Adjuncts to colonic cleansing before colonoscopy

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Abstract

Pre-procedural cleansing of the bowel can maximize the effectiveness and efficiency of colonoscopy. Yet, efficacy of the current gold standard colonic preparation method – high-volume oral administration of purgative agents 12-24 h prior to the procedure – is limited by several factors, such as patient compliance (due to poor palatability and inconvenience of the dosing regimen) and risks of complications (due to drug interactions or intolerance). Attempts to resolve these limitations have included providing adjunctive agents and methods to promote the colonic cleansing ability of the principal purgative agent, with the aim of lessening unpleasant side effects (such as bloating) and reducing the large ingested volume requirement. Several promising adjunctive agents are bisacodyl, magnesium citrate, senna, simethicone, metoclopramide, and prokinetics, and each are being investigated for their potential. This review provides an up to date summary of the reported investigations into the potencies and weaknesses of the key adjuncts currently being applied in clinic as supplements to the traditional bowel preparation agents. While the comparative analysis of these adjuncts showed that no single agent or method has yet achieved the goal of completely overcoming the limitations of the current gold standard preparation method, they at least provide endoscopists with an array of alternatives to help improve the suboptimal efficacy of the main cleansing solutions when used alone. To aid in this clinical endeavor, a subjective grade was assigned to each adjunct to indicate its practical value. In addition, the systematic review of the currently available agents and methods provides insight into the features of each that may be overcome or exploited to create novel drugs and strategies that may become adopted as effective bowel cleansing adjuncts or alternatives.

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Core tip: Fair bowel cleansing is a prerequisite for unobstructed visualization in colonoscopy. Since the gold standard self-managed preparation procedure and purgative agent-related complications can limit thorough cleansing, several adjunctive agents and methods have been developed. Clinical experience with these adjuncts have led to some being advocated by endoscopists as useful accessory drugs and to others being criticized for causing further adverse effects or providing insufficient additional benefit. In this article, we reviewed several of the agents that are currently used as colonic cleansing adjuncts and provide a subjective evaluation of their practical value based on their evidentiary strengths and drawbacks.

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INTRODUCTION

A number of purgative agents are currently in clinical use for bowel preparation prior to colonoscopy. While none has provided optimal safety and efficacy profiles, each represents unique strengths and weaknesses (in terms of efficiency, ingested volume, taste, and time required for preparation) that may help to improve the chances of achieving more thorough bowel cleansing. For instance, polyethylene glycol (PEG) is generally considered an adequate colonic cleansing agent, but its salty taste is highly imitable and cited by patients as a key reason for not completing the dosing regimen; the resultant inadequate bowel preparation has led to these patients frequently requiring repeat colonoscopy, with the extent of unremoved fecal obstruction sometimes completely inhibiting visualization[1].

To overcome the limitations of the main colonic cleansing agents, several adjunct purgative agents and methods have been developed. While some adjuncts have potential for use as independent colonic cleansing agents, they have typically been applied in clinical practice as additive means to complement the main agent; although, some reports exist in the literature of their use as a surrogate under narrow indications. In this article, we review the evidentiary information for several of the agents and methods that are currently used as colonic cleansing adjuncts and discuss the potential of each to facilitate or substitute the cleansing function of the main regimen.

COMMONLY USED ADJUNCTS OF COLONIC CLEANSING AGENTS

Bisacodyl

Bisacodyl is an unabsorbable diphenylmethane derivative with stimulant laxative properties. Adjunct administration of bisacodyl is routinely carried out to facilitate bowel preparation by high-volume balanced purgative solutions, such as PEG. However, systematic evaluations of bisacodyl’s efficacy when used with full-volume PEG have yielded inconsistent results. One study showed that a bisacodyl regimen of 20 mg over a 2 d period shortened the duration of the main gut irrigation procedure and produced no side-effects[2]. However, a study of the effective benefit of bisacodyl to the PEG-based regimen found that it provided no significant improvement in cleansing quality as compared with a PEG-only regimen[3]. Another study suggested that the benefit of providing bisacodyl adjunct to the main regimens based on isosmotic solutions (such as PEG) was a reduction in the volume of purgative agent that needed to be ingested to achieve effective bowel cleansing[4]. Similarly, when 15 mg of bisacodyl was administered with a PEG-based regimen not only was a lower volume of the main solution required (down to 2 L from the 4 L required for the PEG-only regimen) but the patients showed a better compliance rate and reported experiencing less nausea during the preparative period[5].

Comparative analysis of the adjunctive benefits of bisacodyl to another common adjunctive agent - magnesium citrate (MC, discussed below) - confirmed the positive feature of bisacodyl substantially reducing the PEG volume necessary for complete cleaning but indicated that patients preferred MC, likely due to its lower rate of side-effects[6]. Indeed, bisacodyl administration carries a risk of inducing the life-threatening condition of ischemic colitis[7,8], and this potential complication, though rare, is a serious consideration for cautious application. Further research is needed to determine the precise indications for bisacodyl use that will correspond with maximal efficacy and safety profiles of this adjunctive agent.

MC and MC-adjunctive regimens (oral sodium picosulfate/MC)

MC is a salt compound that functions as an osmotic laxative and is administered as a hyperosmolar saline solution. The solution draws water into the colonic lumen, thereby increasing intraluminal fecal volume and stimulating gut motility. Clinical application of MC as an adjunctive agent to the main isosmotic purgative solution regimens has been reported to provide effective cleansing with substantially reduced volumes. Similar to the volume-reducing effects of bisacodyl, MC adjunctive application increased cleansing efficacy of the main PEG solution so that only 2 L of the main agent was required (vs 4 L) and significantly enhanced patient tolerance of the cleansing regimen[9]. As cited above, MC was also indicated by patients as preferable to bisacodyl, likely because of fewer unwanted side-effects[10].

The osmotic laxative action of MC is enhanced by co-administration of a stimulant laxative agent. Sodium picosulfate/MC combination preparations (marketed under the trade names Picolax, Picoprep, Prepopik, Picolax, Citrafleet, and Picolight) are well-established in clinical practice in the United Kingdom and Korea, and have recently been approved for use in the United States[11]. Several studies have compared the efficacies of sodium picosulfate/MC preparations with conventional isosmotic cleansing agents, such as PEG, as well as another common saline laxative (sodium phosphate). In one comparative analysis of single-regimens of sodium phosphate, PEG, and sodium picosulfate/MC, the latter two agents were found to have similar bowel cleansing performance (as indicated by the Ottawa bowel preparation assessment tool)[12]. Yet, another comparative analysis of single-regimen sodium picosulfate/MC (Picolax) and PEG showed the two to be comparable in preparation efficacy but indicated that the former was superior in promoting patient compliance since it produced significantly less nausea/vomiting and posed less difficulty for patient consumption[13]. The lower level of nausea/vomiting was confirmed by another comparative analysis of a generic sodium picosulfate/MC preparation and PEG, but in this study former was shown to produce superior bowel cleansing than the 3 L of PEG[14]. Still
another study revealed a higher rate of patient preference for the sodium picosulfate/MC preparation when repetitive administrations were required among subjects who experienced similar clinical side effects to the different regimens evaluated[14].

In an attempt to gain a better understanding of the efficacy and safety profiles of sodium picosulfate/MC preparations as an independent cleansing regimen, a meta-analysis was performed by Tan and Tjandra[18]. The sodium picosulfate/MC preparations were found to be superior to PEG-based regimens, as they produced the statistically significant benefit of fewer adverse events and a comparable level of bowel cleansing. Indeed, the European Society of Gastrointestinal Endoscopy (ESGE) guidelines for bowel preparation for endoscopy published in 2013 cited the comparable levels of bowel cleansing achieved between the different regimens, as reported in the collective literature[19].

Despite the promising findings related to the bowel cleansing efficacy of MC, this osmotic laxative has some drawbacks. MC should be cautiously applied to patients with renal insufficiency or failure, who risk detrimental accumulation of magnesium due to inefficient clearance by the impaired kidney[17]. Moreover, concurrent medications or medical conditions that can influence renal and intestinal function may also lead to elevated magnesium levels in serum, a condition known as hypermagnesemia that is accompanied fluid and electrolyte imbalance. Hypermagnesemia itself is a risk factor for cardiovascular and neuromuscular complications[18], and particular caution should be taken in elderly patients who are already at risk for these types of disorders and have worse prognoses related to them. Indeed, age-related increases in blood levels of sodium, potassium, and urea have been shown following MC administration[18]; it is theorized that these potentially detrimental responses may stem from age-related decrement of renal function and reduced intestinal peristalsis, as well as concurrent medications[20].

**Senna**

Extracts from the Senna genus of plants have well-established stimulant laxative properties. The collective investigations into the various known senna glycosides have revealed that upon ingestion these derivatives are activated by intestinal flora and directly interact with the gut mucosa to stimulate bowel movement and to inhibit electrolyte and water absorption. Senna has proven useful as a bowel preparative agent when applied at high doses, both alone and as an adjunct. However, the side-effect of considerable abdominal pain has limited its use, and in the meantime balanced solution-type cleansing agents have largely substituted its role as a colonoscopy preparative agent[21,22]. As an adjunct, senna is commonly applied with PEG, and the collective clinical experience has led to its being generally characterized as an effective agent to intensify the main agent’s cleansing ability.

Adjunct senna has been shown to decrease the volume of PEG required to achieve effective bowel cleansing and to be associated with higher rate of patient tolerance than full-dose (4 L) PEG[23]. Another study also reported improved compliance of subjects with senna adjuvant and low-volume PEG, but demonstrated it was less effective at bowel cleansing than full-dose PEG alone[24]. It is important to note that senna is not widely used in the United States and has not gained approval from the nation’s federal drug administration for its use as a colonic cleansing agent[25]; as such, fewer studies on its efficacy and safety profiles are available, especially when compared to the extensive research findings that have been published for bisacodyl. Nonetheless, the collective findings on senna suggest that it is an adequate adjunct colonic cleansing agent in that it lessens the volume of PEG solution but may not be an effective bowel cleansing agent in isolation due to its side effect of abdominal pain. Comparative analyses with other adjuncts should be carried out in order to gain a better understanding of its efficacy and safety.

**Simethicone**

As an anti-gas and anti-flatulent agent, simethicone has been suggested (and applied in clinic) as an accessory agent of colonic preparation using the standard bowel preparation regimens[26]. When combined with the traditional PEG preparatory solution, simethicone significantly decreases the formation of foam and patients have less complaints of gas-related side-effects[26,27]. Adjunctive administration also has been shown to eliminate bubbles and improve the cleansing quality of the sodium phosphate preparation[27]. However, a meta-analysis of the overall studies of simethicone adjunctive efficacy failed to demonstrate a superior colonic cleansing ability[28]. There is still no consensus in the field as to whether simethicone should be recommended for adjuvant use; for example, the American Society for Gastrointestinal Endoscopy recommended its use and the ESGE recommended against its routine application as part of the standard pre-procedural preparation[28]. Undoubtedly, further investigations are needed to confirm the usefulness of simethicone as an adjunct agent for colonoscopy preparation.

**Metoclopramide and other prokinetics**

Metoclopramide is a well-established dopamine antagonist, which sensitizes tissues to the action of acetylcholine. This agent exerts an appreciable influence on peristalsis of the upper gastrointestinal regions but has no appreciable effect on the colon[29]. Therefore, the clinical utility of adjunctive metoclopramide is limited to improvement of nausea or bloating side-effects related to the main colonic cleansing agent, but it is not itself a colonic preparation per se[30]. Some investigators have expressed skepticism concerning the action of metoclopramide, reporting no apparent influence of this adjunct on the abdominal symptoms[31,32]. In general, however, metoclopramide use is limited by its associated risk of
causing extrapyramidal symptoms.

New prokinetic drugs have been developed and introduced to the market over the past decades and systematic investigations into their usefulness as adjuncts for bowel preparation are beginning to accumulate in the literature. A study of mosapride, a selective 5-hydroxytryptamine-4 receptor agonist, administered at a dose of 15 mg immediately prior to ingestion of the 2 L of PEG solution provided superior colonic cleansing than the same PEG regimen administered with placebo[33]. Itopride, another prokinetic, was also reported to decrease uncomfortable abdominal symptoms when used as an adjunct to the standard PEG or MC colonic preparations[34].

Others

Gatorade sports drink has been combined with PEG 3350 powder (MiraLAX®) to provide better tolerability of the PEG solution by decreasing the volume required. Gatorade is not an isosmotic solution and represents an alternative to the main PEG solution that is required for bowel cleansing, thereby enhancing patients’ compliance with the preparation procedure. However, the exact efficacy and safety profiles of these agents remain to be definitely established and cautious selection of adjuncts by endoscopists with ample experience remains necessary.

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