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Bowel Preparation for Capsule Endoscopy: A Prospective Randomized Multicenter Study

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Background/Aims: The ability to visualize the small bowel mucosa by capsule endoscopy is limited. Moreover, studies involving small-bowel preparation with purgative drugs have failed to establish which preparations produce better images and higher diagnostic yields. The aim of this study was to evaluate the efficacies and diagnostic yields of different bowel preparations. **Methods:** A cohort of 134 patients with suspected small bowel disease was randomly assigned to 3 groups. Patients in group A (n=44) fasted for 12 h before being administered an M2A capsule (Given Imaging, Yoqneam, Israel). Patients in group B (n=45) were asked to drink two doses of 45 mL of sodium phosphate (NaP) with water during the afternoon and evening on the day before the procedure and to drink at least 2 L of water thereafter. Patients in group C (n=45) drank 2 L of a polyethylene glycol (PEG) lavage solution the evening before the procedure. **Results:** Overall cleansing of the small bowel was adequate in 43% of patients in group A, 77% of those in group B, and 56% of those in group C (group A vs group B, p=0.001). Diagnoses for obscure gastrointestinal bleeding were established in 9 patients (39%) in group A, 16 patients (69%) in group B, and 14 patients (50%) in group C. No significant difference in diagnostic yield was observed between groups. **Conclusions:** Bowel preparation with NaP for capsule endoscopy improved small-bowel mucosal visualization when compared to 12-h overnight fasting. **(Gut and Liver 2009;3:180-185)**

Key Words: Capsule endoscopy; Sodium phosphate

INTRODUCTION

Capsule endoscopy is a highly effective method for evaluating the entire small bowel during its normal peristalsis without inconvenience of patients. The diagnostic algorithm for small bowel disease has thus been adapted to exploit the excellent diagnostic yield of capsule endoscopy compared to that of conventional methods.[1-4]

Despite its diagnostic accuracy, the yield of capsule endoscopy can be limited by intestinal contents, food, and air bubbles. To obtain better mucosal images via capsule endoscopy, some clinicians have prepared the small bowel using purgative agents, such as, simethicone, polyethylene glycol (PEG), and sodium phosphate (NaP).[5-9] These studies have generally shown that preparation before capsule endoscopy increases the quality of images and the diagnostic yield. However, a comparative analysis to establish the most effective preparation for capsule endoscopy is lacking.

The aim of this prospective, randomized, single-blind, multi-center study was to evaluate the quality of visualization and the diagnostic yield produced by three methods of bowel preparation.

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MATERIALS AND METHODS

A total of 135 patients at 9 tertiary academic hospitals were enrolled for the evaluation of suspected small bowel disease, including obscure gastrointestinal bleeding, Crohn's disease, chronic abdominal pain and diarrhea, and familial polyposis syndrome. All evaluations took place between October 2004 and September 2007. We excluded pregnant women, patients with suspicious gastrointestinal obstruction, patients with any implanted electromedical device (e.g., cardiac pacemaker or defibrillator), and patients less than 18 years old. When capsule endoscopy was scheduled, the patients were assigned to Group A, B, or C by using randomization lists. Group A fasted overnight before swallowing the mouth-to-anus (M2A) capsule (Given Imaging, Yoqneam, Israel) in the morning, without any supplementary bowel preparation. Group B self-administered two bottles of oral NaP, 2 bottles (45 mL each; Solin®, Korea Pharma Co., Ltd., Seoul, Korea) with water, drinking one bottle at 3:00 p.m. and the second at 7:00 p.m. the day before the procedure; Group B patients were also asked to drink at least 2 L of clear liquid before midnight on the day before the procedure. Group C ingested 2 L of a PEG/electrolyte lavage solution (Colyte®, Taejoon Pharm Co., Ltd., Seoul, Korea) 16 h before the procedure. All patients were requested to ingest a liquid diet after a regular breakfast the day before the procedure and were allowed to drink clear liquid for 2 h and have a liquid diet for 4 h after swallowing the capsule. At least two expert endoscopists, unaware of the type of bowel preparation, evaluated the capsule endoscopy findings. The gastric emptying time (GET) and the small intestinal transit time (SITT) were automatically calculated. The GET was defined as the time from the first gastric image to the first duodenal image and the SITT was defined as the time from the first duodenal image to the first cecal image.

The primary study outcome was to evaluate the effects of bowel preparation on the quality of images obtained by capsule endoscopy. Although few previous studies on bowel preparation for capsule endoscopy are available, including several studies with a small sample size reported in abstract form, we used these reports to calculate the necessary sample size for our study. The secondary study outcome was to evaluate the effect of preparation on diagnostic yield. We used the standard defined by Viazis *et al*.[6] to evaluate the effects of bowel preparation. Obstacles such as intestinal contents, intraluminal gas, bile, and food were evaluated. The intestinal mucosa was defined as clean if, at any time, less than 25% of the mucosal surface was covered by intestinal contents, concentrated bile, intraluminal gas, and food. By using a timer, investigators recorded the exact time period during which the small intestinal mucosa was not clean. The percentage of the SITT during which the small intestinal mucosa was not clean was then calculated as an objective score. Small bowel cleansing was considered "adequate" if the objective score was less than 10% and "inadequate" if the score was 10% or greater. All investigators independently evaluated all of the digital image streams and the objective score reported for each patient was the mean of the values provided by these investigators.

A subset of patients then underwent further evaluation (double balloon enteroscopy, Meckel's scan, Tc^{99} red cell scan, small bowel series, or computerized tomography) to confirm findings of capsule endoscopy. Final diagnoses were established through further evaluation or capsule endoscopy alone with a definite positive finding. In the diagnosis of Crohn's disease, capsule endoscopy results were defined as positive if four or more obvious clear ulcers, erosions, or regions with clear exudates and mucosal hyperemia and edema were identified. The patient's history and clinical course of the disease were considered before a diagnosis of Crohn's disease was made. The test subjects completed a questionnaire and evaluated the difficulty and side effects of the preparatory method.

1. Ethical considerations

All of the patients provided written consent to undergo capsule endoscopy. This study was approved by the Institutional Review Board of Medical Ethics and the Human Clinical Trial Committee at each hospital.

2. Statistical analysis

Quantitative data were summarized as the mean and standard deviation (SD). Continuous measures were analyzed using analysis of variance (ANOVA). Nonparametric data were compared by the Kruskal-Wallis test and categorical measures were compared by using the chi-square test or Fisher's exact test. p-values <0.05 were considered statistically significant, and all statistical analyses were performed using SPSS 11.5 (SPSS Inc., Chicago, IL, USA). When each variable was compared to the other two, categorical data were analyzed using the chi-square test with Bonferroni correction. The significance level was therefore adjusted to $p<0.017$.

RESULTS

1. Patient characteristics

A total of 135 patients underwent capsule endoscopy. Among the patients in Group A, one patient was ex-

cluded because the capsule did not traverse the duodenum. Consequently, 134 patients (85 men and 49 women) were analyzed. Groups A, B, and C contained 44, 45, and 45 subjects, respectively. Mean ages were as follows: 53.1 years for Group A, 50.0 years for Group B, and 45.7 years for Group C. The most common indication in all three groups was obscure overt gastrointestinal (GI) bleeding in each group. No significant difference was observed among the three groups in terms of age, sex, or indication (Table 1).

2. Transit time and quality of images

The mean GET was 34.9 min for Group A, 47.2 min for Group B, and 25.2 min for Group C. The mean SITT was 321.8 min for Group A, 313.5 min for Group B, and 337.6 min for Group C. The capsule reached the cecum in 33 patients in Group A (75%), 33 patients in Group B (73%), and 32 patients in Group C (71%). No significant difference was difference was observed among groups regarding GET, SITT, or the percentage of patients in whom the capsule reached the cecum. All capsules were retrieved except one which was blocked at ileum because of a stricture with Crohn's disease. After 4 weeks later, retention capsule was spontaneously eliminated. The number of patients with "adequate" cleansing of the small intestine was 19 in Group A (43%), 33 in Group B (77%), and 25 in Group C (56%). The mean percentage of patients with "adequate" cleansing was significantly different among the three groups (p=0.002). In comparison with the other subgroups, Group B had significantly better image quality than Group A (p=0.001; Table 2). No significant difference in image quality was observed Group B and C, or between Group A and C.

3. Diagnostic yield of capsule endoscopy

In patients with obscure gastrointestinal bleeding, a definite diagnosis was established for nine patients (39%) in Group A, 16 patients (69%) in Group B, and 14 patients (50%) in Group C (p=0.111). In patients with non-obscure gastrointestinal bleeding, a definite diagnosis was established for 14% of patients in Group A, 27% in Group C, and 33% in Group C (p=0.739; Tables 3 and 4). No significant difference was observed among groups in terms of diagnostic yield.

4. Tolerability of preparation

All patients completed the preparations without significant adverse effects. Thirty-one patients (69%) in Group B and 24 patients (56%) in Group C had no complaint associated with the preparation. The most common

Table 1. Patient Characteristics and Indications for Capsule Endoscopy

	Group A overnight fast (n=44)	Group B NaP (n=45)	Group C PEG (n=45)	p-value
Age (yr)	53.1±15.7	50.0±17.1	45.7±16.8	0.07
Sex (M/F)	27/17	25/20	33/12	0.20
Indication				0.859
Overt GI bleeding	16	16	19	
Occult GI bleeding	7	7	9	
Chronic abdominal pain	10	10	11	
Chronic diarrhea	4	4	3	
Suspicious Crohn's disease	2	1	2	
Others	5	7	1	

NaP, sodium phosphate; PEG, polyethylene glycol; GI, gastrointestinal.

Table 2. Transit Times and Quality of Image

	Group A overnight fast (n=44)	Group B NaP (n=45)	Group C PEG (n=45)	p-value
GET (min)	34.9±32.3	47.2±61.2	25.2±32.2	0.136
SITT (min)	321.8±116.3	313.5±100.9	337.6±99.3	0.667
ICV passing (No.)	33	33	32	0.924
"Adequate" cleansing number of the small bowel (% of patients)	19 (43%)	33* (77%)	25 (56%)	0.002†

NaP, sodium phosphate; PEG, polyethylene glycol; GET, gastric emptying time; SITT, small intestinal transit time; ICV, ileocecal valve.
*p=0.001, compared with NPO group, p=0.123 compared with PEG group; †p=0.002, comparison among three groups.

Table 3. Capsule Endoscopy Findings in Obscure GI Bleeding

	Group A overnight fast (n=23)	Group B NaP (n=23)	Group C PEG (n=28)	p-value
Positive				0.111
Ulcer	4	7	5	
Erosions	0	2	2	
Angiodysplasias	2	4	4	
Crohn's disease	2	2	1	
Diverticulum	0	1	1	
Tumor/Polyp	1	0	1	
Suspicious				
Erosion	4	2	5	
Submucosal tumor	2	1	0	
Only blood	1	0	0	
Venodilation	1	0	0	
Negative	6	4	9	

GI, gastrointestinal; NaP, sodium phosphate; PEG, polyethylene glycol.

Table 4. Capsule Endoscopy Findings in Non-GI Bleeding

	Group A overnight fast (n=21)	Group B NaP (n=22)	Group C PEG (n=17)	p-value
Positive				0.739
Crohn's disease	1	3	3	
Ulcer	1	2	1	
Submucosal tumor	0	0	1	
Polyposis	0	1	0	
Suspicious				
Nonbleeding angiodysplasia	2	2	1	
Erosions	4	3	2	
Extrinsic compression	0	1	0	
Polyp	1	0	0	
Negative	14	10	9	

GI, gastrointestinal; NaP, sodium phosphate; PEG, polyethylene glycol.

Table 5. Patient Questionnaire on Preparation Tolerability by Group

	Group B NaP	Group C PEG	p-value
How easy to complete?			NS
Easy	31	25	
Slightly difficult	6	10	
Moderately difficult	4	6	
Extremely difficult	4	4	
Unable to finish	0	0	
Side effect			NS
Nausea	12	20	
Vomiting	6	5	
Abdominal pain	2	7	
Bloating	2	4	

NaP, sodium phosphate; PEG, polyethylene glycol; NS, not significant.

adverse effect was nausea in Groups B and C. No patient complained of a complication associated with capsule ingestion. All capsules were retrieved, but the passage of one capsule was delayed due to blockage at the ileum because of a stricture associated with Crohn's disease (Table 5).

DISCUSSION

Many studies have reported that capsule endoscopy is an effective tool for the evaluation of small bowel disease, with investigators using various methods to prepare patients to improve mucosal visualization.[1-4] Generally, although these methods associated with preparation of capsule endoscopy increase the quality of image, bowel preparation for capsule endoscopy has not been standardized.[5-9] The present study is the first prospective randomized multicenter study comparing 12-h overnight fast, NaP,

and PEG, which is the most common purgative agent for capsule endoscopy. Our study showed that bowel preparation with NaP for capsule endoscopy improved the small bowel mucosa visualization, as compared to those of 12-h overnight fast.

Preparation methods involving PEG and NaP were derived from methods used with colonoscopy. However, because capsule endoscopy visualizes the small bowel rather than the colon, colonic purgation methods intended as preparation for colonoscopy may not be suitable. In studies with PEG, various doses (ranging from 500 mL to 4 L) were adapted for use in capsule endoscopy, with contradictory results.[6-8,10-12] Some studies showed that PEG preparation before capsule endoscopy improved visualization of the small intestine, whereas other studies showed no significant difference between PEG treatment and control groups. In the present study, preparation with PEG affected neither the quality of the capsule endoscopy image nor its diagnostic yield compared to 12-h overnight fasting. To the best of our knowledge, the present study is the first to compare NaP and PEG as preparation methods for capsule endoscopy. We observed no difference in image quality between patients prepared with NaP plus 2 L of clear liquid vs those prepared with 2 L of PEG. This is in contrast to previous studies on preparation for colonoscopy demonstrating that superior cleansing is achieved when PEG is administered wholly or in part on the day of the procedure.[13,14] The fact that PEG treatment conferred no additional benefit in the present study likely reflects differences in administration time and the amount of PEG used. In addition, sample size may also be an important factor affecting both the primary and secondary outcomes. Prior to the study, we calculated the required sample sized based on the findings of previous studies. However, because these studies were few in number and also relied upon small sample sizes, our sample size have been insufficient to detect differences between the preparations studied.

Unfortunately, as there is no gold standard for capsule endoscopy recordings, capsule endoscopy is not always diagnostic, and a significant number of false positive and false negative findings occur. Careful consideration must be given to the interpretation of capsule endoscopy findings. Pennazio *et al.*[15] divided the findings of capsule endoscopy into three groups, including positive, suspicious, and negative findings. In the present study, we were not able to confirm all positive findings obtained via capsule endoscopy by means of surgery, enteroscopy, or other studies. Further evaluation for obscure GI bleeding was only done in 4 patients from Group A, 10 from Group B, and 7 from Group C respectively. Final diagnosis based on further evaluation agreed with the findings of capsule endoscopy, and there was no change in the initial diagnosis during follow-up of patients who were diagnosed by capsule endoscopy findings alone. For suspicious findings, further evaluation was done 4 in Group A, 1 in Group B, and 1 Group C which showed the false positive results of capsule endoscopy and the initial diagnosis was changed in these patients. Therefore, for patients who showed suspicious findings, we recommend performing additional studies. No significant difference was observed among groups for the diagnostic yield in non-obscure GI bleeding. We interpreted these results based on the fact that the most common indications were chronic abdominal pain and diarrhea, which were possibly due to functional disease, such as irritable disease, as opposed to organic disease. It is unclear whether the method of preparation influences GET, SITT, or cecal completion rate. Although some investigators have reported that bowel preparations such as PEG increased passage beyond the ileo-cecal valve (ICV),[8,16] we observed no significant difference in passage beyond the ICV according to preparation method.

The present study has some limitations. Our study was multi-center study with multiple investigators. Images of all capsule endoscopies were not reviewed by all investigators; at least two investigators from each hospital reviewed the images from their cases alone. Therefore, our study results may reflect inter-observer differences. The kappa value may have decreased in response to the relatively small sizes at each hospital and the fact that not all investigators reviewed the study design. However, to reduce such inter-observer differences, the authors called a meeting before the start of the study to thoroughly objectify evaluation of images.

Many aspects of preparation for capsule endoscopy is not established. Previous studies on preparation for capsule endoscopy have been extremely heterogeneous in terms of type of preparation, dose, and time of administration. In addition, the evaluation system for bowel cleanliness tends to differ for each study, because methods for assessing the quality of images are chosen arbitrarily. Future comparative studies to determine the optimal preparation method for capsule endoscopy will require an objective, standardized method to evaluate cleanliness. It is our hope that additional studies on preparation methods for capsule endoscopy, ideally examining several preparatory methods and purgative agents (including prokinetics) will be continued, so that we can compare the results with our own. In this study, no significant difference wa observed between the NaP and PEG groups in terms of visualization of the small bowel.

However, preparation with NaP before capsule endoscopy improved mucosal visualization compared to 12-h overnight fasting.

In conclusion, the results of our prospective study suggest that bowel preparation with NaP improves the quality of capsule endoscopy images. Nevertheless, no significant difference in diagnostic yield was observed among groups. Additional, larger scale studies on the effect of various bowel preparation methods on the diagnostic yield of capsule endoscopy are required.

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REFERENCES

1. Costamagna G, Shah SK, Riccioni ME, et al. A prospective trial comparing small bowel radiographs and video capsule endoscopy for suspected small bowel disease. Gastroenterology 2002;123:999-1005.
2. Lewis B, Swain P. Capsule endoscopy in the evaluation of patients with suspected small intestinal bleeding: results of a pilot study. Gastrointest Endosc 2002;56:349-353.
3. Mylonaki M, Fritscher-Ravens A, Swain P. Wireless capsule endoscopy: a comparison with push enteroscopy in patients with gastroscopy and colonoscopy negative gastrointestinal bleeding. Gut 2003;52:1122-1126.
4. Cheon JH, Kim WH. Recent advances of endoscopy in inflammatory bowel diseases. Gut Liver 2007;1:118-125.
5. Albert J, Göbel CM, Lesske J, Lotterer E, Nietsch H, Fleig WE. Simethicone for small bowel preparation for capsule endoscopy: a systematic, single-blinded, controlled study. Gastrointest Endosc 2004;59:487-491.
6. Viazis N, Sgouros S, Papaxoinis K, et al. Bowel preparation increases the diagnostic yield of capsule endoscopy: a prospective, randomized, controlled study. Gastrointest Endosc 2004;60:534-538.
7. van Tuyl SA, den Ouden H, Stolk MF, Kuipers EJ. Optimal preparation for video capsule endoscopy: a prospective, randomized, single-blind study. Endoscopy 2007;39:1037-1040.
8. Dai N, Gubler C, Hengstler P, Meyenberger C, Bauerfeind P. Improved capsule endoscopy after bowel preparation. Gastrointest Endosc 2005;61:28-31.
9. Niv Y, Niv G. Capsule endoscopy: role of bowel preparation in successful visualization. Scand J Gastroenterol 2004;39:1005-1009.
10. Wei W, Ge ZZ, Lu H, Gao YJ, Hu YB, Xiao SD. Purgative bowel cleansing combined with simethicone improves capsule endoscopy imaging. Am J Gastroenterol 2008;103:77-82.
11. Fireman Z, Paz D, Kopelman Y. Capsule endoscopy: improving the transit time and the image view. World J Gastroenterol 2005;11:5863-5866.
12. Ben-Soussan E, Savoye G, Antonietti M, Ramirez S, Ducrotté P, Lerebours E. Is a 2-liter PEG preparation useful before capsule endoscopy? J Clin Gastroenterol 2005;39:381-384.
13. Kastenberg D, Chasen R, Choudhary C, et al. Efficacy and safety of sodium phosphate tablets compared with PEG solution in colon cleansing: two identically designed, randomized, controlled, parallel group, multicenter phase III trials. Gastrointest Endosc 2001;54:705-713.
14. Aronchick CA, Lipshutz WH, Wright SH, Dufrayne F, Bergman G. A novel tableted purgative for colonoscopic preparation: efficacy and safety comparisons with Colyte and Fleet Phospho-Soda. Gastrointest Endosc 2000;52:346-352.
15. Pennazio M, Santucci R, Rondonotti E, et al. Outcome of patients with obscure gastrointestinal bleeding after capsule endoscopy: report of 100 consecutive cases. Gastroenterology 2004;126:643-653.
16. Fireman Z, Kopelman Y, Fish L, Sternberg A, Scapa E, Mahaina E. Effect of oral purgatives on gastric and small bowel transit time in capsule endoscopy. Isr Med Assoc J 2004;6:521-523.