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REVIEW

Combination could be another tool for bowel preparation?

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Abstract

Optimal bowel preparation increases the cecal intubation rate and detection of neoplastic lesions while decreasing the procedural time and procedural-related complications. Although high-volume polyethylene glycol (PEG) solution is the most frequently used preparation for bowel cleansing, patients are often unwilling to take PEG solution due to its large volume, poor palatability, and high incidence of adverse events, such as abdominal bloating and nausea. Other purgatives include osmotic agents (*e.g.*, sodium phosphate, magnesium citrate, and sodium sulfate), stimulant agents (*e.g.*, senna, bisacodyl, and sodium picosulfate), and prokinetic agents (*e.g.*, cisapride, mosapride, and itopride). A combination of PEG with an osmotic, stimulant, or prokinetic agent could effectively reduce the PEG solution volume and increase patients' adherence. Some such solutions have been found in several published studies to not be inferior to PEG alone in terms of bowel cleansing quality. Although combination methods showed similar efficacy and safety, the value of these studies is limited by shortcomings in study design. New effective and well-tolerated combination preparations are required, in addition to rigorous new validated studies.

Key words: Bowel preparation; Colonoscopy; Inadequate bowel cleansing; Combination methods; Intolerance

Core tip: Selecting optimal purgatives is essential for achieving effective bowel preparation. Although polyethylene glycol is the most widely used solution, there are several agents for bowel cleansing including osmotic and stimulant agents. Thus, combination methods of these agents could be an option to improve the cleansing quality and patients' adherence. We reviewed comparison studies between combination and single agent preparations. The biggest benefit of combinations in most studies is to reduce the volume of cleansing solutions, which could improve patients' compliance for bowel preparation. However, new effective and well-tolerated combination preparations are required for more effective bowel preparations.

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INTRODUCTION

Adequate bowel preparation is one of the most important prerequisites for effective and safe colonoscopy. Suboptimal bowel preparation leads to a lower cecal intubation rate, prolonged procedural time, reduced adenoma detection rate, and increased risk of procedural-related complications[1-3]. To achieve excellent or good bowel preparation, effective purgatives are essential. Several bowel preparation agents for colonoscopy are available, including polyethylene glycol (PEG)-based solutions that contain a nonabsorbable polymer; osmotic agents such as sodium phosphate (NaP), magnesium citrate, and sodium sulfate; and stimulant agents such as senna, bisacodyl, and sodium picosulfate. Finally, several prokinetic agents, intended to improve bowel motility, may be used, such as cisapride, mosapride, and itopride. Comparison studies have investigated several agents to identify the best colonic cleansing agents in terms of effectiveness, compliance, and safety[4,5]. However, none have shown consistent results regarding a clean colon, which is vital because up to 20%-25% of all colonoscopies may have an inadequate bowel preparation[6].

Although the use of a single bowel preparation agent is efficient and comfortable for patients, the compliance and adverse events of purgatives vary. Therefore, several studies have evaluated various combinations of two agents to improve compliance and reduce adverse events. Such combinations include the addition of laxatives to PEG solution or a combination of two types of laxatives, such as sodium picosulfate/magnesium citrate (SP/MC)[1,7]. In our present investigation, we reviewed only those studies that compared combination and single agent preparations. Here, the combination methods have been classified as the combination of PEG with osmotic, stimulant, or prokinetic agents and as the combination of osmotic and stimulant agents.

SEARCH STRATEGY

We conducted a bibliographic search of the PubMed (MEDLINE) database from January 1, 1994 to April 30, 2015 using the following keywords: "bowel preparation", "bowel cleansing", "polyethylene glycol", "sodium phosphate", "sodium picosulfate", "magnesium citrate", "bisacodyl", and "senna". The search specifically included English-language medical journals, with the exception of one Korean study[8]. All papers identified by the electronic database search were reviewed and additional references were identified from the references listed in each paper.

COMBINATION METHODS FOR BOWEL CLEANSING

Combination of PEG and osmotic agents

PEG and NaP are the two most widely studied solutions for bowel preparation. Despite a high volume and unpleasant taste, PEG has a good cleansing effect. Currently, aqueous NaP, a low-volume hyperosmotic agent, is not recommended due to safety issues, with acute phosphate nephropathy reported following the use of NaP. Thus, patients with impaired renal function, dehydration, hypercalcemia, or hypertension treated with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers should not use this solution[9-11]. The Food and Drug Administration in the United States recommend that NaP was used as a laxative at the lower dose. In response to the disadvantages of these two agents, Bae *et al*[12] reported that 2 L PEG with a single dose of 45 mL NaP provided good cleansing quality and compliance, which was similar to 4 L PEG. Although the serum levels of sodium and phosphorus increased and the serum levels of calcium and potassium decreased after bowel preparation using 2 L PEG and NaP, there were no serious adverse events. Another study in Korea showed that 2 L PEG plus 90 mL NaP resulted in better bowel preparation quality than 4 L PEG, although the frequency of hyperphosphatemia was higher[8]. A low dose PEG plus NaP was not inferior for bowel cleansing and patients showed better compliance than those with a full-dose single agent. In addition, the electrolyte imbalance resulting from elevated sodium and phosphate was acceptable.

Sequential intake of PEG and sodium sulfate is another PEG and osmotic agent combination option. Sodium sulfate does not cause renal tubular injury in animal models[13]. A randomized, controlled trial examining bowel preparation quality showed that 473 mL oral sulfate solution plus 2 L sulfate-free PEG was not inferior to 2 L PEG solution containing ascorbic acid or 10 mg bisacodyl plus 2 L sulfate-free PEG[14]. In that study, the combination method of PEG and sodium sulfate given in a split dose had a bowel preparation success rate of 93.5%. Although vomiting was more frequent in the PEG plus sodium sulfate group, serious adverse events did not occur.

Studies have also investigated the use of combination regimens of magnesium citrate and PEG for bowel preparation before colonoscopy. A study published in 1997 showed that oral magnesium citrate taken 2 h prior to PEG reduced the volume of PEG required for bowel cleansing, decreased endoscopic time, enhanced the preparation quality, and was better tolerated by patients[15]. A recent prospective randomized study was performed in patients who

ingested 250 mL magnesium citrate on the day before the procedure followed by 2 L PEG on the day of the procedure and in those who received 4 L PEG in a 1-d or split-dose (2 L + 2 L) regimen[16]. Colonic cleansing (excellent or good according to the Aronchick scale) was more satisfactory in the combination group than in the 1-d 4 L PEG group. Moreover, patients preferred the combination preparation than either 4 L PEG preparations.

A new combination protocol for bowel preparation using 2 L of magnesuim sulphate mineral water and 2 L of low-volume PEG with electrolyte was studied in 13914 European patients[17]. Excellent or good bowel cleansing was achieved in 13378 (96.23%) patients and it proved that combination method was effective in large population.

Taken together, the results of the above studies show that the addition of osmotic agents to PEG solution could reduce the PEG volume, thereby improving patients' bowel preparation compliance and bowel cleansing quality.

Combination of PEG and stimulant agents

Bisacodyl has long been used as a laxative, despite the risk of ischemic colitis at high doses. However, the efficacy of a regimen of 15 mg bisacodyl at bedtime and 2 L PEG in the morning was similar to that of a 4 L PEG regimen in terms of bowel cleansing, cecal intubation time, and adenoma detection rates and did not increase the incidence of ischemic colitis[18]. A modified regimen of 15 mg bisacodyl plus 2 L split-dose PEG (1 L given the day before and on the day of colonoscopy) resulted in a 90.6% good or satisfactory bowel preparation rate, compared with 77% in a 4 L PEG group (P = 0.003)[19]. In addition, adherence to the regimen instructions was higher in the bisacodyl plus PEG group than in the 4 L PEG alone group (97.1% *vs* 87.3%, P = 0.003).

One meta-analysis examined the use of low-volume PEG and bisacodyl for bowel preparation before colonoscopy[20]. This meta-analysis included six randomized controlled studies and found no statistically significant differences in the rates of satisfactory and excellent bowel preparations between 2 L PEG with bisacodyl 10-20 mg and 4 L PEG. However, patients who received 2 L PEG with bisacodyl had a significantly less nausea, vomiting, and bloating than those who received 4 L PEG. A newly developed electrolyte-free PEG (MiraLAX; Merck, Whitehouse Station, NJ, United States) combined with a carbohydrate-electrolyte solution (Gatorade; PepsiCo, Chicago, IL, United States), which have the advantages of low volume and improved palatability, was inferior to regular 4 L PEG in a meta-analysis of various randomized controlled trials[21]. Accordingly, the ability of the MiraLAX-Gatorade plus bisacodyl regimen to improve bowel preparation has been studied[22]. The combination of MiraLAX-Gatorade and 20 mg bisacodyl produced similar rates of excellent/good bowel cleansing compared with 4 L PEG. Therefore, low-volume PEG with bisacodyl might be a reasonable regimen if it is proven in additional trials to not increase the risk of ischemic colitis.

Sodium picosulfate, another stimulant agent, has been combined with low-volume PEG solution for bowel preparation. A combination trial of sodium picosulfate and PEG was compared with NaP tablet in a prospective randomized crossover design in Japan[23]. The colon cleansing effectiveness of a combination of 2 L PEG with 150 mL sodium picosulfate was not significantly different from that of NaP. However, the patients' overall satisfactory impressions of the preparations were worse in the combination group than in the NaP group (60.5% *vs* 77.9%, P = 0.001) because the frequency of nausea was higher in the PEG and sodium picosulfate group.

High-dose senna (24 tablets, each containing 12 mg of concentrated extract of sennosides), an anthraquinone derivative that promotes the accumulation of water and electrolytes in the colonic lumen and stimulates intestinal motility, has been shown to be an effective colon cleanser with good patients' compliance and overall tolerance of colon cleansing compared with PEG[24]. However, about 30% of patients reported abdominal pain and cramps after taking senna. For that reason, a combination method of a half-dose of senna (12 tablets of 12 mg) and 2 L PEG was compared with high-dose senna (24 tablets)[25]. The combination group showed a similar colonic cleansing quality as the high-dose senna group (90.1% *vs* 88.3%, P = 0.62). On the other hand, the rates of moderate-to-severe abdominal pain related to bowel preparations were 6% in the combination group and 15.2% in the high-dose senna group (P = 0.009). The half-dose combination method of senna and PEG could be a reliable alternative method to the standard high-dose senna regimen.

Combination of PEG and prokinetics

Prokinetics stimulate colonic peristalsis and may be used as an adjuvant agent for bowel preparation. One prokinetic, cisapride, has been used in an attempt to improve colonic cleansing. A combined regimen of cisapride and PEG improved colonoscopy visualization and alleviated symptoms such as vomiting[26,27]. However, cisapride has been withdrawn from the market because of serious cardiac adverse events. The efficacy of other prokinetics, including mosapride and itopride, for bowel preparation before colonoscopy has been studied. Mishima *et al*[28] showed that patients who received 5 mg mosapride citrate or 50 mg itopride hydrochloride 30 min before administration of PEG solution had fewer uncomfortable abdominal symptoms than those who received placebo. However, the addition of mosapride or itopride did not improve bowel cleansing quality. A randomized controlled study

Table 1 Summary of the combination methods reviewed in this study

Combination agents	Comparable agents	Study methods	Preparation scales	Results	Weakness of combinations
PEG + osmotic agents					
PEG 2 L + NaP 45 mL (n = 130)[12]	PEG 4 L (n = 141)	RCT, single center in South Korea	Ottawa	The bowel preparation quality and rate of adverse events were not different between the two groups	Serum sodium and phosphorus were increased and serum calcium and potassium were decreased in the combination group
PEG 2 L + NaP 90 mL (n = 277)[8]	PEG 4 L (n = 249)	RCT, single center in South Korea	Aronchick	The overall and segmental bowel preparation quality of the combination group was better	Occurrence of hyperphosphatemia was greater in the combination group.
PEG 2 L + oral sulfate 473 mL (n = 186)[14]	PEG 2 L with ascorbic acid (n = 185)	RCT, 24 centers in the United States	Aronchick	Successful preparation rates were identical in the two groups	Vomiting was more frequent in the combination group
PEG 2 L + magnesium citrate 250 mL (n = 73)[16]	PEG 4 L on the day before (n = 79) and in split-dose (n = 80)	RCT, single center in South Korea	Aronchick	The bowel preparation of the combination group was more satisfactory than that of the day before group. Patient satisfaction was highest in the combination group	
PEG + stimulant agents					
PEG 2 L + bisacodyl 15 mg (n = 78)[18]	PEG 4 L (n = 76)	RCT, 2 centers in Italy	Ottawa	The bowel cleansing quality and adenoma detection rate were equivalent in the two groups. Mucosal visibility was superior in the combination group	
PEG 2 L in split dose + bisacodyl 15 mg (n = 138)[19]	PEG 4 L (n = 126)	RCT, single center in Italy	Harefield	The good or satisfactory preparation rate and adherence to the drinking instructions were higher in the combination group	
PEG 2 L + bisacodyl 10-20 mg (n = 761, meta-analysis from six studies)[20]	PEG 4 L (n = 779)	RCT, 6 studies in the United States, Norway, Canada, and Australia	Aronchick and Ottawa	The preparation quality was similar in the two groups. The incidence of adverse events such as nausea, vomiting, and bloating was lower in the combination group	
MiraLAX-Gatorade + bisacodyl 20 mg (n = 383)[22]	PEG 4 L (n = 395)	Retrospective database analysis in the United States	Aronchick	The rates of excellent or good bowel cleansing were similar in the two groups	
PEG 2 L + sodium picosulfate 150 mL (n = 41)[23]	NaP tablets (total 50 g, n = 50)	Crossover design trial, single center in Japan	Likert	The effectiveness of colonic cleansing was not different between the two groups	Patients' overall impressions were worse and the frequency of nausea was higher in the combination group
PEG 2 L + senna 12 tablets (n = 141)[25]	Senna 24 tablets (n = 145)	RCT, single center in Italy	Aronchick	The preparation quality was similar in the two groups. The incidence of abdominal pain was lower in the combination group	
PEG + prokinetic agents					
PEG 2 L + mosapride 5 mg (n = 103) or itopride 50 mg (n = 103)[28]	PEG 2 L plus placebo (n = 99)	RCT, single center in Japan	Aronchick	There were fewer uncomfortable abdominal symptoms in the PEG with prokinetic group	The addition of prokinetics did not improve the bowel cleansing effect
PEG 2 L + mosapride 15 mg (n = 124)[29]	PEG 2 L plus placebo (n = 125)	RCT, single center in Japan	Aronchick	The optimal cleansing rate of left-sided colon was higher in the PEG with mosapride group. Patients who had previous colonoscopy experience felt that the bowel preparation was easier after mosapride addition	
Osmotic + stimulant agents					
SP/MC 2 sachets[1] (n = 140)[33]	PEG 4 L (n = 145)	RCT, 3 centers in Italy	Boston	The bowel cleansing quality was similar in the two groups. Tolerability and palatability was better in the SP/MC group	
SP/MC 2 sachets[1] (n = 296)[34]	PEG 2 L with bisacodyl 10 mg (n = 302)	RCT, 12 centers in the United States	Aronchick and Ottawa	The quality of bowel cleansing was similar in the two groups. Patients' acceptability and tolerability on a questionnaire were greater in the SP/MC group	

SP/MC 2 sachets[1] (n = 304)[35]	PEG 2 L with bisacodyl 10 mg (n = 297)	RCT, 10 centers in the United States	Aronchick and Ottawa	The overall colon cleansing was superior and the tolerability was better with the SP/MC regimen	
SP/MC 2 sachets[1] + PEG 2L (n = 282) or PEG 1 L (n = 303)[37]	SP/MC 3 sachets[1] (n = 307)	RCT, single center in South Korea	Aronchick and Ottawa	The cleaning efficacy of the right colon of the SP/MC plus PEG 2 L group was better than that of the SP/MC group	Nausea and bloating were more frequent in the SP/MC plus PEG 2 L group than in the SP/MC group
Magnesium citrate 2 sachets[2] and senna (n = 160)[40]	Magnesium citrate 2 sachets[2] (n = 182)	RCT, single center in the United Kingdom	Likert	Adequate visualization of colonic mucosa was better in the combination group	Incidence of abdominal cramps was higher in the combination group

[1]One packet contains 10 mg sodium picosulfate, 3.5 g magnesium oxide and 12 g citric acid; [2]One sachet contains 11.6 g magnesium carbonate and 17.8 g anhydrous citric acid. PEG: Polyethylene glycol; NaP: Sodium phosphate; SP/MC: Sodium picosulfate plus magnesium citrate; RCT: Randomized controlled trial.

showed that a 2 L PEG plus 15 mg of mosapride citrate regimen had significantly higher optimal bowel cleansing in left-sided colon than 2 L PEG plus placebo[29]. In addition, in the subgroup that had previous colonoscopy experience, the patients receiving PEG plus mosapride reported easier bowel cleansing than before.

Combination of osmotic and stimulant agents

SP/MC in powder form is a mixture of sodium picosulfate 0.01 g, magnesium oxide 3.5 g, and citric acid 12.0 g[30]. When the powder is dissolved in water, the magnesium oxide and citric acid form magnesium citrate. This low-volume bowel-cleansing agent has dual osmotic and stimulant activity and has been used in many countries, including the United States. Two studies showed that SP/MC had adequate efficacy for bowel cleansing and similar patient satisfaction compared with PEG[31,32]. Moreover, two sachets of SP/MC showed better tolerability and palatability than PEG with or without bisacodyl in a few studies, as well as efficient cleansing quality[33-35]. On the other hand, one study showed that SP/MC provided a lower quality of bowel cleansing than PEG containing ascorbic acid[36]. Thus, one study compared all three regimens: three packets of SP/MC, two packets of SP/MC with 1 L PEG, and two packets of SP/MC with 2 L PEG[37]. The combination group of two packets of SP/MC and 2 L PEG showed better cleansing efficacy in right-sided colon than the other two groups. However, the combination of SP/MC with 2 L PEG was the least preferred because of nausea and abdominal bloating. Hyponatremia accompanied by seizure and mental change has been reported after using SP/MC[38,39]. Electrolyte imbalance is also a potential problem with SP/MC, especially in older patients.

Senna has also been combined with magnesium citrate for bowel preparation before colonoscopy. One study showed that patients who received magnesium citrate plus senna granules were more likely to have adequate visualization of the colonic mucosa than those who took magnesium citrate alone[40].

CONCLUSION

Although the use of a split-dose regimen of a 4 L PEG solution is strongly recommended for elective colonoscopy, the rate of adequate bowel cleansing is only approximately 85%[41]. The remaining 15% may have insufficient bowel cleansing for colonoscopy, which results in missed precancerous lesions and increased costs related to early repeated procedures. Thus, for patients who presented with an inadequate preparation at a previous colonoscopy, combination methods for bowel preparation should be considered, even though none have consistently shown improved efficacy and safety because of small sample sizes and the use of different measurements of bowel cleansing quality. Table 1 demonstrates the main results and weakness of combination methods reviewed in this study. Nevertheless, the biggest benefit of combinations in most studies is the reduced cleansing solution volume. Accordingly, patients tend to experience less adverse events such as abdominal bloating or nausea, which could improve the compliance of patients for bowel preparation.

To consistently confirm the efficacy of combination regimens, a newer study with new agents such as prucalopride should be performed. Furthermore, simplified instructions for patients are essential for any successful combination regimen.

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