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Recent Advances in Optimal Bowel Preparation

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Abstract High-quality bowel preparation is essential for colonoscopy to detect both subtle findings as well as large masses, particularly in the proximal colon. Unfortunately, approximately one quarter of all colonoscopies performed in the United States are hampered by inadequate bowel preparation, which has been shown to impair the detection of both small and large polyps. Based on several prospective, randomized studies comparing day-prior bowel preparation with split-dose preparation, split dosing is emerging as a best practice. In addition to improving the quality of the bowel preparation, split dosing is also acceptable to patients, and recent guidelines for preoperative fasting are compatible with split dosing, as clear liquids can be safely consumed up until 2 hours prior to the procedure. The other decision endoscopists must make is which bowel purgative product to select. Currently available options include polyethylene glycol solutions, which are formulated with or without electrolytes; sodium phosphate tablets; and oral sulfate solutions. Selection of the most effective purgative for bowel preparation should be guided by an analysis of both safety and efficacy data.

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Target Audience: This activity has been designed to meet the educational needs of practicing clinicians who wish to review and update their knowledge of recent advances in optimal bowel preparation for patients who are undergoing colonoscopy.

Statement of Need/Program Overview: Colonoscopy remains the gold standard for detection of polyps and precancerous lesions that may lead to colorectal cancer, yet less than half of individuals 50 years of age or older undergo screening colonoscopy. Mounting evidence suggests that fear of bowel preparation is a key reason many patients avoid colonoscopy. In addition, results from randomized clinical trials and clinical practice suggest that suboptimal bowel preparation occurs with surprising frequency, in as many as 25% of all cases. Therefore, addressing the safety, tolerability, and effective administration of colon-cleansing regimens may enhance patient compliance, lead to a higher-quality bowel preparation, and improve polyp detection.

Educational Objectives: After completing this activity, the participant should be better able to:

1. Describe the American Society of Anesthesiologists' guidelines regarding PM/AM split dosing.
2. Discuss patient acceptance in optimal bowel preparation.
3. Recognize the importance of adequate bowel preparation, including its role in detection of flat lesions.
4. Discuss the overall safety of bowel preparations.
5. Identify future research directions for emerging agents in optimal bowel preparation.

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Introduction

Philip S. Schoenfeld, MD, MSEd, MSc (Epi)

Colorectal cancer (CRC) is the third most common cancer among both men and women in the United States, as well as the third leading cause of cancer-related mortality in this population.[1] Routine screening of adults beginning at 50 years of age can significantly reduce the number of deaths caused by CRC; 2004 data indicated that early detection is associated with a 5-year survival rate above 90%, although this rate may have since changed.[2] Colonoscopy is the gold standard for detection of early signs of CRC, such as polyps and precancerous lesions, but this procedure is avoided by many patients because they dislike or even fear the required bowel preparation.[3,4] In addition to patients' reluctance to undergo the necessary colon cleansing regimen, a poor-quality bowel preparation can have negative consequences for the endoscopist, including incomplete visualization of the colon, missed pathology, and procedural difficulties. Reports from both randomized clinical trials and clinical practice suggest that suboptimal bowel preparation occurs in as many as 25% of all cases and may contribute to missed detection of lesions, particularly smaller lesions (polyps ≤9 mm).[5,6]

Clearly, suboptimal bowel preparation prior to colonoscopy can have a significant impact on both the quality of the colonoscopy performance and the endoscopist's ability to identify adenomas during the colonoscopy. As was shown in the EPAGE study, suboptimal preparation prior to colonoscopy significantly decreased the identification of polyps.[5] In this study, patients undergoing colonoscopy were stratified according to the completeness of the bowel preparation, with preparation being defined as either high-quality (completely clean or clear liquid), intermediate-quality (liquid and stool that could be aspirated), or low-quality (liquid and stool that could not be completely aspirated). As is shown in Figure 1, patients with a high-quality preparation had a polyp identification rate of 30%, compared to a rate of 24% among patients who had a low-quality preparation (P=.007). An additional finding from the EPAGE study concerned the presence of polyps greater than 10 mm, which can be assumed to be adenomas or large adenomas and which are more likely to develop into colon cancer. Polyps greater than 10 mm in size were found in 6% of patients with a high-quality preparation, compared to 4% of patients with a low-quality preparation (P=.016); thus, suboptimal bowel preparation can reduce the identification rate of large adenomas by a significant amount. In addition, poorer-quality bowel preparation negatively affects withdrawal time—as the endoscopist may have to spend extra time removing liquid stool—as well as being associated with increased time required to reach the cecum and possibly failure to reach the cecum because of retained stool.

In a University of Michigan study involving 486 patients at average risk for colon cancer who had normal screening colonoscopies, the recommendation that patients return for a repeat colonoscopy in less than 10 years was found to correlate with suboptimal bowel preparation.[7] This study found that patients were much more likely to be told to return for a repeat colonoscopy in 10 years, as is recommended by the American College of Gastroenterology (ACG) guidelines, if they had excellent bowel preparation, while they were more likely to be told to come back in 3–5 years if they had only a fair preparation. Specifically, the proportion of patients told to return for a repeat colonoscopy in 10 years was 90% for patients with excellent bowel preparation versus 26% for those with fair preparation (P<.001). Thus, fully 31% of all patients with normal screening colonoscopies did not receive a recommendation for a 10-year interval between colonoscopies as advocated by the ACG guidelines.

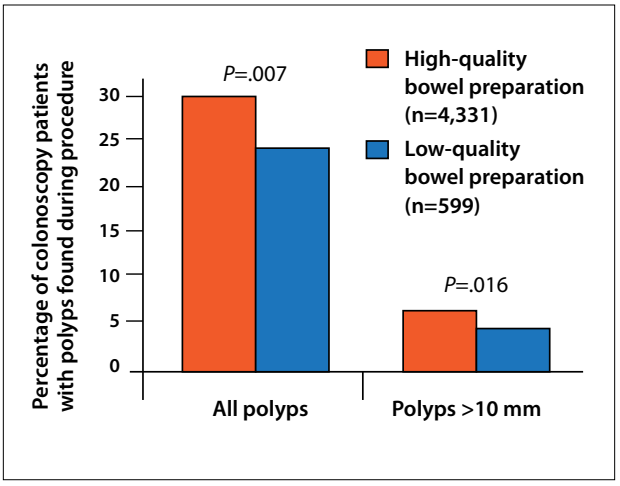

Figure 1. Suboptimal bowel preparation significantly decreases identification of polyps during colonoscopy.

High-quality bowel preparation=completely clean preparation or clear liquid.

Low-quality bowel preparation=liquid and stool that cannot be completely aspirated.

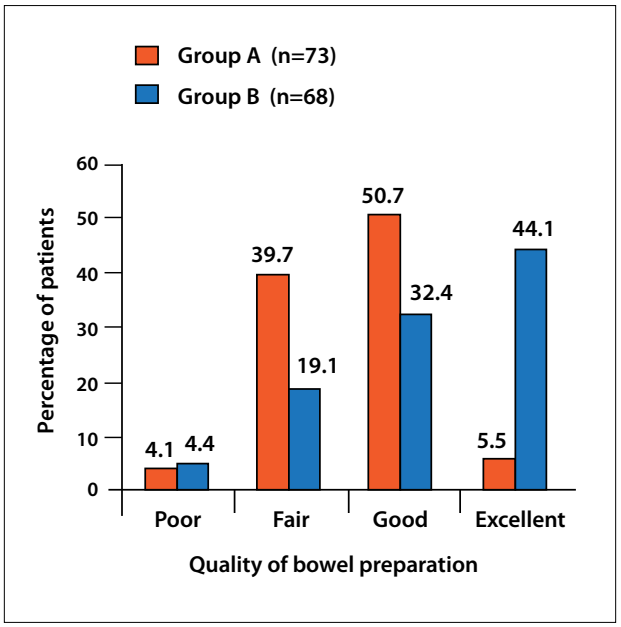

Figure 2. Split dosing of bowel purgative provides a higher percentage of satisfactory results than evening-only dosing.

Group A=4 L of PEG-ELS on the night before the procedure.

Group B=2 L of PEG-ELS on the evening before and 2 L on the morning of the procedure.

PEG-ELS=polyethylene glycol electrolyte solution.

Data from Aoun et al.[9]

Split Dosing Improves the Quality of Bowel Preparation

According to the 2008 ACG guidelines on colorectal cancer screening, 1 of the strongest recommendations for improving bowel preparation is that all patients undergoing screening or surveillance colonoscopy should receive split-dose bowel preparation, in which at least half of the bowel purgative is consumed on the day of the colonoscopy.[8] The importance of such a regimen is that purgative taken within 6 hours of colonoscopy can better clean the ascending colon and cecum, areas which otherwise might acquire a coating of chyme if 12 hours have elapsed since consumption of the bowel purgative.

In a randomized controlled trial by Aoun and colleagues that examined the effect of split dosing on bowel preparation prior to colonoscopy, patients (N=141) consumed either 4 L of polyethylene glycol electrolyte solution (PEG-ELS) on the night before the procedure (group A), or 2 L of PEG-ELS the night before the procedure and another 2 L on the morning of the procedure (group B). According to endoscopists blinded to which preparation each patient had received, patients who consumed the split-dose preparation had a 44% likelihood of having an excellent bowel preparation, compared to only 6% among patients who had consumed all 4 L of PEG-ELS the night before the procedure (Figure 2).[8]

Another important finding is that split dosing reduced the likelihood of achieving only a fair preparation—which resulted in patients in the University of Michigan study being told to come back for a repeat test in fewer than 10 years even though they were not at particular risk for disease. In the Aoun study, fair preparations were reported in only 19% of patients who received split dosing, compared to 40% of patients who consumed all the bowel purgative solution the day before.[9] Based on these data, as well as data from many other randomized controlled trials, splitting the patient's bowel preparation seems to be the single intervention most likely to produce excellent bowel cleansing at the time of colonoscopy.

Financial Disclosure

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PM/AM Split Dosing: A Review of Recent Studies

David M. Kastenberg, MD

Despite the demonstrated advantages of a split-dosing regimen for bowel preparation, such a substantial change in long-standing practice is likely to face stiff opposition from physicians who are accustomed to having patients prepare for colonoscopy using traditional, day-prior dosing. However, the greater efficacy of split dosing, which has been demonstrated in a number of clinical studies, could provide sufficient incentive for doctors to alter traditional practice. Table 1 summarizes relevant findings in 6 recent trials. Overall, if a study is comparing same-day dosing to day-prior dosing, day-of-colonoscopy dosing will always come out on top, regardless of the structure of the study or which agents are being compared.

Studies of PM/AM Split Dosing

The Aoun study (n=141) compared PEG-ELS consumed the night before the procedure to split dosing.[1] It is important to mention that the split-dose group was able to eat a regular diet the entire day prior to the procedure, until about 6:00 PM, while the day-prior dose group was restricted to a clear liquid diet. Despite having fewer dietary restrictions, the split-dose group achieved a greater number of adequate bowel preparations: 77% versus 56% (*P*=.011).

The Parra-Blanco study (n=177) compared 2 different preparations: PEG-ELS and sodium phosphate.[2] The PEG-ELS arm compared night-prior dosing to day-of-colonoscopy dosing; for the latter regimen, patients consumed their bowel purgative on the morning of the procedure. In the sodium phosphate arm, patients received either split-dose sodium phosphate administered over 2 days or sodium phosphate administered on the day prior to the procedure. In both arms, superior adequacy of bowel preparation was achieved when the bowel purgative was dosed on the day of the procedure rather than the day prior (79% vs 27% for PEG-ELS; 80% vs 7% for sodium phosphate; *P*<.01 for both comparisons).

In an interesting study by Chiu and colleagues (n=121), all enrolled patients had had polyps detected during a screening colonoscopy (for which PEG-ELS was administered the night prior to the procedure); these patients were then referred for therapeutic colonoscopy.[3] The patients were randomly divided into 2 groups: those who received PEG-ELS on the day of the therapeutic colonoscopy (n=60) and those who received the bowel purgative the night before (n=59).

Table 1. Summary of 6 Studies Comparing Day-Prior and Split-Dosing Bowel Preparation Regimens

Study	Purgative	Split dose or day-of-colonoscopy dosing (adequate preparation)	Day-prior dosing (adequate preparation)	*P*-value
Aoun E, et al[1]	PEG-ELS	(split) 77%	56%	.011
Parra-Blanco A, et al[2]	PEG-ELS Sodium phosphate	(day-of) 79% (split) 80%	27% 7%	<.01
Chiu H-M, et al[3]	PEG-ELS	(day-of) 93%	72%	.003
Ell C, et al[4]	PEG-ELS PEG-Asc	(split) 95% (split) 89%		NS
Bitoun A, et al[5]	Sodium phosphate PEG-Asc		64% 73%	NS
Di Palma JA, et al[6]	OSS PEG-Asc	(split) 97% (split) 96%		NS
Di Palma JA, et al[6]	OSS PEG-Asc		82% 80%	NS

NS=not significant; OSS=oral sulfate solution; PEG-Asc=polyethylene glycol electrolyte solution plus ascorbic acid; PEG-ELS=polyethylene glycol electrolyte solution.

This study found that bowel preparation for the therapeutic colonoscopy was better among patients who received their bowel preparation on the day of the colonoscopy rather than the night before (*P*=.003), and more lesions were detected in patients who consumed their bowel preparation on the day of the therapeutic colonoscopy (*P*=.028).

The Ell study and the Bitoun study led to US Food and Drug Administration (FDA) approval of PEG-ELS plus sodium ascorbate and ascorbic acid (PEG-Asc).[4,5] The Ell study was undertaken in Germany and compared split-dose administration of 4 L of PEG-ELS (2 L PM and 2 L AM of procedure; n=155) to 2 L of PEG-Asc solution split so that 1 L was taken in late evening and 1 L was taken in the morning before the colonoscopy (n=153). In this study, both regimens showed similar efficacy, and both had good colon cleansing rates. The Bitoun study (n=352), which was conducted in France, compared PEG-Asc and sodium phosphate solution for bowel preparation prior to elective colonoscopy.[5] Both agents in this study were dosed the day prior to the procedure, and adequacy rates were far below those achieved in the Ell study (73% for PEG-Asc and 64% for sodium phosphate).[4,5]

The Di Palma study (n=364) compared 2 study preparations—960 mL of oral sulfate solution (OSS) and PEG-Asc—using both day-prior and split-dose regimens.[6] In the split-dosing arm of the study, adequate colon cleansing rates were high and comparable between the 2 products (97% for OSS vs 96% for PEG-Asc). Similarly, comparable rates of cleansing were observed when both agents were dosed the day prior to the procedure, but adequacy rates were far lower than with split dosing (82% for OSS vs 80% for PEG-Asc).

Finally, the Abdul-Baki study examined the use of tegaserod as an adjunct agent to PEG-ELS for elective colonoscopy in 382 patients.[7] This placebo-controlled, double-blind study featured 4-arm randomization to compare tegaserod to placebo, each with either day-prior or split-dose PEG-ELS administration. Although tegaserod did not make a significant difference in either arm of the study, the cleansing rates were far superior with split dosing compared to day-prior dosing. Although this study was not designed to compare cleansing rates between day-prior dosing and split dosing, the researchers noted that split dosing resulted in "better colon cleansing, adherence, and tolerance."

Efficacy and Safety Considerations

While better bowel preparation is an important goal for many reasons, a key factor is that better cleansing allows for improved detection of adenomas. In a prospective, observational, multicenter trial conducted at 21 centers in 11 European countries (n=5,832), Froehlich and coworkers found that the detection of polyps depended on cleansing quality.[8] In this study, detection of any adenomas and detection of adenomas greater than 1 cm was significantly better in the adequately prepared group. Similarly, the Parra-Blanco study (n=177) found superior detection of flat lesions in adequately cleansed patients.[2] Finally, an analysis by Harewood and colleagues examined data from the Clinical Outcomes Research Initiative's National Endoscopic Database for the period from January 1, 2000 to December 31, 2001 (n=93,004) and found that small polyps (≤9 mm) were detected significantly more often when bowel preparation was adequate.[9]

While this improvement in adenoma detection certainly supports the adoption of split dosing, safety concerns about split dosing must also be addressed. One concern about split dosing that has been discussed by both anesthesiologists and gastroenterologists is that split dosing could result in patients having a large volume in their stomach before the procedure, which may lead to complications such as aspiration. In 1 study that addresses this concern, patients undergoing general anesthesia were divided into 2 groups: a control group that was instructed not to consume solids or liquids for 12 hours and a study group that was permitted to take clear liquids up until 2 hours prior to the procedure.[10] Patients were then intubated, a nasogastric tube was placed, the stomach was aspirated, and the volume and pH of the stomach contents were recorded. An analysis of residual gastric volume found no significant difference between the control group and the study group (19 mL vs 21 mL, respectively; *P*=.58). Additionally, an interesting finding of this study was that the pH was slightly higher in the study group, which would actually be preferable in the rare case when aspiration does occur.

In a second study, researchers tried to assess the risk of aspiration following split-dose bowel preparation by evaluating 2 groups: patients who were scheduled for upper endoscopy and those who were coming for both upper endoscopy and colonoscopy.[11] Among patients undergoing colonoscopy, the researchers looked at 2 different populations: patients who had consumed their bowel preparation the night before (n=47) and those who had received a split-dose preparation (n=254). During the endoscopy, stomach contents were aspirated to measure volume. The mean volumes of stomach contents were not significantly different among patients whose bowel preparation had taken place the night before the procedure versus those who had received a split-dose preparation (20.2 mL vs 19.7 mL, respectively). While patients who had upper endoscopy alone had significantly less volume recovered from their stomachs (mean volume=14.6 mL), the difference is probably clinically irrelevant.

These studies and others support guidelines for preoperative fasting that recommend a minimum fasting period

for clear liquids of 2 hours for most patients.[12] While these guidelines are not hard-and-fast rules, they are appropriate based on the data, and following them can help clinicians address various safety concerns, such as dehydration. If physicians tell patients that they must fast for 12 hours prior to a procedure, patients will be at greater risk for dehydration, which is a potentially serious complication facing patients taking a colon purgative. In addition, a 12-hour or greater interval between bowel preparation and procedure prevents patients from taking their bowel preparation in the most effective way. Thus, guidelines allowing patients to consume clear liquids up until 2 hours before their procedure are not only appropriate and proper for gastroenterology, they also can lead to more effective and safer colonoscopy.

Acceptability of Split Dosing

Split dosing is not only effective, it is also well tolerated; indeed, there is no evidence that tolerance decreases with split dosing compared to day-prior dosing. Direct comparisons documented in clinical studies have found that split dosing is associated with less bloating, no change in patients' willingness to undergo the same type of bowel preparation a second time, no difference in adverse events, and no increase in patients' need to stop on the way to the endoscopy suite due to bowel movements.[1,2,7,13] In addition, patients may be more satisfied with split dosing, possibly because it allows them to reduce the required volume of fluid that must be consumed at 1 sitting, which is frequently a main factor in patient acceptance; in general, a 1-L preparation is better than a 2-L preparation, which is certainly better than a 4-L preparation. Finally, among patients who were interviewed about their willingness to try split dosing (n=300), 85% said they were willing to get up in the middle of the night to take the morning dose if it meant the doctor would get a better view of the colon; in a subset of patients interviewed just prior to colonoscopy (n=107), 78% had actually complied with this instruction.[14]

Given the aforementioned benefits of split dosing, the next challenge is to address barriers to its acceptance. The 4 key steps to this process are convincing doctors that split dosing is more effective for achieving a clean colon; convincing them that split dosing is important for the performance of a quality colonoscopy, as it improves adenoma detection; convincing doctors that patient safety is not compromised and, in fact, is likely enhanced by split dosing; and finally, convincing them that split dosing is at least as well tolerated as day-prior dosing. Once doctors are convinced of these points, I believe they will present the benefits to patients, who will inevitably accept day-of-colonoscopy dosing.

Finally, clinicians should note that split dosing or dosing on the day of the procedure is not necessarily an inflexible regimen. For example, patients who are not among the clinician's first procedures of the day may be scheduled to come in at 11 AM, in which case they only have to get up at 7 AM. Similarly, patients who are having their colonoscopy in the afternoon can undergo morning-only dosing, which allows them to enjoy better sleep the night before and less interference with the workday prior to their procedure.[15]

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Efficacy and Safety of Bowel Preparations

Lawrence B. Cohen, MD

The importance of a high-quality bowel preparation is demonstrated in Figure 3. In this endophotograph, we see a large superficial spreading polyp in the proximal colon. The ability to identify important, albeit subtle, findings in the colon is highly dependent upon the quality of bowel cleansing. A high-quality colonoscopy is impossible without a high-quality bowel preparation.

This conclusion was reconfirmed by a recent study from Columbia University.[1] This retrospective analysis of more than 12,000 colonoscopies found that the bowel preparation in 24% of colonoscopies was considered by the examiner to be inadequate (a fair or poor rating using a nonvalidated bowel preparation scale). This figure is consistent with the results of prior studies that report an inadequate bowel preparation in roughly 1 quarter of all examinations. The researchers analyzed the rate of missed lesions in patients with an inadequate bowel preparation. This was done by examining the number of lesions detected during a repeat colonoscopy performed within 1–3 years of the index examination. The adenoma miss rate overall was 42%, including 27% that were advanced adenomas. These findings demonstrate that a suboptimal bowel preparation leads to a significant rate of missed lesions, both large and small.

A variety of purgatives are available for precolonoscopy bowel cleansing. This discussion will focus primarily on PEG-ELS bowel preparations; that is, preparations containing polyethylene glycol 3350 with electrolytes (PEG-ELS). A PEG preparation without electrolytes is commercially available (MiraLAX, Schering-Plough) and will be discussed in a subsequent section.

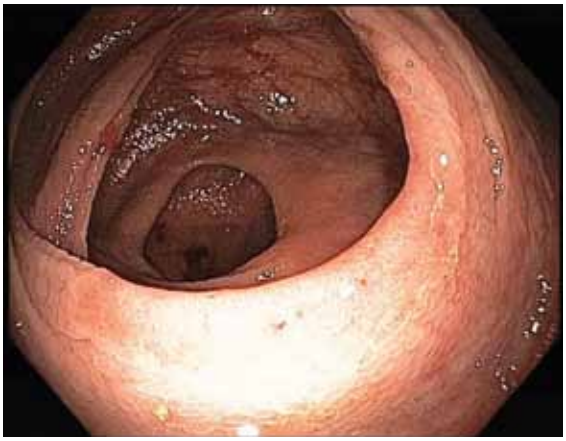

Figure 3. Endophotograph of a large, flat polyp in the proximal colon.

Maximizing the Quality of Bowel Preparation

When considering the use of a PEG-ELS–based preparation, the first decision is whether to use a 4-L or a 2-L preparation. Eight published studies are available comparing the efficacy and tolerability of 4-L versus 2-L PEG formulation. Of these 8 studies, 6 demonstrated that 2-L PEG was as effective as 4-L PEG.[2] Considering that patient tolerability is improved with a 2-L preparation, an argument can be made for using the 2-L PEG preparation for the majority of patients undergoing a colonoscopic examination.

There are two 2-L PEG preparations commercially available. One consists of PEG-ELS plus bisacodyl tablets (HalfLytely & Bisacodyl Tablet Bowel Prep Kit, Braintree) while the other combines PEG-ELS with ascorbic acid and sodium sulfate (PEG-Asc; MoviPrep, Salix). In a prospective, blinded, head-to-head study, patients receiving PEG-Asc were nearly twice as likely to have an excellent-quality bowel preparation as patients receiving PEG plus bisacodyl tablets (69.2% vs 38.2%; P=.01).[3] Further, 92% of patients receiving PEG-Asc had a bowel preparation rated good or excellent. Additionally, the proportion of patients having 1 or more adenomas detected on colonoscopy was nearly twice that in the PEG-Asc arm compared with those receiving PEG plus bisacodyl (39% vs 20%; P=.04). These findings demonstrate that 2-L PEG formulations are not equally effective.

Safety and Tolerability of PEG Formulations

PEG solutions are well tolerated by most patients, although there is interindividual variation. For example, some patients report no side effects after consuming 2-L PEG, while others experience troublesome nausea and/or vomiting. I am unaware of any predictors for determining in advance which patients will have difficulty tolerating 2-L PEG. Regarding the safety of PEG formulations, these products are generally very safe. Adverse events have been reported with PEG, however, including hypona-

tremia (usually occurring in patients who consume large quantities of electrolyte-free solution), hypernatremia, hypokalemia, hypomagnesemia, and pulmonary aspiration. Rarely, patients may experience an allergic reaction, Mallory-Weiss tear, or pancreatitis.

Personally, the 2-L PEG-ELS bowel preparation is my default bowel preparation in practice. That notwithstanding, patients with a history of chronic constipation, a failed previous attempt at bowel preparation, or chronic use of narcotics receive a more vigorous bowel preparation. In such cases, I recommend that they begin preparation 2 days prior to colonoscopy. They will consume 10 oz (1 bottle) of magnesium citrate 2 days prior to colonoscopy and PEG-Asc the day prior to examination.

Oral Sodium Phosphate

In December 2008, the FDA issued a news release recommending that over-the-counter formulations of sodium phosphate solution not be used for bowel preparation.[4] In addition, they also requested that a boxed warning be added to the product label of sodium phosphate tablets (OsmoPrep, Salix).[5] Concern regarding sodium phosphate is due to the risk of acute phosphate nephropathy, a condition in which phosphate injures the renal tubules and leads to chronic kidney disease. Risk factors for this complication include older age; hypovolemia or reduced intravascular volume; baseline renal insufficiency; bowel obstruction; active colitis; and concurrent use of diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and possibly nonsteroidal anti-inflammatory drugs.[5]

Regarding the efficacy of sodium phosphate tablets, a study comparing sodium phosphate tablet to 2-L PEG plus bisacodyl tablet found that the proportion of patients with an excellent bowel preparation was significantly greater in patients receiving sodium phosphate than those receiving PEG (64.4% vs 38.8%; *P*<.0001; Table 2).[6]

The phosphate tablet preparation is clearly an effective purgative for colonoscopy bowel preparation. Certain precautions are necessary, however, when using this product. My recommendation is to restrict its use to patients less than 60 years of age who are otherwise healthy, without significant comorbidities, and have no risk factors for developing nephrocalcinosis (see above). Further, patients receiving sodium phosphate tablets should be adequately hydrated before, during, and after colonoscopy and the 2 doses of sodium phosphate tablet must be separated by a minimum of 10–12 hours.

Oral Sulfate Solution

Oral sulfate solution (OSS) was approved as a bowel preparation in 2010. Two studies comparing OSS to a PEG-based preparation have been published.[7,8] One compared OSS to 2-L PEG-Asc (MoviPrep). The proportion of patients with a good or excellent bowel cleansing was comparable in both arms of the study.[7] A second study comparing OSS to 4-L PEG-ELS demonstrated a higher mean bowel cleansing score with OSS compared to the PEG preparation (3.7 vs 3.2; *P*<.001).[8] The proportion of patients with an excellent bowel preparation was significantly greater in the OSS group compared to the PEG group (71.4% vs 34.3%; *P*<.001).[8]

Use of OSS has been associated with various gastrointestinal adverse events, including abdominal cramps, bloating, nausea, and vomiting, as well as hyperphosphatemia and hyperkalemia. Limited data on the tolerability and safety of OSS are currently available, however, and we will have to await further studies before conclusions regarding these issues can be drawn.

Table 2. Comparison of Sodium Phosphate (NaP) Tablets (OsmoPrep, Salix) to 2-L Polyethylene Glycol Electrolyte Solution (PEG-ELS; HalfLytely & Bisacodyl Tablet Bowel Prep Kit, Braintree)

	Patients (%)		
Overall score	**NaP tablet N=205**	**2-L PEG-ELS N=206**	***P*-value**
Excellent	64.4%	38.8%	<.0001
Good	25.4%	43.2%	NR

NR=not reported.

Conclusion

The selection of a bowel preparation for precolonoscopy cleansing should be based on a consideration of the relative efficacy and safety of the available products. This is best accomplished by a careful review of well-designed, published trials. Today, with several effective and safe agents available, use of a product with little or no published data is to be discouraged.

Financial Disclosure

Lawrence B. Cohen, MD, has received consulting fees and fees for non-CME/CE services from Salix Pharmaceuticals.

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Efficacy and Safety of Polyethylene Glycol 3350 without Electrolytes for Bowel Preparation

Carol A. Burke, MD

When considering the use of agents that are not approved by the FDA for use as bowel preparations, clinicians should bear in mind that the key aspects of high-quality colonoscopy are patient safety and excellent colon cleansing, which affects maximal adenoma detection rate and interval CRCs. Factors associated with high-quality colonoscopy also include technical aspects of the examination—such as withdrawal time, cecal intubation rate, detailed mucosal inspection, adequate insufflation, and completeness of polypectomy—all of which are affected by the quality of the bowel preparation. As has been discussed previously, split dosing has a strong base of evidence supporting its impact on many aspects of quality colonoscopy, including procedure efficiency, patient safety, and adenoma detection rate. When practitioners select a bowel preparation from among the variety that are available, the chief considerations should typically include safety—which is affected by the product's physiologic parameters, including tonicity, electrolyte balance, and osmotic balance—and efficacy.

In addition to the various bowel preparations discussed in the previous section, another preparation that some practitioners prescribe off-label is PEG 3350 (without electrolytes) administered in approximately 2 L of Gatorade sports drink (PepsiCo, Inc.). This preparation is used because of its perceived patient tolerability. This iso-osmotic combination is hypotonic and not electrolyte-balanced. The safety of PEG 3350 plus Gatorade bowel preparation is not proven, and it is not FDA-approved as a bowel preparation.

The 2006 consensus document on bowel preparation published by the American Society for Gastrointestinal Endoscopy (ASGE) stated that studies comparing full-volume, 4-L PEG-ELS preparations to low-volume, 2-L PEG 3350 (MiraLAX) administered in combination with bisacodyl tablets had clearly demonstrated equal efficacy in terms of colonic cleansing and improved overall patient tolerance; a grade 1A recommendation.[1] What is little appreciated regarding the utility of PEG 3350 dissolved in a sports drink are the potential safety issues due to inadequate electrolyte concentrations in the preparation. The FDA-approved PEG-ELS bowel preparations contain at least 8 g of sodium, 1 g of potassium, and 4 g of chloride. In contrast, PEG 3350 combined with approximately 2 L of Gatorade contains less than 1 g each of these electrolytes: sodium, 0.88 g; potassium, 0.24 g; and chloride, 0.72 g.

Efficacy

There are 2 recently published studies comparing PEG 3350 (MiraLAX) to PEG-ELS (GoLYTELY, Braintree). The first study compared the combination of PEG 3350 plus Gatorade and 20 mg of bisacodyl with 4 L of PEG-ELS given in a split-dose manner.[2] For both groups, the first dose of bowel preparation was given at 3 PM the day before the examination and the second part was given 4 hours before leaving their home for the colonoscopy. Bisacodyl tablets were also given at 3 PM the day prior to the examination for patients in the PEG 3350 group. One hundred ninety patients were enrolled in the study (87 in the PEG 3350 plus Gatorade arm and 103 in the PEG-ELS arm); in both groups, 55% of patients were female, and nearly 70% of examinations were performed in the morning. This study found that individuals randomized to PEG-ELS had a higher percentage of "excellent" or "good" bowel preparations. Excellent preparations were observed

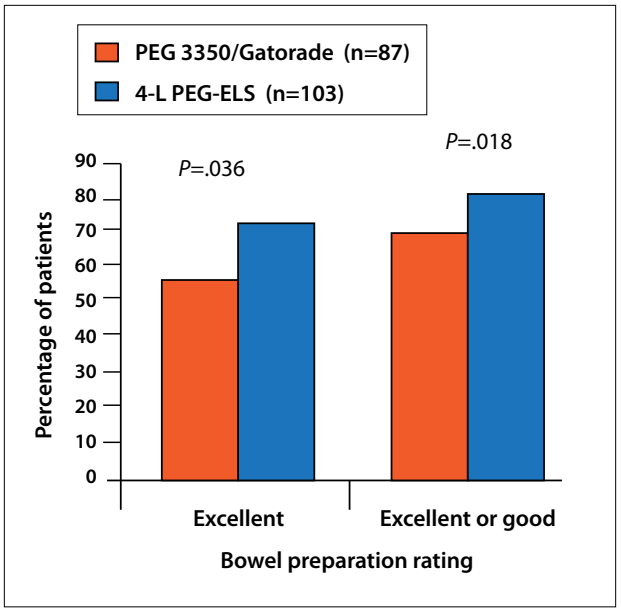

Figure 4. Efficacy of PEG 3350 (MiraLAX, Schering-Plough) and Gatorade versus 4-L PEG-ELS (GoLYTELY, Braintree): Enestvedt study.[2]

PEG=polyethylene glycol; PEG-ELS=polyethylene glycol electrolyte solution.

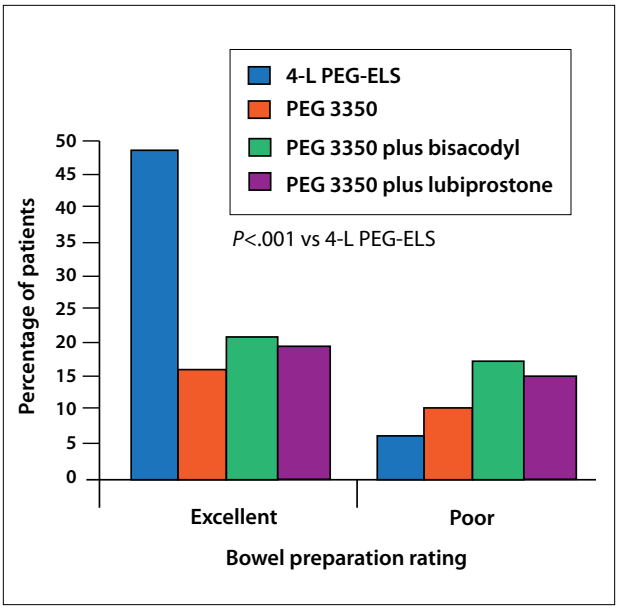

Figure 5. Efficacy of PEG 3350 (MiraLAX, Schering-Plough) preparations versus 4-L PEG-ELS (GoLYTELY, Braintree): Hjelkrem study.[3]

PEG=polyethylene glycol; PEG-ELS=polyethylene glycol electrolyte solution.

in 70% of patients who received PEG-ELS versus 55% of patients who received PEG 3350 plus Gatorade (*P*=.036); good or excellent preparations were observed in 83% and 68%, respectively (*P*=.018; Figure 4). In terms of tolerability, over 80% of patients in both groups found their assigned preparation easy to take and acceptable, although the proportion of patients willing to take the preparation again was slightly lower in the PEG-ELS group compared to the PEG 3350 plus Gatorade group (83% vs 95%; *P*=.006).

A second randomized study compared 4-L PEG-ELS (GoLYTELY) with a variety of PEG 3350 and Gatorade regimens (combined with bisacodyl, lubiprostone, or no laxative).[3] A total of 425 patients were enrolled: 106 were randomized to 4-L PEG-ELS, 106 to PEG 3350 without adjunct laxatives, 107 to PEG 3350 plus bisacodyl, and 106 to PEG 3350 plus lubiprostone. Females comprised 43–52% of each group, and over half of the procedures in each group were performed in the morning. Laxatives—either 24 µg of lubiprostone or 10 mg of bisacodyl—were given at noon the day before the examination, the first half of the split dose was given at 4 PM the day before the procedure, and the second half was given 5 hours before the procedure; overall, this dosing schedule was similar to that of the previously discussed study.

The efficacy of each bowel preparation regimen was measured according to the Ottawa Bowel Preparation Scale. Overall, the percentage of patients with an excellent bowel preparation (Ottawa score <5) was significantly higher in the PEG-ELS group compared to all of the PEG 3350 groups (Figure 5). Likewise, poor bowel preparation (Ottawa score=10) was significantly less common in the 4-L PEG-ELS group compared to the PEG 3350 groups. However, no significant difference was seen among the 4 groups in terms of the percentage of patients found to have 1 or more polyps (51% for 4-L PEG-ELS, 47% for PEG 3350 alone, 43% for PEG 3350 plus bisacodyl, and 57% for PEG 3350 plus lubiprostone; *P*=.346).

Approximately 2–3 times as many patients assigned to the 4-L PEG-ELS preparation said they experienced distress when taking their bowel preparation, compared to patients in the 3 PEG 3350 groups. However, patients' actual reports of adverse events—including nausea, bloating, and abdominal cramping—were not significantly different among the groups. Moreover, patients' sense of well-being following their bowel preparation was not significantly different among the various groups.

Safety

Many practitioners have changed their practice and no longer prescribe sodium phosphate preparations due to safety concerns about acute phosphate nephropathy, turning instead to a preparation of PEG 3350 and Gatorade, which

is presumed to be safe. However, in 2006, shortly after the original ASGE consensus document on bowel preparation was published, an article was published that described severe hyponatremia in a 73-year-old woman who had been given PEG 3350 and Gatorade.[4] This patient developed a tonic-clonic seizure due to hyponatremia caused by syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Hyponatremia is a state in which sodium levels are less than 135 mEq/L; it can be caused by vomiting, diarrhea, or other events in which excessive salt or fluid is lost, including SIADH, excessive perspiration, renal dysfunction, and adrenal or thyroid dysfunction. Many drugs commonly taken by patients undergoing colonoscopy can contribute to the release of ADH, including thiazide diuretics, NSAIDs, ACE inhibitors, opioid derivatives, selective serotonin reuptake inhibitors, tricyclic antidepressants, and antipsychotics. In addition, if a patient is not tolerating the bowel preparation and begins to vomit or feel nauseous, a release of antidiuretic hormone (ADH) from the posterior pituitary can occur. When ADH is released in association with volume depletion, the kidneys begin to conserve free water, which can result in hypo-osmolality and hyponatremia.[5]

Several studies have investigated whether hyponatremia is associated with use of PEG 3350 plus Gatorade bowel preparations. In a presentation given at the 2011 Digestive Disease Week conference, Lewis and co-investigators reported 3 cases of hyponatremia among individuals at the University of Michigan who had received a PEG 3350 bowel preparation.[6] Using a modified FDA Adverse Event Reporting System, these investigators then identified 9 other cases of severe hyponatremia (serum sodium <130 mEq/L) related to administration of PEG 3350 and Gatorade.[7] These patients were found to range in age (35–76 years); most were male; 8 of 9 required hospitalization; and 2 required admission to the intensive care unit. Five of these patients had no medical problems that could be attributable to the hyponatremia; 2 were on antihypertensive medications or diuretics; 2 were hypothyroid; and there were no data available on 1 patient. One patient developed supraventricular tachycardia requiring correction, and another patient had syncope and seizures. Because of the severity of the adverse events associated with the PEG 3350 plus Gatorade bowel preparation in these cases, none of these patients underwent colonoscopy.

In 2009, the ASGE revisited their statement on bowel preparation.[8] The revised comments regarding PEG 3350 state that this product "has been approved and marketed as an agent to treat constipation," and they specifically note that PEG 3350 solutions without electrolytes are not approved for bowel preparation, concluding that "the volume required and safety for use as a bowel preparation has not been adequately defined." This revised statement should give practitioners pause, and considering the available data, neither efficacy nor improved tolerability should be considered an advantage of PEG 3350 plus Gatorade preparations.

Summary

Bowel preparations containing PEG 3350 and Gatorade have recently been shown to be less effective than PEG-ELS for bowel cleansing. There is no decrease in adverse events with PEG 3350 preparations versus PEG-ELS, although there is some suggestion of better overall patient satisfaction with PEG 3350 preparations. The safety of PEG 3350 preparations has not been proven, and there are emerging concerns over serious adverse events related to hyponatremia when PEG 3350 is used as a bowel preparation. The ASGE's 2009 revised statement on the use of PEG 3350 as a bowel preparation elucidates the current limitations regarding its use, and emerging data show that it is not more efficacious or better tolerated than FDA-approved formulations for which safety has been proven.

Financial Disclosure

Carol A. Burke, MD, has received consulting fees and fees for non-CME/CE services from Salix Pharmaceuticals.

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Question-and-Answer Forum

What data are most likely to convince reluctant physicians to implement split dosing in their practice?

Dr. David M. Kastenberg In my opinion, efficacy is the deciding factor. Data showing efficacy for split dosing are consistent and also dramatic. I believe that once some doctors are convinced that split dosing is far more effective, then the rest will follow.

Dr. Lawrence B. Cohen We have to remember that this is not a small problem involving a small fraction of patients; one quarter of all patients have inadequate bowel preparation, many of whom will have repeat examinations at an earlier interval than would otherwise be recommended, which increases costs and places added burdens on both physicians and patients.

Dr. Philip S. Schoenfeld One of the strongest recommendations from the most recent ACG guidelines for colon cancer screening stated that all patients undergoing screening and surveillance colonoscopy should have their bowel cleansing split, which I believe should be fairly persuasive. Based on these data, splitting the bowel preparation is the single intervention that is most likely to produce excellent bowel cleansing at the time of colonoscopy.

Many gastroenterologists understand that improved bowel cleansing is possible with split dosing, but they believe their patients will resist such a regimen. Are there any strategies that can help to address this resistance?

DMK I think doctors are creatures of habit, like everyone else; they have been performing bowel cleansing a certain way for years, they are comfortable with this method, and they think they are getting good results. However, once they look at their adenoma detection rates, they may realize that their old approach is not perfect. Factors that can help reluctant doctors make the switch to split dosing include the efficacy data I discussed, the recommendations of the ACG, and the fact that more and more of their colleagues are using split dosing.

Dr. Carol A. Burke I have also noticed that the implementation of split dosing can be encouraged by sharing data on residual gastric volumes and the American Society of Anesthesiologists' guidelines with physicians who may be practicing with anesthesiologists.

Why do so many physicians continue to use bowel preparations that are not approved, such as PEG 3350 (MiraLAX) plus Gatorade?

CAB I think physicians are driven by patient preference, and patients get information from websites that tell them that PEG 3350 is cheaper and more palatable. Unfortunately, patients are not aware of the evidence suggesting that other products are more effective, nor do they realize the importance of achieving a high-quality bowel preparation.

What factors should be considered before prescribing sodium phosphate as a bowel preparation, considering the black-box warning concerning possible kidney damage?[1]

LBC In my clinic, we screen patients with a questionnaire, asking them if they have a history of a number of conditions, including chronic renal disease. We also do not give sodium phosphate to anyone over 55 years of age. The patients I am most concerned about are not those who know they have renal insufficiency, but those who may be walking around with undiagnosed Stage II or III chronic disease.

CAB An interesting study was published by the Israeli Society of Pediatric Gastroenterology and Nutrition, which found acute toxicity from oral phosphate soda preparations at a rate of 0.041% in children (3 cases out of 7,320), and all of these cases resolved with treatment.[2] While this study did not shed any light on the cause of this toxicity, it continued to recommend sodium phosphate for bowel preparation in children undergoing colonoscopy.

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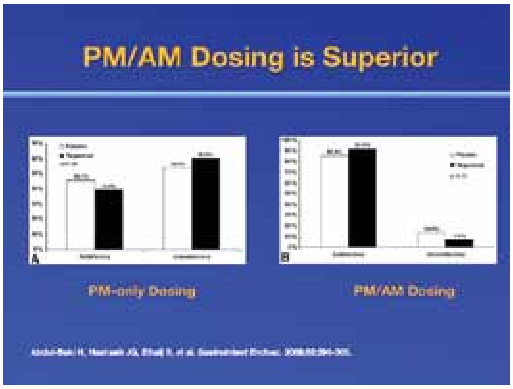

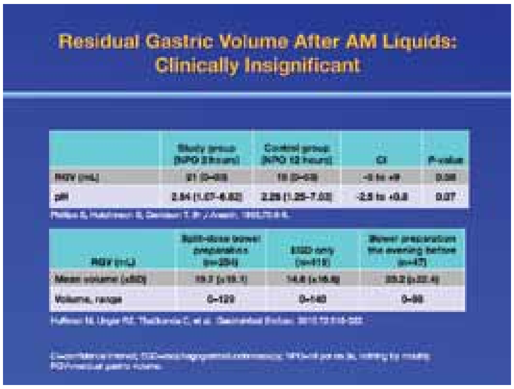

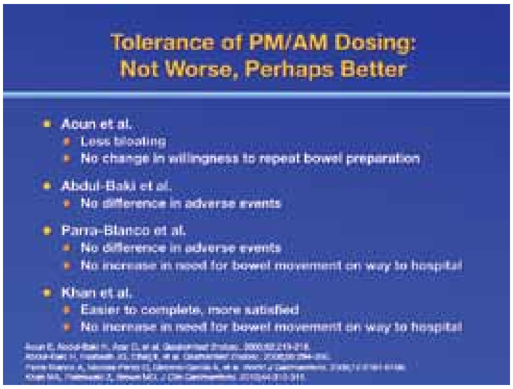

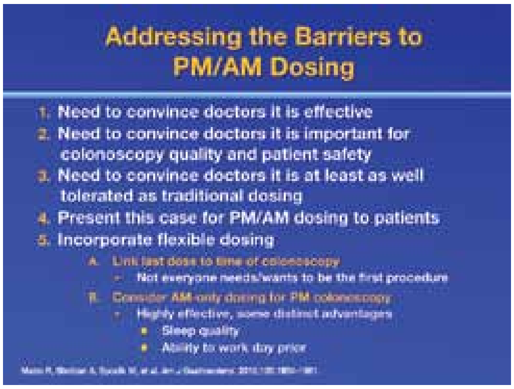

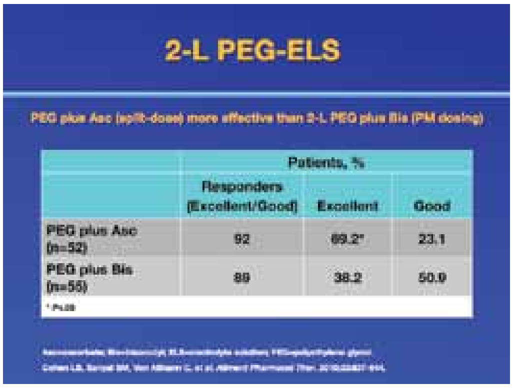

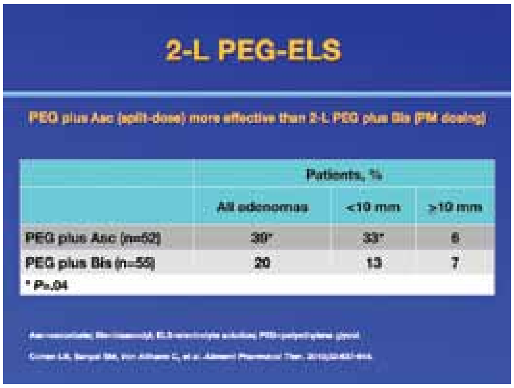

Oral Sulfate Solution Versus 2-L PEG plus Asc

Non-inferiority study design—comparable efficacy

	OSS	2-L PEG plus Asc	*P*-value
Bowel Prep Score	3.59	3.47	.05
% Excellent	63.3	52.5	NS
% Good	33.9	43.2	NS

Oral Sulfate Solution Versus 4-L PEG

Oral sulfate solution (split-dose) better efficacy than 4-L PEG (PM dosing)

	OSS	4-L PEG	*P*-value
Mean Bowel Prep Score	3.7	3.2	<.001
% Excellent	71.4	34.3	<.001
% Good	27.0	55.2	NR

Comparison of Electrolyte Concentration in Bowel Preparations

- 255 grams PEG 3350 dissolved in 64 oz of Gatorade

	PEG+ELS (grams per regimen)	MiraLAX-Gatorade (grams per 2 L)	PEG+ELS versus MiraLAX-Gatorade
Sodium	8.35	0.88	~9x higher
Potassium	1.06	0.24	~5x higher
Chloride	4.23	0.72	~6x higher

Safety of MiraLAX-Gatorade Bowel Preparation

Hyponatremia
Sodium <135 mEq/L

- Vomiting
- Diarrhea
- Excess perspiration
- Renal disease
- Adrenal dysfunction
- Thyroid dysfunction
- Syndrome of inappropriate antidiuretic hormone secretion

Results: University of Michigan Patients

Age	Gender	Indication for procedure	Baseline sodium (mmol/L)	Creatinine (mg/dL)	Sodium at presentation (mmol/L)	Symptoms	Treatment	Sodium at discharge (mmol/L)
57	F	Surveillance (history of polyps)	n/a	0.5	122	N, V, HA, CP	IV saline	140
50	F	Screening	137	0.8	123	N, V, S	IV saline	141
76	F	Rectal bleeding	139	0.8	128	N, V	IV saline	134

MiraLAX-Gatorade Bowel Preparations

- Not as effective as PEG-ELS for bowel cleansing
- No decrease in adverse events versus PEG-ELS
  - Suggestion of better patient satisfaction
- Safety not proven
  - Concerns over serious adverse events related to hyponatremia

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