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REVIEWS

Improving Colonoscopy Outcomes: Split Regimen, Low-volume Preparation and Addition of Simethicone

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Abstract

In the field of colonoscopy preparation, the focus is on improving patient experience, optimizing bowel cleansing efficacy, and exploring innovative technologies. The ongoing advancements made colonoscopy preparation more tolerable, effective, and accessible for patients, ultimately improving the overall quality of the procedure.

Current evidence supports low volume preparations and split dose regimen in most cases. Adding simethicone to PEG might bring some advantages in terms of better visibility and tolerability. In this mini review we present the main evidence regarding the low volume PEG/citrate/simethicone colonoscopy preparation solution.

Keywords: bowel preparation, simethicone, low-volume PEG, split dose.

Rezumat

Colonoscopia reprezintă un instrument esențial în prevenția cancerului colorectal, prin detectarea și îndepărtarea leziunilor pre-canceroase. Succesul procedurii depinde în mare măsură de o pregătire adecvată a intestinului, care asigură o vizualizare clară a mucoasei colonice și reduce riscul de rezultate fals-negative. Soluțiile tradiționale de curățare a intestinului, în special preparatele pe bază de polietilenglicol (PEG) cu volum mare sunt eficiente, dar pot cauza disconfort semnificativ și o aderență scăzută din partea pacienților.

Formulele de PEG cu volum redus, cu citrat și simeticonă, oferă un gust îmbunătățit, o eficacitate comparabilă în curățarea colonului cu soluțiile standard de PEG, dar cu o acceptabilitate superioară și mai puține efecte secundare, cum ar fi disconfortul abdominal și greața. Regimurile de administrare în două doze îmbunătățesc și mai mult rezultatele curățării intestinului, în timp ce alternativele emergente pentru populațiile speciale, cum ar fi pacienții vârstnici, cei cu boli inflamatorii intestinale (IBD) sau cu comorbidități, necesită abordări personalizate. În concluzie, soluțiile de PEG cu volum redus sunt tot mai preferate datorită siguranței, confortului și eficienței lor, având potențialul de a îmbunătăți atât rezultatele colonoscopiilor, cât și aderența pacienților.

Cuvinte cheie: colonoscopie, simeticonă, soluție PEG cu volum redus.

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INTRODUCTION

Colonoscopy serves as a crucial tool for preventing colorectal cancer by detecting and removing precancerous lesions.[1] Adequate bowel preparation ensures a clear view of colonic mucosa allowing the endoscopist to identify and evaluate abnormalities, reducing the chances of false-negative results. Also, if polyps are found, a well-prepped colon allows for immediate removal or biopsy. A proper preparation can also expedite the procedure, minimizing the time taken for examination and can potentially minimize discomfort during the procedure.

Bowel-cleansing solutions typically contain laxatives that induce bowel movements and help remove stool, allowing better mucosal visualization during the procedure.[2] Abdominal discomfort and nausea are commonly reported side effects, potentially impacting patients' daily routines and well-being during the preparation phase. Certain preparations necessitate substantial fluid intake or fasting with a risk of dehydration or electrolyte imbalances. This presents a concern, especially for individuals with specific health conditions or vulnerabilities.

Collectively, these challenges significantly impact patient compliance. The discomfort of the preparation, taste and palatability of the solution related problems and other inconveniences associated with existing preparations might discourage individuals from undergoing colonoscopies or following the preparation regimen diligently.[3]

The high-volume polyethylene glycol (PEG) solution, with a volume of 4L, is the most common and effective solution used for bowel preparation, although the ingestion of the large volume might be challenging for some individuals. Other common side effects include abdominal discomfort or cramping, bloating, and nausea. These effects are temporary and usually diminish after bowel movements cease.

Another type of osmotic laxative used in bowel preparations is sodium phosphate. However, its use has declined due to potential risks of electrolyte imbalances and kidney damage. Magnesium citrate may be used in some preparations but is less common.[4]

Low volume, simethicone solutions

Low-Volume solutions aim to reduce the volume of solution needed for bowel cleansing. They often combine PEG with additives like citrate or simethicone to improve taste, palatability, or patient tolerance.[5,6]

Low-volume PEG (Polyethylene glycol) with citrate and simethicone refers to a specific colonoscopy bowel preparation solution-trade name Clensia (*AlfaSigma*, Italy). This preparation is aimed at cleansing the colon effectively while reducing the volume of solution a patient needs to consume. The active ingredients include PEG 4000, sodium sulphate, citric acid, sodium citrate, sodium chloride, potassium chloride and simethicone.

Citrate is often added to bowel preparation solutions to improve taste and palatability and might also have a mild laxative effect, contributing to bowel cleansing.[7] The reduced volume of solution (2L) makes it more palatable and easier to consume, potentially improving patient compliance. The solution has been specially formulated to prevent electrolyte imbalances and without ascorbates and aspartame, rendering it safe for patients with phenylketonuria or glucose-6-phosphate dehydrogenase deficiency.[9]

Simethicone is an anti-foaming agent that reduces gas bubbles in the digestive tract, potentially improving visualization of colonic mucosa and patient comfort during the preparation process. Simethicone might be useful to enhance bowel preparation by eliminating bubbles that typically appear in the ascending colon. This might theoretically increase the chances of identifying smaller proximal adenomas. The main concern when injecting simethicone through the working channel of the endoscope is that the residual simethicone in the biopsy channel might encourage the formation of biofilm increasing the risk of bacterial colonization. By adding simethicone to PEG solution one can benefit from its advantages without any infectious risks.[5,8-10]

According to European Society of Gastrointestinal Endoscopy (ESGE) Guideline from 2019, the low-volume PEG (Polyethylene glycol) with citrate and simethicone it is one of the recommended options for colonic preparation. It has been adopted by the ESGE guideline after two randomized trials. One compared 2L PEG/citrate/simethicone (Clensia) with 4L Polyethylene glycol (PEG-4L) solution and there was no difference in bowel cleansing, compliance and safety, but gastrointestinal tolerability and acceptability were better for the low volume solution. The another randomized controlled trial compared 2L PEG/citrate/simethicone (Clensia) with the 2L Polyethylene glycol plus ascorbate (2L PEG-ASC) solution and the bowel cleansing, safety, acceptability and willingness to repeat the preparation and compliance were equivalent.[2] *see supplementary material in the appendix*

When compared to PEG 4L or PEG-ASC, the low volume PEG/citrate/simethicone containing solution has shown comparable effectiveness in colon cleansing with no significant differences in successful cleansing rates for different parts of the colon or in reaching the cecum during colonoscopies. Safety-wise, it exhibited similar low incidence of adverse events to its comparators and was well-tolerated, with no serious adverse events reported. Low-volume PEG (Polyethylene glycol) with citrate and simethicone tended to offer better gastrointestinal tolerance and was associated with a lower incidence of certain discomforting symptoms like anal irritation compared to PEG solutions and stood out in its higher acceptability among patients. It was reported to be easier to consume, causing less distress, and had a notably higher rate of willingness among patients to undergo the same preparation for future colonoscopies compared to PEG solutions.[12]

Split dose administration

The current recommended regimen in the ESGE guideline is the split-dose regimen that better results in terms of successful bowel cleansing.[13,14] Traditionally, patients were instructed to consume the entire preparation solution the night before the colonoscopy. However, a split-dose regimen involves dividing the preparation solution into two doses: the first taken the evening before the procedure and the second dose taken on the morning of the colonoscopy. The split-dose regimen has gained popularity because it offers several advantages over the single-dose (evening before) regimen. By dividing the preparation into two doses, the second dose taken closer to the procedure helps to ensure better bowel cleansing. This can lead to improved visibility and effectiveness of the colonoscopy, reducing the chances of missed lesions or polyps. Splitting the preparation into two doses may improve patient tolerance. Drinking a smaller volume at a time may be more manageable for patients, reducing the likelihood of nausea, bloating, or discomfort often associated with consuming a large volume of liquid all at once. Patients might be more likely to adhere to the split-dose regimen compared to the full-dose regimen, as it's perceived as more tolerable and less burdensome.[15]

Maintaining an interval of no more than 8 hours between the final dose of bowel preparation and the colonoscopy significantly enhances the quality of bowel preparation. Beyond this timeframe, a viscous bile-stained mucus enters the colon and spreads across the mucosa, particularly in the right colon, potentially covering small or flat lesions containing high dysplasia. These specific lesions pose a considerable challenge for endoscopists as they have a high likelihood of being overlooked during colonoscopy. However, the morning dose on the same day, as well as a split dose, effectively clears this material, potentially boosting the effectiveness of colonoscopy in detecting small adenomas.[16]

The Italian Society of Digestive Endoscopy initiated a randomized, multicentric, prospective study to compare the effectiveness of two different low-volume bowel preparation regimens in patients undergoing early morning colonoscopies. The ERACLES study compared two bowel preparation regimens for morning colonoscopies. The split-dose regimen proved more effective in cleansing but raised concerns about incontinence during the trip to the hospital. Surprisingly, the classic day-before regimen had slightly lower efficacy but garnered higher patient preference for future colonoscopies. Both regimens showed similar compliance and tolerability. In specific situations, like early morning procedures, the day-before regimen emerged as an acceptable alternative due to adequate cleansing and better patient acceptance, challenging the established split-dose standard.[17]

Special situations: IBD

An important population of patients undergoing repeated colonoscopy procedures are the inflammatory bowel disease (IBD) patients. The bowel preparation for the IBD patients undergoing these procedures repeatedly to evaluate the disease severity and screening for colonic malignancy is extremely paramount and can lead to a low compliance. Existing studies indicate IBD patients tend to be less satisfied with bowel preparation compared to others, with some experiencing heightened symptoms post-colonoscopy, possibly linked to the preparation process. Clinicians should acknowledge these challenges, especially as guidance for preparing IBD patients for colonoscopy largely relies on expert opinions.[15]

In terms of bowel preparation options for IBD, oral polyethylene glycol (PEG) is preferred over oral or enema phosphate containing preparation due to fewer mucosal lesions and clearer interpretations. However, there's variability in recommended PEG volumes, typically taken before the procedure until clear fluid evacuation, with no specific guidelines for high-volume diarrhea or frequent bowel movements. Adjusting PEG volume or using phosphate enemas or a combination could be reasonable in such cases.

For IBD patients with suspected, quiescent or mildly/moderately active disease, full colonoscopies with proper bowel preparation (preferably using oral PEG) are recommended for precise inspection and biopsies. Yet, in severely active IBD cases, the risks associated with full colonoscopy and preparation outweigh the benefits, making flexible sigmoidoscopy without or with minimal preparation a safer option. In these cases, delaying ileo-colonoscopy until clinical improvement is advisable to mitigate procedural risks.[18]

In a recent study, over 25% of individuals with inflammatory bowel disease (IBD) did not adhere to recommended colonoscopy intervals (waiting more than 3 years on average). One reason for this could be the impact of bowel preparation. When dealing with ulcerative colitis, achieving good bowel cleansing is challenging, leading to a lower quality of preparation and making it tougher to detect abnormal growths amidst the inflammation.[19]

However, ensuring high-quality preparation, especially with oral PEG, is crucial in IBD cases, particularly during remission, to enhance the chances of identifying dysplastic lesions. Several innovative techniques have emerged to streamline cancer surveillance procedures, such as chromoendoscopy, narrow-band imaging, fluorescence endoscopy, confocal laser endomicroscopy, and optical coherence tomography. These methods aim to reduce the number of biopsy samples needed and shorten examination times but they demand impeccable bowel cleansing for optimal effectiveness.[20]

For assessing Crohn's disease in the small bowel, evaluations like wireless video-capsule endoscopy and anterograde double-balloon enteroscopy can be done without bowel preparation, but most experts advise cleansing to ensure accurate detection of small-bowel mucosal changes. Recommendations suggest using 1.5-2.0 L of oral PEG for wireless capsule endoscopy and anterograde double-balloon enteroscopy. However, for retrograde double-balloon enteroscopy, a standardized bowel cleansing of 2-4 L of PEG is always necessary.[21] A low-volume PEG with citrate and simethicone can increase visibility by reducing the bubbles in the small bowel and might be an interesting option in these patients.

Special situations: special patients' categories

In elderly, frail patients, the necessity of colonoscopy can be contentious. Despite their heightened risk for colorectal cancer, there's debate about the benefits of screening due to lower diagnostic yields in those aged 80 or older with shorter life expectancies. Bowel preparation for colonoscopy in this demographic segment presents challenges, with studies indicating varying tolerance levels for different preparation methods. Elderly patients, prone to electrolyte imbalances and other conditions, might face risks with certain preparations, such as sodium phosphate (NaP) solutions that can induce electrolyte disturbances.[22]

The PEG-based low-volume preparations, especially in split doses, have shown more promising for the elderly patients offering improved tolerability and comparable effectiveness in cleansing. For the high-risk individuals, pre-assessment for electrolyte disturbances is recommended.[13]

Diabetic patients also might present challenges for bowel preparation, showing poorer outcomes compared to non-diabetic counterparts, possibly due to factors like disease duration, associated constipation and poor glycemic control.[23,24] Monitoring electrolytes post-procedure is crucial, especially in those with cardiac or renal issues.

Patients with chronic kidney disease should avoid NaP preparations due to potential adverse events like hypovolemia and electrolyte shifts, while adequate hydration throughout the bowel preparation process is crucial for high-risk patients, including those on certain medications or elderly individuals.[25]

In patients with heart failure, caution is advised with both NaP and classic PEG preparations due to concerns about fluid shifts and electrolyte disturbances. Lower volume PEG formulations and split dosing might be safer options, with continued emphasis on maintaining cardiac medications during preparation.[26]

In essence, while PEG-based preparations generally appear safer for patients with electrolyte imbalances, liver or heart issues, cautious consideration and careful monitoring during preparation remain vital, especially when dealing with conditions prone to fluid retention.[22]

CONCLUSIONS

Anticipated trends in colonoscopy preparation include the development of personalized bowel preparation protocols, more patient-friendly formulations and advancements in split-dose regimens. Additionally, technological innovations like artificial intelligence and virtual reality may be integrated for real-time assessment of bowel cleanliness.

The comparative analysis of bowel preparation solutions reveals that when compared to PEG 4L, or PEG-ASC, the low-volume PEG/citrate/simethicone solution exhibit similar effectiveness in colon cleansing and similar safety profiles with an excellent gastrointestinal tolerance and high patient acceptability.

SUPPLEMENTARY MATERIAL

2L PEG/citrate/simethicone vs PEG 4L[11]

Colon cleansing

In the assessment of colon cleansing, both groups demonstrated similar success rates for bowel preparation. The effectiveness of 2L PEG/citrate/simethicone was found to be on par with PEG 4 L, as the 95% confidence interval for the difference in proportions between these treatment groups fell entirely within the equivalence range of -15% to 15%. No significant distinctions were observed between the groups regarding the successful cleansing rates for different parts of the colon (right, mid, and recto-sigmoid).

Furthermore, the completeness and duration of colonoscopies were comparable in both treatment groups. The frequency of successful bowel cleansing was notably higher when following the split-dose regimen compared to the day-before approach for both preparations ($\chi 2$ test, P = 0.0026 for Clensia and P = 0.0259 for PEG).

Regarding mucosal visibility, 2L PEG/citrate/simethicone achieved an optimal visibility of approximately 63%, slightly higher than the 55% attained with PEG 4 L, though this difference did not reach statistical significance (p = 0.12).

Safety and tolerability

Throughout the study, no serious adverse events (SAEs) were reported, and no participants discontinued their involvement due to adverse effects. The incidence of adverse events (AEs) stood at 8% following 2L PEG/citrate/simethicone and 7.2% following PEG 4 L, with no statistically significant difference observed (P = NS). Among the most common AEs were headaches (5.6% in the 2L PEG/citrate/simethicone group and 3.8% in the PEG 4 L group) and vomiting (0.9% in the 2L PEG/citrate/simethicone group and 1.0% in the PEG 4 L group). There were no clinically significant changes noted in serum electrolytes, body weight, or vital signs following either treatment. 2L PEG/citrate/simethicone exhibited notably better gastrointestinal tolerance when compared to PEG 4 L. The incidence of patients experiencing nausea, bloating, abdominal pain/cramps, and anal irritation was lower with 2L PEG/citrate/simethicone than with PEG 4 L (25.4% vs. 37%, P < 0.01).

Compliance and acceptability

2L PEG/citrate/simethicone exhibited significant superiority over PEG 4 L in terms of acceptability, specifically in patients' self-reported ease of taking the preparation. A higher percentage of individuals reported no distress while consuming 2L PEG/citrate/simethicone (72.8% versus 63% for PEG 4 L; P = 0.0314). Moreover, in terms of willingness to undergo the same preparation for future colonoscopies, 2L PEG/citrate/simethicone demonstrated a notably higher rate of willingness among patients (93.9% versus 82.2% for PEG 4 L; P = 0.0002).

2L PEG/citrate/simethicone vs. low volume PEG with ascorbic acid[9]

Efficacy

The successful bowel cleansing rate was 78.3% with 2L PEG/citrate/simethicone and 74.3% with PEG-ASC. Notably, the efficacy of 2L PEG/citrate/simethicone was considered equivalent to PEG-ASC, as the 95% confidence interval (CI) for the difference between the two groups in successful colon cleansing ranged within -4.8% to 12.6% for the PP population falling within the equivalence range of -15% to 15%.

The split-dose regimen (86.2% for 2L PEG/citrate/simethicone and 78.7% for PEG-ASC) demonstrated a higher rate of successful bowel cleansing compared to the full-dose regimen (75% for 2L PEG/citrate/simethicone and 72.5% for PEG-ASC) in both groups.

Likewise, the split-dose regimen showed higher rates of excellent and good cleansing in the right colon (73.4% for 2L PEG/citrate/simethicone and 70.5% for PEG-ASC) compared to the full-dose regimen (52.9% for 2L PEG/citrate/simethicone and 55.1% for PEG-ASC).

Regarding mucosal visibility, there was no significant difference between 2L PEG/citrate/simethicone (53.9%) and PEG-ASC (50.5%). However, in a sub-analysis of patients who adhered to the recommended additional fluid intake (51.3% in 2L PEG/citrate/simethicone and 48.2% in PEG-ASC), optimal mucosal visibility was higher for 2L PEG/citrate/simethicone (57.9%) compared to PEG-ASC (43.5%).

Optimal mucosal visibility was also more frequent with the split-dose regimen compared to the full-dose regimen in both groups. Additionally, the cecum was reached in 94.8% of patients in the 2L PEG/citrate/simethicone group and 96.4% of patients in the PEG-ASC group, showing no significant difference.

Safety and tolerability

There were no serious adverse events (SAEs) reported during the study, and no patients withdrew from the study due to adverse effects. In total, 9.2% of patients in the 2L PEG/citrate/simethicone group and 9.3% in the PEG-ASC group experienced adverse events. The most reported adverse events were headaches (5.1% in 2L PEG/citrate/simethicone and 1.6% in PEG-ASC), chills (0.5% in 2L PEG/citrate/simethicone and 2.1% in PEG-ASC), and vomiting (0.5% in 2L PEG/citrate/simethicone and 1.6% in PEG-ASC). Laboratory parameters remained unchanged throughout the study. Regarding gastrointestinal symptoms (such as nausea, bloating, abdominal pain, and anal irritation), most patients in both groups did not report distress. However, there was a notable difference in the incidence of anal irritation, which was significantly lower in the 2L PEG/citrate/simethicone group compared to the PEG-ASC group ($P = 0.03$).

Acceptability and compliance

Most patients experienced either no distress or mild distress during the administration of both bowel cleansing agents, with 81.4% in the 2L PEG/citrate/simethicone group and 80.8% in the PEG-ASC group reporting such sensations ($P = 0.74$). Moreover, a significant percentage of patients expressed willingness to use the same solution for potential future colonoscopies, with 90.2% in the 2L PEG/citrate/simethicone group and 90.7% in the PEG-ASC group indicating their willingness ($P = 0.86$). Additionally, high rates of optimal compliance were observed, with 93.4% of patients in the 2L PEG/citrate/simethicone group and 94.8% in the PEG-ASC group adhering to the recommended regimen ($P = 0.75$).

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