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The Evolution of Bowel Preparation and New Developments

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Bowel preparation is essential for successful colonoscopy examination, and the most important factor is the bowel preparation agent used. However, selection of a bowel preparation agent invariably involves compromise. Originally, bowel preparation was performed for radiologic and surgical purposes, when the process involved dietary limitations, cathartics, and enemas, which had many side effects. Development of polyethylene glycol (PEG) solution led to substantive advancement of bowel preparation; however, despite its effectiveness and safety, the large volume involved, and its salty taste and unpleasant odor reduce compliance. Accordingly, modified PEG solutions requiring consumption of lower volumes and sulfate-free solutions were developed. Aqueous sodium phosphate is more effective and better tolerated than PEG solutions; however, fatal complications have occurred due to water and electrolyte shifts. Therefore, aqueous sodium phosphate was withdrawn by the US Food and Drug Administration, and currently, only sodium phosphate tablets remain available. In addition, oral sulfate solution and sodium picosulfate/magnesium citrate are also available, and various studies have reported on adjunctive preparations, such as hyperosmolar or stimulant laxatives, antiemetics, and prokinetics, which are now in various stages of development. (**Korean J Gastroenterol 2014;63:268-275**)

Key Words: Bowel preparation; Colonoscopy; Polyethylene glycols; Sodium phosphate; Picosulfate sodium

INTRODUCTION

Colonoscopy is considered the optimal and standard method for evaluation of the colon. For successful colonoscopy, a skilled colonoscopist, patient cooperation, and adequate bowel preparation are necessary. Poor bowel preparation reduces the quality of colonoscopy, increases complication risk, reduces polyp detection rates, increases pain by extending insertion times, and increases medical costs. Thus, adequate bowel preparation is essential for successful colonoscopy and this largely depends on the type of agent used for bowel preparation. An ideal bowel preparation agent

would be easily taken, inexpensive, have an excellent cleansing effect, and would not cause fluid or electrolyte shifts. Here, we review the development of a bowel preparation agent from a historical perspective and describe agents currently being developed (Table 1).

DEVELOPMENTS IN BOWEL PREPARATION

Colonoscopy preparations evolved from radiologic and surgical preparations.¹ Early mechanical preparation methods involved dietary limitation, administration of cathartics, and enemas during the preceding 72 hours. After admin-

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Table 1. The US Food and Drug Administration (FDA)-approved Bowel Preparation Agents for Colonoscopy

Bowel preparation agents	Characteristics	Advantages	Disadvantages	Cautions
4-Liter PEG	Not approved by the FDA for split dosing	Safe and effective	High-volume, may cause nausea, abdominal fullness, and bloating salty taste and unpleasant smell	Contraindicated in patients with ileus, gastrointestinal obstruction, gastric retention, bowel perforation, toxic colitis or toxic megacolon, hypersensitivity to components of it
4-Liter sulfate-free PEG	Not approved by the FDA for split dosing	Safe and effective Less salty and more tolerable (palatable)	High-volume may cause nausea, abdominal fullness, and bloating	Same as 4-liter PEG
2-Liter PEG with bisacodyl	Not approved by the FDA for split dosing	Low-volume Effective and tolerable	May cause discomfort, abdominal fullness, cramping, nausea, and vomiting	Contraindicated in patients with gastrointestinal obstruction, bowel perforation, toxic colitis and toxic megacolon, gastric retention, ileus Fluid and electrolyte disturbances can lead to serious adverse events such as cardiac arrhythmias, seizures and renal impairment
2-Liter PEG with ascorbic acid	Approved by the FDA for split dosing	Low-volume Ascorbic acid acts as a flavoring	May cause malaise, nausea, vomiting, abdominal pain, dyspepsia	Same as 2-liter PEG with bisacodyl
Sodium phosphate tablets	Avoid in patient with renal disease, congestive heart failure, or concomitant medications that can affect renal function	Low-volume Effective and tolerable	May cause bloating, nausea, abdominal pain, and vomiting	Contraindicated in patients with acute phosphate nephropathy, gastrointestinal obstruction, gastric bypass or stapling surgery, bowel perforation, toxic colitis and toxic megacolon, allergy to components of it Fluid and electrolyte disturbances can lead to cardiac arrhythmias, seizure, and renal impairment
Oral sulfate solution	Approved by the FDA for split dosing	Safe and effective	May cause discomfort, abdominal distension, abdominal pain, nausea, and vomiting May cause temporary elevation of uric acid	Same as 2-liter PEG with bisacodyl
Sodium picosulfate/magnesium citrate	Approved by the FDA for split dosing	Low-volume Effective and tolerable (good taste, less nauseating)	May cause headache, nausea, proctalgia	Contraindicated in patients with allergic to components of it, gastric retention, ulcers, renal impairment, bowel perforation, congestive heart failure, inflammatory bowel disease, hypermagnesemia, gastrointestinal obstruction, ileus, toxic colitis and toxic megacolon

PEG, polyethylene glycol.

istration of clear liquid or low-residue foods, preparation was completed using cathartics and enemas. However, these preparation processes required a significant amount of time, were uncomfortable for patients, sometimes caused nutrition defects, and disturbed fluids and electrolytes. In the 1970s, approximately 10 liters of oral lavage solution was used, which caused severe fluid and electrolyte disturbances and discomfort, thus, its use was restricted in patients with cardiac, renal, or hepatic impairment. Mannitol was used for preparation, which does not cause hypersorption or osmotic

diarrhea. However, cases of intestinal gas explosion attributed to the presence of inflammable gases, chiefly hydrogen and methane produced by colonic bacteria, were reported during polypectomy or surgery, therefore, the use of mannitol was discontinued.^{2,3}

In the 1980s, Davis et al.⁴ developed an osmotically balanced, polyethylene glycol-electrolyte lavage solution (PEG solution) that did not cause loss of water or electrolyte or suffer from the risk of gas explosion. The cleansing effectiveness and safety of PEG solution were confirmed by many stud-

ies,⁵⁻⁷ and it continues to be the preparation method of choice. However, the large volume required, as well as its salty taste, and unpleasant smell reduce compliance, thus, sulfate-free, low-volume PEG solutions were developed. Sodium phosphate (NaP) solution osmotic agent developed in the 1990s⁸, which had the advantage of a low administered volume versus PEG solution, however, its disadvantages included risks of hyperphosphatemia, hypocalcemia, and hypokalemia in patients with renal failure, congestive heart failure, advanced liver disease, or an aphthous ulcer-like mucosal lesion. Around the same time, another bowel preparation method, pulsed rectal irrigation combined with magnesium citrate was developed.⁹ This method involves ingestion of 10 ounces of magnesium citrate the evening before the procedure and a 30-minute infusion of short pulses of warm tap water through a rectal tube immediately before colonoscopy.¹⁰ This regimen showed no significant differences in terms of quality of colonic cleansing versus PEG solution⁹; however, it required more time and skilled nursing. Nevertheless, it remains a good alternative when a full-volume PEG solution cannot be tolerated.

TYPES OF BOWEL PREPARATION AGENTS

Bowel preparation agents can be classified according to three types.

- PEG solutions, oral gut lavage solutions with high-volumes.
- osmotic agents, such as sodium phosphate, magnesium citrate, lactulose, and mannitol, which draw plasma water into the bowel lumen.
- stimulants, such as castor oil, senna, sodium picosulfate, and bisacodyl, which stimulate the colonic peristalsis.

1. Polyethylene glycol solutions

1) Overview

Since the original development of an osmotically balanced PEG solution, better solutions have been developed. PEG solutions are more effective and better tolerated than regimens of diet combined with cathartic agents, high-volume balanced electrolyte solutions, or mannitol-based solutions,^{10,11} and the original 4-liter dosing regimen rapidly became the standard bowel preparation method due its characteristics of being rapid, safe, and effective. The primary mechanism

responsible for minimizing water and electrolyte shifts involves the inhibition of sodium ion absorption by sulfate ions. Chloride ions needed for absorption of sodium ions are replaced by sulfate ions, resulting in reduced absorption of sodium ions, and little water is exchanged across the colonic membrane, which reduces electrolyte disturbance.

PEG solutions do not require a long period of dietary restriction, and are safe for use in children, elderly persons, and in patients with renal, hepatic, or cardiac problems.¹²⁻¹⁵ In addition, because they do not cause macroscopic or histologic mucosal alterations, they can also be used safely in patients with inflammatory bowel disease. However, PEG solutions are contraindicated in patients with gastric outlet obstruction, high-grade small-bowel obstruction, significant colonic obstruction, perforation, diverticulitis, and hemodynamic instability, and in patients who are allergic to polyethylene glycol. In addition, PEG solutions have been classified by the US Food and Drug Administration (FDA) as pregnancy category C, and have been associated with Mallory-Weiss tear, toxic colitis, pulmonary aspiration, hypothermia, cardiac arrhythmias, pancreatitis, and inappropriate anti-diuretic hormone secretion.^{11,16,17}

Disadvantages of PEG solutions include the large volume required, a salty taste and unpleasant smell, due to the presence of sodium sulfate, and these reduce patient compliance. In practice, approximately 5% to 15% of patients do not complete the preparation.^{10,18,19} Furthermore, the additional use of enemas does not offer any improvement in the efficacy of PEG solutions, but considerably increases patient discomfort.²⁰ Divided regimens are superior and better tolerated than the standard 4-liter single dose regimen.²¹ In one study, ingestion of PEG solution less than 5 hours before the procedure resulted in better preparation than when administered more than 19 hours beforehand.²² According to a recent study, the method and/or timing of administration are more important determinants of quality of preparation than dietary restriction,²³ and in another study, walking exercise during bowel preparation was found to improve colonoscopic bowel cleansing without significantly increasing patient discomfort.²⁴ Addition of 10 mg of oral bisacodyl to PEG was not found to result in significant improvement of colonic cleansing or overall patient tolerance when used as an adjunct with full-volume PEG.²⁵ However, in another study, in which efficacy and patient tolerance to 4 liters of PEG were

compared with that for 2 liters of PEG preceded by a stimulant laxative bisacodyl (20 mg), the 2-liter regimen was found to be more acceptable than the 4-liter regimen by patients and to be equally effective in terms of cleansing the colon.²⁶⁻²⁸ In addition, 2 liters of PEG plus magnesium (296 mL) or bisacodyl (20 mg) was shown to provide better preparation quality and patient satisfaction and to reduce preparation time than the 4-liter PEG only regimen.^{26,29,30} In a study on the use of senna, its addition was found to be effective, safe, and well tolerated, like bisacodyl³¹⁻³⁴; however, abdominal pain was reported by some patients administered high-dose senna (24 mg).³⁵ On the other hand, the addition of prokinetic agents to PEG did not result in improvement of bowel preparation, but reduced nausea and abdominal distress.³⁶⁻³⁸

2) Sulfate-free PEG

In an effort to overcome the objectionable smell and taste of standard PEG solutions, sulfate-free and flavored solutions have been developed.³⁹ These are less salty, more palatable, and comparable to standard solutions in terms of effective colonic cleansing and overall patient tolerance.⁴⁰ Nevertheless, the volume of sulfate-free PEG required was not reduced, and thus, several attempts have been made to reduce the amount of standard PEG solution required. In one study, equally effective bowel preparation and significantly fewer clinical symptoms were observed for 20 mg oral bisacodyl in 2 liters of sulfate-free PEG than the traditional 4 liters of PEG solutions.⁴¹

3) Low-volume PEG solutions

Low-volume PEG solutions were developed for reduction of symptoms associated with high-volume PEG, such as bloating and cramping. Low-volume (2 liters) PEG solutions containing bisacodyl or magnesium citrates were compared to full-volume PEG solution (4 liters), and demonstrated satisfactory efficacy. In addition, 2 liters of PEG solution containing ascorbic acid, which acts as a flavoring and cathartic, was found to be as effective as full-volume PEG solution,⁴² and has been approved by the FDA as a bowel preparation agent for split dosing. Combining over-the-counter polyethylene glycol 3350 laxative powder and Gatorade (PepsiCo Inc., Purchase, NY, USA) or Crystal Light (Kraft Foods Inc., Northfield, IL, USA) (or another clear liquid of choice) has also been shown to improve the taste and tolerability of the preparation; however, this 2-liter regimen has not been approved by the FDA.^{11,43}

2. Sodium phosphate solutions

1) Overview

Aqueous sodium phosphate is a low-volume hyperosmotic solution containing 48 g (400 mmol) of monobasic sodium phosphate and 18 g (130 mmol) of dibasic sodium phosphate per 100 mL.⁴⁴ Sodium phosphate, an osmotic agent, draws water from plasma into the bowel lumen, and causes peristalsis and bowel cleansing due to water retention. Thus, the use of sodium phosphate can cause large fluid and electrolyte shifts. In one meta-analysis, sodium phosphate was found to be more effective for bowel cleansing and better tolerated than PEG solution,⁴⁵ whereas another found that sodium phosphate solutions were superior to PEG solutions and were better tolerated, but not significantly more effective than PEG.⁴⁶ The main reasons for the improved tolerability were a better flavor and a smaller sodium phosphate solution volume.^{47,48} In addition, because of their effectiveness and lower cost, colonoscopists are more likely to consider sodium phosphate solutions more acceptable.^{10,49} However, it should be added that patients with renal failure, liver disease with ascites, or severe heart disease were excluded from most of these studies. Patients with compromised renal function, dehydration, hypercalcemia, hypertension on angiotensin-converting enzyme (ACE) inhibitors, or angiotensin receptor blockers (ARBs) have experienced phosphate nephropathy after taking oral sodium phosphate solutions.⁵⁰ These effects appear to be age- and dose-related.⁵¹ In addition, sodium phosphate solutions have been associated with hypocalcemia, hypokalemia, increased plasma osmolality, hyponatremia, and, conversely, hypernatremia.^{38,52,53} Rare adverse events, such as nephrocalcinosis with acute renal failure have also been reported, particularly in patients taking ACE inhibitors, ARBs, or diuretics.^{53,54} Renal failure due to hyperphosphatemia (acute phosphate nephropathy) has recently been reported even in patients with normal kidney function.^{11,55}

This complication occasionally causes permanent damage to renal function and some patients require dialysis for a long period of time. Furthermore, it can occur several months after colonoscopy examination, thus, continuous observation is required. In fact, in the United States, aqueous sodium phosphate solutions received a black box warning from the FDA for acute phosphate nephrotoxicity on

December 11, 2008, and are now only available by prescription in tablet form for bowel cleansing.

Sodium phosphate also causes temporary colonic mucosal changes, and the aphthous ulcerations produced may mimic inflammatory bowel disease,⁵⁶ limiting the use of sodium phosphate in patients suspected or with a diagnosis of inflammatory bowel disease. Although contraindicated in children under five years of age, several studies have assessed sodium phosphate in pediatric populations and demonstrated efficacies similar to those of PEG.^{13,57} In addition, the efficacy of sodium phosphate in elderly persons is similar to that in younger adults and comparable to that of PEG.^{58,59} Addition of cisapride to sodium phosphate did not result in improvement of the quality of bowel preparation,³⁸ and the addition of carbohydrate-electrolyte oral rehydration solution protected against intravascular volume contraction during preparation and was well-tolerated, and improved bowel cleansing.^{60,61} However, carbohydrate-electrolyte solution can cause hyperglycemia in diabetes patients and hyperkalemia in patients with renal insufficiency, thus, such patients require close attention. In a study conducted for determination of preference for a sodium phosphate tablet preparation in patients who had previously taken a PEG solution for previous colonoscopy, sodium phosphate tablets were preferred.⁶² In another study, liquid sodium phosphate was found to be better tolerated and more effective in colon cleansing than a 40-tablet sodium phosphate preparation.⁴⁸ Conduct of further comparative studies on sodium phosphate tablet and liquid preparations is needed.

2) New sodium phosphate agents

Two large, identically designed, randomized, controlled, parallel group, multicenter phase III trials that compared sodium phosphate tablets and PEG solution for colon cleansing showed equivalent results for colon cleansing, fewer gastrointestinal side effects, and better patient toleration for the tablets.⁴⁷ Subsequently, sodium phosphate tablets were approved by the FDA in 2000. Each 2 g sodium phosphate tablet contains 1,500 mg of active ingredients (monobasic and dibasic sodium phosphate) and 460 mg of microcrystalline cellulose as a tablet binder.¹⁰ However, microcrystalline cellulose is insoluble in the gastrointestinal tract, obscures mucosal visualization, is time-consuming to remove during colonoscopy. A modified formulation with half the microcrystalline cellulose content and a lower total dose of sodium

phosphate was developed, and use of this formulation showed good results in efficacy and tolerability studies.^{63,64}

3. Other bowel preparation agents

1) Oral sulfate solution

Oral sulfate solution, an osmotic laxative, has been approved by the FDA for split dosing with 2 liters of PEG solution and ascorbic acid. It was developed based on animal safety studies, in which its safety was compared with that of sodium phosphate solution,⁶⁵ and a subsequent study on its effectiveness and safety in humans.⁶⁶ In another study, oral sulfate solution was found to be more effective than sulfate-free PEG (administered as a single dose) with similar tolerability.⁶⁷

2) Sodium picosulfate/magnesium citrate

In 2012, sodium picosulfate and magnesium citrate were approved by the FDA for split dosing for colonoscopy in adults. This regimen was compared with PEG solution and sulfate-free PEG solution, and found to be equally or more effective in colon cleansing and to show better tolerability.^{68,69} In one study, sodium picosulfate and magnesium citrate were compared with sodium phosphate and shown to be as effective, but to have better taste and patient tolerability,⁷⁰ however, in another study, this regimen was found to be less effective than oral sodium phosphate in terms of bowel cleansing.⁷¹ Several later studies confirmed that this regimen provides effective bowel preparation.^{72,73}

CONCLUSIONS

Adequate bowel preparation is essential for successful colonoscopy examination, and this largely depends on the type of agent used for bowel preparation. Nevertheless, poor bowel preparation is frequent, resulting in reduced quality of colonoscopy, including reduction of polyp detection rates and increase of complication risk, pain, and medical costs. Thus, selection of the most appropriate agent for each patient is important, and administration methods such as split dosing, patient education including dietary modifications, and walking exercise are also essential for successful examination.

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