±2.09	0.751*
Total Ca (mg/dL)	8.2–10.2	9.52±0.43	9.59±0.40	0.523*	9.07±0.48	9.58±0.32	<0.001*	9.57±0.41	9.57±0.30	0.933*
IP (mg/dL)	2.7–4.5	3.61±0.39	3.60±0.46	0.883*	5.19±1.03	3.73±0.39	<0.001*	3.43±0.47	3.43±0.54	0.988*
Mg (mg/dL)	1.8–2.8	2.28±0.20	2.21±0.16	0.145*	2.12±0.18	2.09±0.17	0.570*	2.25±0.22	2.19±0.13	0.273*
Uric acid (mg/dL)	4.5–8.2	5.35±1.41	5.69±1.26	0.322*	5.60±1.39	5.93±1.22	0.335*	5.31±1.28	5.76±1.32	0.179*
AST (IU/L)	8–41	24.47±9.25	22.03±6.16	0.230*	26.09±8.09	22.97±4.67	0.070*	24.42±9.00	23.14±5.42	0.510*
ALT (IU/L)	5–40	26.72±19.18	23.07±12.41	0.380*	29.16±17.89	23.20±9.46	0.105*	27.03±19.07	24.59±11.15	0.544*
Alb. (g/dL)	3.5–5.3	4.68±0.22	4.73±0.27	0.407*	4.63±0.23	4.65±0.21	0.699*	4.63±0.23	4.70±0.28	0.283*
Urine protein	Negative			1.000†			0.894†			0.666†
i) Negative		28 (87.5)	27 (90.0)		26 (81.3)	23 (76.7)		29 (93.5)	26 (89.7)	
ii) Trace		4 (12.5)	3 (10.0)		4 (12.5)	5 (16.7)		2 (6.5)	3 (10.3)	
iii) ≥1+(1+, 2+, 3+)		0 (0)	0 (0)		2 (6.3)	2 (6.7)		0 (0)	0 (0)	
Urine blood	Negative			0.672†			1.000†			1.000†
i) Negative		28 (87.5)	27 (93.3)		29 (90.6)	28 (93.3)		29 (93.5)	27 (93.1)	
ii) Trace		4 (12.5)	2 (6.7)		2 (6.3)	1 (3.3)		2 (6.5)	2 (6.9)	
iii) ≥1+(1+, 2+, 3+)		0 (0)	0 (0)		1 (3.1)	1 (3.3)		0 (0)	0 (0)	

NaP, sodium phosphate; PEG, polyethylene glycol; WBC, white blood cells count; Hb., hemoglobin; Hct., hematocrit; Plt., platelet; FPG, fasting plasma glucose; BUN, blood urea nitrogen; Cr., creatinine; eGFR, estimated glomerular filtration rate; Na, sodium; K, potassium; Cl, chloride; TCO_2, total carbon dioxide; Ca, calcium; IP, inorganic phosphorus; Mg, magnesium; AST, aspartate transaminase; ALT, alanine transaminase; Alb., albumin. All data are expressed as mean±standard deviation or number (percentage), as appropriate. Laboratory tests were conducted three times in all of the participants: i) baseline (the day of enrollment and allocation); ii) visit 1 (the day of colonoscopy and post-preparation); and iii) visit 2 (1 week follow-up after colonoscopy). eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) study equation: eGFR (milliliter per minute per 1.73 m^2)=186.3×(serum creatinine)$^{-1.154}$×(age)$^{-0.203}$ (×0.742 if the individual was female).

**p*-value was calculated using the independent t-test.

†*p*-value was calculated using the Fisher-Freeman-Halton extension of Fisher's probability test.

two groups. However, in urine analysis, an increased frequency of proteinuria was observed at post-preparation among the participants (NaP: increased from 12.5% to 18.8%; PEG: increased 10.0% to 23.4); most of these changes were minimal and non-significant, and were normalized during the follow-up period. After bowel cleansing, however, significant fluctuations in serum chemistry and electrolytes were noted in both groups. Generally, such fluctuations were common and of a greater magnitude in the NaP group. Potassium (K^+) and calcium (Ca^{2+}) levels were decreased more significantly in the NaP group, compared with the PEG group (Fig. 4A and B). Inorganic phosphorus (PO_4^{3-}) levels were significantly higher in the NaP group than the PEG group (Fig. 4C). However, the mean changes from baseline were generally mild and transient, and none of the changes in laboratory tests resulted in serious complications or adverse events in our study. Additionally, these abnormalities disappeared and no statistically significant changes were noted in the follow-up laboratory tests.

DISCUSSION

The present study was designed to compare the efficacy and safety of a 32 tablets NaP dosing regimen with 4-liters PEG solution. Other factors such as patient-related outcomes and procedural parameters were analyzed as well. The results of this study show that the NaP regimen is an effective, well-tolerated, safe, and acceptable regimen for bowel preparation prior to colonoscopy. Although serum phosphorus levels were increased in the NaP group and serum calcium and potassium levels were decreased after bowel preparation in the NaP group, compared with the PEG group, there were no serious complications recorded, and these values returned to their normal levels during follow-up laboratory tests at 1 week after the colonoscopy.

Many previous studies on bowel preparation have employed the OBPQS.[23-25] In this study, the overall quality of bowel preparation in the two groups (NaP vs. PEG) was not significantly different. Similarly, there were no statistically significant differences in the PDR and ADR between both groups. However, there was a trend for a better OBPQS score in the NaP group, compared with the PEG group, in all individual colonic segments (right-colon, mid-colon, and rectosigmoid-colon), although the difference was small and not statistically significant. Moreover, the overall fluid amounts in the colonic lumen were much more in the PEG group than in the NaP group (0.6 vs. 0.1, $p<0.001$). Bowel preparation using PEG leads to greater accumulation of fluids because of the large volume, and therefore, more time may be needed for this agent to pass through the body. Our study also showed that a significantly higher proportion of patients in the NaP group had an adequate level of bowel cleansing, compared with that in the patients in the PEG group (62.5% vs. 33.3%, $p=0.022$). The results of our study are in agreement with those of earlier studies.[26,27]

Among the results of the current study, we observed a few interesting findings regarding the procedure-related parameters according to the use of two purgatives, although these findings were not statistically significant. The mean WT was longer in the PEG group than in the NaP group, with no significant differences in PDR and ADR between two groups. On the other hand, the mean CIT was longer in the NaP group compared with the PEG group, with no sig-

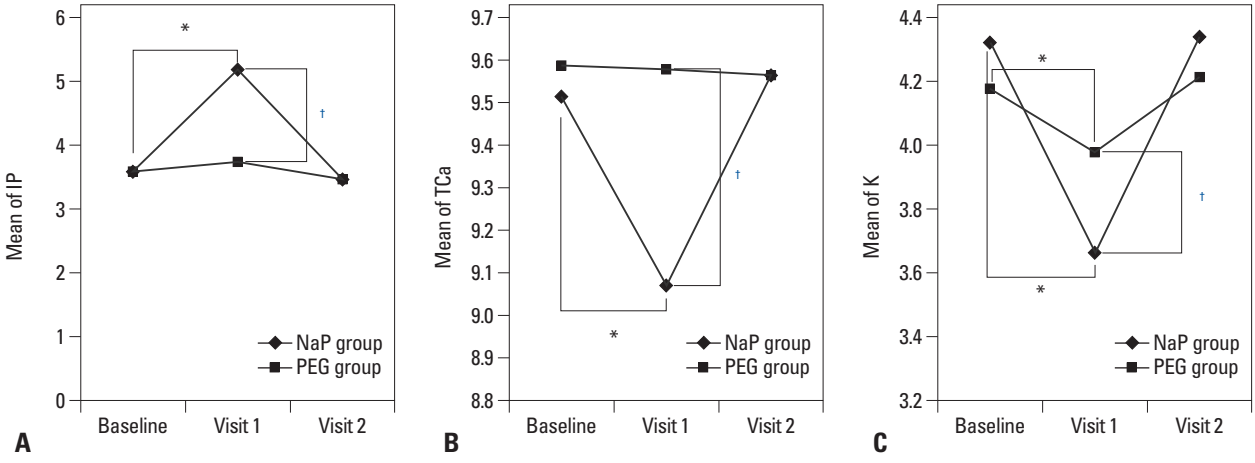

Fig. 4. Comparison of laboratory tests results between two groups during the study period. (A) Inorganic phosphorus. (B) Total calcium. (C) Potassium. *$p<0.05$ by the paired t-test; †$p<0.05$ by independent t-test. NaP, sodium phosphate; PEG, polyethylene glycol; TCa, total calcium; K, potassium; IP, inorganic phosphorus.

nificant difference in the CIR and TIIR between the groups. A possible explanation for these findings in our study could be increased amounts of fluids in the lumen in the PEG group and decreased amounts of fluids (i.e., dehydrated or sticky colonic lumen) in the NaP group. In clinical practice, if there are fluids in the lumen, colonoscopists will spend their time in suction of these fluids, especially during the withdrawal phase, because careful observation of the colon may be interfered with by these fluids, while such fluids may be helpful during intubation of the colonoscope as they may acts as lubricants. NaP acts as an osmotic laxative, which cleanses the colon by drawing fluids into the large intestine. Thus, the colonic lumen may be dehydrated and sticky. Actually, most of the colonoscopists sometimes experience this phenomenon in their routine clinic practice. This could contribute to the prolonged CIT during the intubation phase. However, to confirm these results, further large-scale studies focusing on the association with bowel preparation agents and procedural parameters are required.

Patient-related outcomes, such as compliance, tolerability and acceptance, satisfaction, and preference, are one of the most important factors in research and evaluation of bowel preparation agents. Previous studies have shown that the NaP bowel-cleansing regimen was superior to the PEG regimen in terms of tolerability and acceptance, as well as satisfaction.[17,28-30] In accordance with previous studies, our study also showed that the percentages of participants who had an overall impression (tolerability and acceptance) that taking the bowel preparation agent was "very easy" or "easy" were 84.4% (27/32) and 26.7% (8/30) in the NaP group and PEG group, respectively. In addition, patients assigned to the NaP regimen were much more satisfied than those assigned to the PEG regimen (satisfaction VAS score; NaP vs. PEG, 8.5 vs. 5.5, $p<0.001$). There were statistically significant differences in the willingness to repeat the same regimen in the future (preference) between the NaP group and the PEG group (93.8% vs. 30.0%, $p<0.001$). These results are not surprising since there is a requirement to ingest a large volume (4 liters) of PEG. In the current trial, although sulfate-free type of PEG was used for the participants of the PEG group to minimize the effect of unpleasant taste and smells, the relatively tasteless and odorless NaP tablets, compared with PEG solution, were significantly better tolerated and favored by the patients; the percentages of participants who replied that the study drug tasted "very good" or "good" in the NaP and PEG groups were 84.4% (27/32) and 50.0% (15/30), respectively. Also, this may be one of the reasons for the differences in patient-related outcomes, such as tolerability and preference, between the groups. Thus, these features (odorless, tasteless), as well as a low volume of NaP tablets, may be another advantage over the PEG-bowel cleansing regimen. Among subjective adverse events reported by the participants, our results were similar to those in previous studies.[28,31] A significantly fewer number of patients taking NaP tablets reported nausea and vomiting, compared with the number of patients receiving the PEG solution (25.0%, 12.5% vs. 50%, 43.3%). There were no significant differences in abdominal pain and bloating between the groups. In the overall analysis, compliance in both groups was relatively high compared to that in previous studies of bowel preparation regimen.[29,32] The participants in our study were thoroughly instructed on how to ingest the bowel preparation agent and its importance for a complete colonoscopy. This may have increased motivation of the participants in the study and contributed to high compliance rates in the two groups.

To evaluate the safety of the NaP tablet and PEG solution, the laboratory data, measured three times, before (baseline) and after bowel preparation (visit 1) and at 1 week follow-up (visit 2), were compared. After bowel preparation, there were transient fluctuations in a few specific serum chemistry parameters and electrolytes in both groups. These results of our study were similar to those reported previously in other clinical trials.[33,34] As expected, fluctuations in electrolyte levels were more common in the NaP group, compared with the PEG group. The most significant change was seen in the mean $PO4^{3-}$ levels among participants taking NaP tablets. The mean $PO4^{3-}$ level in the NaP group increased to 1.58 mg/dL, compared with almost no change in the mean $PO4^{3-}$ level in the PEG group. Symptoms of hyperphosphatemia are induced by subsequent hypocalcemia and may include muscle cramps, tetany, and occasional disturbance of consciousness, in serious cases especially. However, no laboratory changes in the NaP group resulted in serious complications in the present study. Additionally, there were no clinical manifestations of these electrolyte changes, and none of the patients required specific treatment for these changes. Also, at visit 2, these electrolyte abnormalities returned to the baseline and there were no significant safety concerns, such as acute phosphate nephropathy and acute renal calcinosis. There are several possible explanations for the results among the participants of the NaP group: first, the mean post-preparation values were within the normal reference ranges, which may indicate a minor clinical

importance, albeit a statistically significant decrease in serum K^+ and Ca^{2+} levels in the NaP group. Second, the study population consisted of relatively healthy adults with normal renal function. The patients were carefully enrolled with completed inclusion criteria and those with cardiac, renal and other serious underlying diseases rigorously excluded from the study before randomization. Previously, Hookey, et al.[35] extensively reviewed the literature regarding the safety of oral NaP solutions in adults. In their review, the investigators found that oral NaP solutions were generally safe and most of the adverse events occurred when these agents were used in high doses or in patients in whom their use was contraindicated, such as in patients with renal impairment or important comorbidities. Third, sodium phosphate ingredients (NaH_2PO_4 plus $NaHPO_4$) in the 32-tablets regimen comprised less than 20% of those in the 90 mL-NaP solution regimen (tablet vs. solution; total 48.0 grams, 59.4 grams, respectively), which was withdrawn and prohibited for use in bowel preparation of colonoscopy by the Korea Food and Drug Administration. Furthermore, the tablet-type NaP formulation could force patients to ingest more liquids than the solution-type NaP formulation. Theoretically, the patients receiving NaP solution for bowel preparation could only take this solution without the need for ingestion of additional water, while the patients receiving NaP tablets would ingest more water. Indeed, inadequate hydration appears to be an important element in the reported cases of complications after the use of the NaP-based regimen as well as predisposing risk factors (old age, underlying diseases, and concomitant medications) and inappropriate dosing (overdosing).

There are some limitations associated with this study. First, this was a single center trial. Thus, there may be unforeseen confounding factors that may affect patient recruitment, assessment of bowel cleansing quality, and other data. However, we designed this study as a randomized controlled trial to minimize selection bias. Also, all of the investigators, including colonoscopist, who were involved in this study were blinded, and all colonoscopists evaluating the bowel cleansing quality performed calibration exercises including 30 colonoscopies prior to commencement of the study. Second, we only included outpatients without serious comorbidities who were to undergo elective colonoscopy. Thus, our results may not be applied to inpatients or to patients undergoing an emergency colonoscopy. However, expanding the inclusion criteria may have potential ethical and medical issues, because the NaP-based regimen has potential risks in such patients and situations. Hence, this study was conducted in relatively healthy Korean adults. Third, the study sample size was relatively small and therefore our study may not have adequate power to detect clinical complications and adverse events, especially in the studied healthy population. Thus, further multicenter and large scale studies are needed to confirm these findings. Despite these limitations, our study has the strength of being the first randomized, controlled pilot study to compare safety, efficacy, patient, and procedural outcomes of two bowel preparation agents in healthy Korean adults. Thus, we believe that this study may be helpful to physicians who perform colonoscopy in clinical practice and to medical researchers who plan to perform further large-scale studies.

In conclusion, NaP tablets, compared with PEG solution, produced equivalent and/or superior colon cleansing, were better tolerated by the patients, and did not cause more complications and side effects, although there were transient electrolyte imbalances. Thus, an oral NaP tablet formulation could make the overall bowel preparation less burdensome and may lead to greater patient participation in CRC screening programs.

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