Adenoma detection rate and tolerability of 2 ultra-low-volume bowel preparations in screening: a noninferiority randomized controlled trial

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Background and Aims: The adenoma detection rate (ADR), recognized as a surrogate marker for colorectal cancer (CRC) incidence and mortality reduction, is closely linked to the efficacy of bowel cleansing. However, there is a dearth of evidence examining the impact on ADR when using 2 distinct very-low-dose bowel cleansing products. This study sought to compare ADR in an immunochemical fecal occult blood test (iFOBT)-based organized screening program by using 1 L of polyethylene glycol plus ascorbate (1L-PEGA) versus sodium picosulfate with magnesium citrate (SPMC), both administered in a split-dose regimen.

Methods: We conducted a comparative, parallel, randomized, noninferiority, and low-intervention clinical trial targeting individuals from a population CRC screening program aged 50 to 69 years with a positive iFOBT result scheduled for a workup colonoscopy in the morning. Participants were randomized to either 1L-PEGA or SPMC for bowel cleansing. The main outcome was ADR, whereas secondary outcomes were bowel preparation quality, safety, tolerability, and satisfaction.

Results: A total of 1002 subjects, 501 were included in each group. There were no differences between groups with respect to pooled ADR (SPMC, 56.5% [95% CI, 52.1-60.8]; 1L-PEGA, 53.7% [95% CI, 49.3-58.0]; relative risk, .95 [95% CI, .85-1.06]); therefore, SPMC demonstrated noninferiority in ADR compared with 1L-PEGA (difference, 2.8%; 2-sided 95% lower confidence limit, –3.4). In addition, there were no significant differences in mean lesions regardless of size and location between arms. Bowel preparation favored 1L-PEGA (96.2% vs 89.2%, $P < .001$), whereas SPMC exhibited significantly higher safety and tolerability, as shown by fewer nonserious treatment-emergent adverse events.

Conclusions: SPMC emerged as a noninferior laxative compared with 1L-PEGA concerning ADR. Despite the superior bowel preparation quality associated with 1L-PEGA, the safety, tolerability, and overall satisfaction of participants were higher with SPMC. (Clinical trial registration number: EudraCT: 2019-003186-18.) (Gastrointest Endosc 2025;101:158-67.)

(footnotes appear on last page of article)

The efficacy of colorectal cancer (CRC) screening through colonoscopy is well established, significantly reducing both incidence and mortality.[1] Critical to the success of screening colonoscopy is the quality of the procedure, with the adenoma detection rate (ADR) identified as a crucial metric inversely linked to the risk of interval CRC.[2,3]

High-quality bowel preparation is paramount for the diagnostic accuracy and safety of colonoscopy; however, it is often difficult for individuals to comply with high-volume laxatives, which may contribute to poor bowel preparation. Inadequate bowel preparation presents substantial challenges, including diminished lesion detection, compromised cecal intubation rates, increased rescheduling frequency, elevated procedural adverse events, and heightened healthcare costs.[4-6] Consequently, the European Society of Gastrointestinal Endoscopy mandates that intestinal cleansing must be adequate in a minimum of 90% of colonoscopies.[7]

Traditional polyethylene glycol (PEG)-based solutions have demonstrated efficacy, but their unpleasant taste and large fluid volumes pose challenges.[8] Reduced-volume split-dose preparations are as effective as large-volume split-dose preparations, with better tolerability and superior compliance.[9] Ultra-low volume solutions (≤1 L), such as 1 L of PEG plus ascorbate (1L-PEGA), oral sulfate solution and sodium picosulfate with magnesium citrate (SPMC), have emerged to further improve tolerability by minimizing liquid intake. A recent meta-analysis evaluating ultra-low-volume (<1 L) bowel preparation suggested that SPMC could be inferior to 1 L of PEG in terms of bowel preparation quality.[10] However, the impact of using the different ultra-low-volume solutions in organized population-based screening programs in terms of clinically meaningful endpoints such as ADR has never been evaluated. Therefore, this study compared 1L-PEGA (Pleinvue; Norgine Limited, Mid Glamorgan, United Kingdom) and SPMC (Citrafleet; Casen Recordati, S.L., Utebo-Zaragoza, Spain) in terms of clinical efficacy (ie, ADR), bowel cleansing quality, adverse events, and tolerability in an immunochemical fecal occult blood test (iFOBT)-based population CRC screening program.

METHODS

Study design

This prospective, randomized, comparative, parallel, non-inferiority, single-blinded, single-center, low-intervention clinical trial was conducted at an organized iFOBT-based program from October 2020 to June 2022. Once a positive iFOBT result was obtained, the colonoscopy was performed within 1 to 2 months. All colonoscopies were performed in a tertiary academic center that follows high quality standards by 12 experienced endoscopists, each having performed more than 400 colonoscopies per year and with known high ADRs (ie, 29.8% in primary colonoscopy screening and 47.1% in iFOBT-based screening). Procedures were performed with patients under spontaneous breathing deep sedation (propofol and remifentanil perfusion) administrated by trained nurses supervised by anesthesiologists in 40-minute time slots.

The study was registered at clinicaltrials.gov (EudraCT: 2019-003186-18), was approved by the Agencia Española del Medicamento y Productos Sanitarios and the Local Ethics Committee of Hospital Clínic of Barcelona on January 21, 2020, and followed the Consolidated Standards for Reporting Trial guidelines. All subjects provided written informed consent. Study data were collected and managed using REDCap tools.[11]

Participants

Eligible subjects were men and women aged 50 to 69 years who presented a positive iFOBT result in the organized population-based CRC screening program of Barcelona. Participants were scheduled for workup colonoscopy in the morning (ie, 9AM to 1:20PM). Exclusion criteria were refusal to participate in the study; severe heart failure (grades III and IV) according to the New York Heart Association Scale of Functional Assessment of Heart Failure, or renal failure (grade IV or V); severe illness that contraindicated a colorectal study; personal history of ulcerative colitis, Crohn's disease, or CRC; colorectal resection; terminal illness or severe illness or disability that contraindicated further study of the colon; mental disabilities or severe mental disorder; language barrier; and individuals who had undergone a colonoscopy during the last 12 months.

Participant enrollment

All iFOBT-positive subjects attended an outpatient visit with an advanced practice nurse specialized in CRC screening who explained the meaning of an iFOBT-positive result and recommended scheduling a workup colonoscopy. After signing the study informed consent, participants were randomized in a 1:1 allocation ratio using a randomly computer-generated sequence created by Excel (Microsoft Corp, Redmond, Wash, USA). Individuals received either a split-dose of 1L-PEGA or a split-dose of SPMC. Endoscopists were blinded to the preparation product. Two weeks after performing the colonoscopy, participants had a second visit with the specialized nurse who explained the results of the examination as well as surveillance strategy if needed.

Bowel preparation regimen

Written and verbal instructions regarding bowel preparation, low-residue diet, timing of bowel preparation consumption, and withholding medications were explained in detail by the nurse. Participants followed a low-residue diet for 2 days before colonoscopy and began a liquid diet at 4:00 pm on the day before the colonoscopy. Both study products were administered on an evening–morning split-dosing regimen. The first dose was intake at 8:00 pm on the day before the colonoscopy and the second dose 4 hours before the colonoscopy.

In the 1L-PEGA group, participants drank 500 mL of water mixed with the first dose (PEG 3350 plus electrolytes) at a rate of 250 mL every 15 minutes. Thereafter, they drank a minimum of 500 mL of mandatory clear liquids like water, tea, infusions, strained juices, or strained broth. The second dose consisted of 500 mL of water mixed with 2 sachets of laxative powders (PEG 3350 plus ascorbate), which subjects had to intake slowly within 30 minutes. After that, they drank a minimum of 500 mL of mandatory clear liquids.

In the SPMC group, subjects drank a total of 250 mL of cold water with the first dose of SPMC. Afterward, they drank a minimum of 1.500 mL of mandatory clear liquids recommended by the laboratory like isotonic drinks, strained broth, or water (but not only water). The second dose was identical to the first dose.

On the morning of the colonoscopy, all participants in both groups were urged to drink as much additional liquid as needed until the stool came out like clear water or clear urine and had to fast for 2 hours before the colonoscopy. For all individuals, administration of the bowel preparation took place at home. We defined "dose" as the amount of laxative product a person must ingest without taking into account the mandatory clear liquids required once the laxative product is finished.

Endpoints

The primary endpoint was ADR, defined as the proportion of colonoscopies in which at least 1 adenoma was detected divided by the total number of colonoscopies. Secondary outcomes were lesion detection rate, bowel preparation assessment, cecal intubation, safety, tolerability and satisfaction. Lesion detection rate was defined as the proportion of colonoscopies in which at least 1 lesion (either adenoma or serrated lesion) was detected. Bowel cleansing was scored by the Boston Bowel Preparation Scale (BBPS)[12] as a standardized measure where each colon section (right-sided colon, transverse, and left-sided colon) was scored by the endoscopist from 0 to 3 (0 = poor, 1 = fair, 2 = good, 3 = excellent). Adequate bowel preparation was considered when the BBPS score was $\geq$2 in each colon section and high-quality bowel preparation when the score was 3 in each colon segment. The colonoscopy was considered complete if the cecum was reached. Incomplete colonoscopies were not taken into account when calculating the rate of colonoscopies with an overall adequate and high-quality bowel preparation. Advanced lesions were defined as an adenoma with high-grade dysplasia and/or villous histology and/or a size $\geq$10 mm and as a serrated lesion with dysplasia and/or a size $\geq$10 mm.

Safety, tolerability, and satisfaction were evaluated with a safety, tolerability, and satisfaction questionnaire (Appendix 1, available online at www.giejournal.org) administered to individuals by the nurse. This questionnaire consisted of an adapted and translated version of the validated Mayo Clinic Bowel Prep Tolerability Questionnaire.[13] Questionnaires were filled in after taking the first and second doses of each product and returned the day of the colonoscopy. If a person had filled in the questionnaire but had left it at home, the participant was asked to send it by e-mail. If a person had not filled in the questionnaire, he or she was asked to answer it on the phone.

Safety was evaluated using the proportion of individuals with nonserious treatment-emergent adverse events (TEAEs) among those who had answered the questionnaire after the total intake of each dose. Symptoms such as nausea, vomiting, abdominal pain, bloating, dizziness, headache, shaking chills, dry mouth, bad mouth taste, or lack of sleep from excessive bathroom use were assessed with a 4-rating scale (ie, none, mild, moderate, or severe). Serious TEAEs are those that can cause death, threaten the life of the subject, require hospitalization or its prolongation, cause disability or permanent or significant disability, or give rise to a congenital anomaly or malformation. Serious TEAEs were recorded 15 days after the colonoscopy during the postexamination nurse appointment.

Tolerability was assessed by asking about the total amount of laxative intake and the reasons for not finishing it, including symptoms such as dry mouth, headache, abdominal pain, bloating, nausea, vomiting, dizziness, shaking chills, and others. In addition, tolerability was also evaluated by asking about the solution's taste, using a 5-rating scale (ie, lousy, bad, acceptable, good, or excellent).

Satisfaction was evaluated by 2 qualitative questions: "Would you be willing to repeat with the same product in a potential future colonoscopy?" (yes or no) and "How do you assess the intake of the laxative solution?" on a 4-rating scale (ie, very difficult, difficult, acceptable, or easy).

Sample size

Sample size calculation was based on the 50% ADR of the iFOBT-based organized screening program at our center. Taking into account the results of 2 studies that compared the efficacy of ultra-low-volume preparations,[14,15] we assumed a noninferiority margin of 10%. We used the sample size and power calculator GRANMO (version 7.12 April 2012; https://www.imim.es/ofertadeserveis/software-public/granmo/). A sample of 501 individuals was required in each group, accepting an alpha risk of .05 and a beta risk of <.2 in a 2-sided test and with 5% dropouts. Noninferiority was established for this outcome if the lower confidence limit (LCL) of the 2-sided 95% confidence interval (CI) for a difference in ADR between the 2 treatment arms was at least −10%.

Statistical analysis

Categorical variables are expressed with absolute (n) and relative (%) frequency. Quantitative variables are expressed as median and interquartile range because they were not normally distributed using the 2-sample Kolmogorov-Smirnov test. To describe the number of lesions per patient, mean, standard deviation, and their 95% CIs were used. Comparisons between both preparations (1L-PEGA and SPMC) were performed using the χ^2 test for categorical variables and the Mann-Whitney U test for quantitative variables. To calculate the 95% CI of the difference in ADR between treatments, the mathematical formula used was $D \pm Z_{2\alpha} \times$ SED, where D was the difference in ADR between SPMC and 1L-PEGA, $Z_{2\alpha}$ was an established value of 1.96, and the SED was the standard error of the difference. SED was calculated with the mathematical SED = $\sqrt{p1(1-p1)/n1 + p2(1-p2)/n2}$.[16]

We assessed study outcomes in both intention-to-treat (ITT) and per-protocol (PP) analyses. Whereas the first analysis included all randomized individuals, the PP analysis was limited to those who completed the study protocol (Fig. 1).

Comparisons using the relative risk (RR) and their 95% CIs were conducted to identify differences between treatments and for the different categories of bowel preparation

(adequate and high-quality preparation and by segments). Estimates of RR with 95% CI were calculated between treatments and laxative nonserious TEAEs, separately by first and second dose. Statistical significances were considered as $P < .05$. All analyses were performed with the use of BM SPSS Statistics for Windows, Version 23.0 (IBM Corp, Armonk, NY).

RESULTS

Participants

Between October 2020 and June 2022, 1002 participants were enrolled and randomized in a 1:1 ratio to the 1L-PEGA group (n = 501) or the SPMC group (n = 501) and were included in main ITT analysis. After excluding participants lost to follow-up (1L-PEGA, 6; SPMC, 17) and those not completing bowel cleansing (1L-PEGA, 45; SPMC, 6), 928 individuals were maintained in the PP analysis (1L-PEGA, 450; SPMC, 478). Study flow of participants is reported in Figure 1. Baseline characteristics of subjects were similar in both groups (Table 1).

Primary outcome: ADR

There was not a statistically significant trend (RR, .95; 95% CI, .85-1.06) for a higher pooled ADR in the SPMC group (56.5%; 95% CI, 52.1-60.8) compared with the 1L-PEGA group (53.7%; 95% CI, 49.3-58.0). As shown in Figure 2, SPMC showed noninferiority in terms of ADR compared with 1L-PEGA in the ITT analysis (difference, 2.8%; 2-sided 95% LCL, –3.4%). The PP analysis showed similar results (Supplementary Fig. 1, available online at www.giejournal.org).

Lesion detection

The number of CRCs diagnosed was 12 (2.4%; 95% CI, 1.3-4.0) in the 1L-PEGA group and 16 (3.2%; 95% CI, 1.9-5.0) in the SPMC group ($P = .41$). The lesion detection rate (1L-PEGA, 65.1% [95% CI, 60.8-69.1]; SPMC, 67.1% [95% CI, 62.9-71.1]; $P = .505$) and advanced lesion detection rate (1L-PEGA, 22.2% [95% CI, 18.7-25.9]; SPMC, 23.6% [95% CI, 20.0-27.4]; $P = .59$) were similar in both groups. As shown in Table 2, no differences were found in the mean number of lesions per patient between the 2 study groups after stratification by size, location, and histology, except for the mean number of proximal serrated lesions, which was higher in the 1L-PEGA group compared with the SPMC group (.32 ± 1.00 [95% CI, .22-.41] vs .23 ± .82 [95% CI, .16-.31], respectively; $P = .034$).

Bowel preparation

The 1L-PEGA group presented with higher BBPS scores, both in total and per segment, than the SPMC group (Table 3). Interestingly, the 1L-PEGA group presented excellent preparations (defined as BBPS of 3 in all segments) more frequently than the SPMC group (57.3% vs 33.9%, respectively; RR, 1.69; 95% CI, 1.46-1.95; $P < .001$) (Table 3). The PP analysis showed similar results (Supplementary Table 1, available online at www.giejournal.org).

Cecal intubation

The rate of cecal intubation was 98.4% in the 1L-PEGA group and 94.8% in the SPMC group (RR, 1.04; 95% CI, 1.01-1.06; $P < .05$). The causes for nonintubation in the individuals who underwent colonoscopy were obstructive CRC (n = 1) and intraprocedural bronchoaspiration (n = 1) in 2 individuals from the 1L-PEGA group and obstructive CRC (n = 2), inadequate bowel preparation and fixation of intestinal loops (n = 1), and inadequate bowel preparation (n = 7) in 10 individuals from the SPMC group.

Safety

The nonserious TEAEs in both groups are shown in Table 4. There were 486 responders in the 1L-PEGA group and 476 in the SPMC group. Generally, individuals in the 1L-PEGA group presented more frequently with nonserious TEAEs than those in the SPMC group, and these differences were more obvious for the second dose where almost half of the individuals presented with any TEAEs with 1L-PEGA. One individual presented serious TEAEs after taking the first dose of 1L-PEGA. The subject was a 59-year-old man, weighing 76 kg and 170 cm tall, with no significant medical history or regular medication use. The evening before his colonoscopy, he prepared a 1-L dose of PEGA mixed with half a liter of water that he consumed over 20 minutes. Following instructions, he drank 250 mL every 15 minutes and then additional fluids. He experienced dizziness, cold sweats, nausea, and briefly lost consciousness, leading to a fall and injuries to his forearm and left shoulder. The second dose, taken the morning of the colonoscopy, was well tolerated. Later that afternoon, he reported pain and was diagnosed with traumatic tendinopathy of the left supraspinatus. This adverse event was reported to the Clinical Trial Unit, which decided it was not necessary to notify any official organization.

Tolerability and satisfaction

Most participants were able to drink the entire bowel preparation. However, 9 of 485 participants (1.9%) in the 1L-PEGA group and 3 of 476 (.6%) in the SPMC group were not able to completely ingest the first dose ($P = .09$), whereas 42 of 483 participants (8.7%) in the 1L-PEGA group and 5 of 476 (1.1%) in the SPMC group were not able to finish the second dose ($P < .001$). The occurrence of nonserious TEAEs related to the laxative in the 42 subjects from the 1L-PEGA group was the reason for not completing the second dose. Considering that some subjects experienced multiple adverse effects, the detailed breakdown is as follows: nausea, 31 subjects; vomiting, 11 subjects; abdominal swelling, 6 subjects; chills, 3 subjects; dizziness, 3 subjects; abdominal pain, 2 subjects; headache, 2 subjects; very bad taste, 3 subjects; bad smell, 1 subject; disgust with the preparation, 1 subject. These

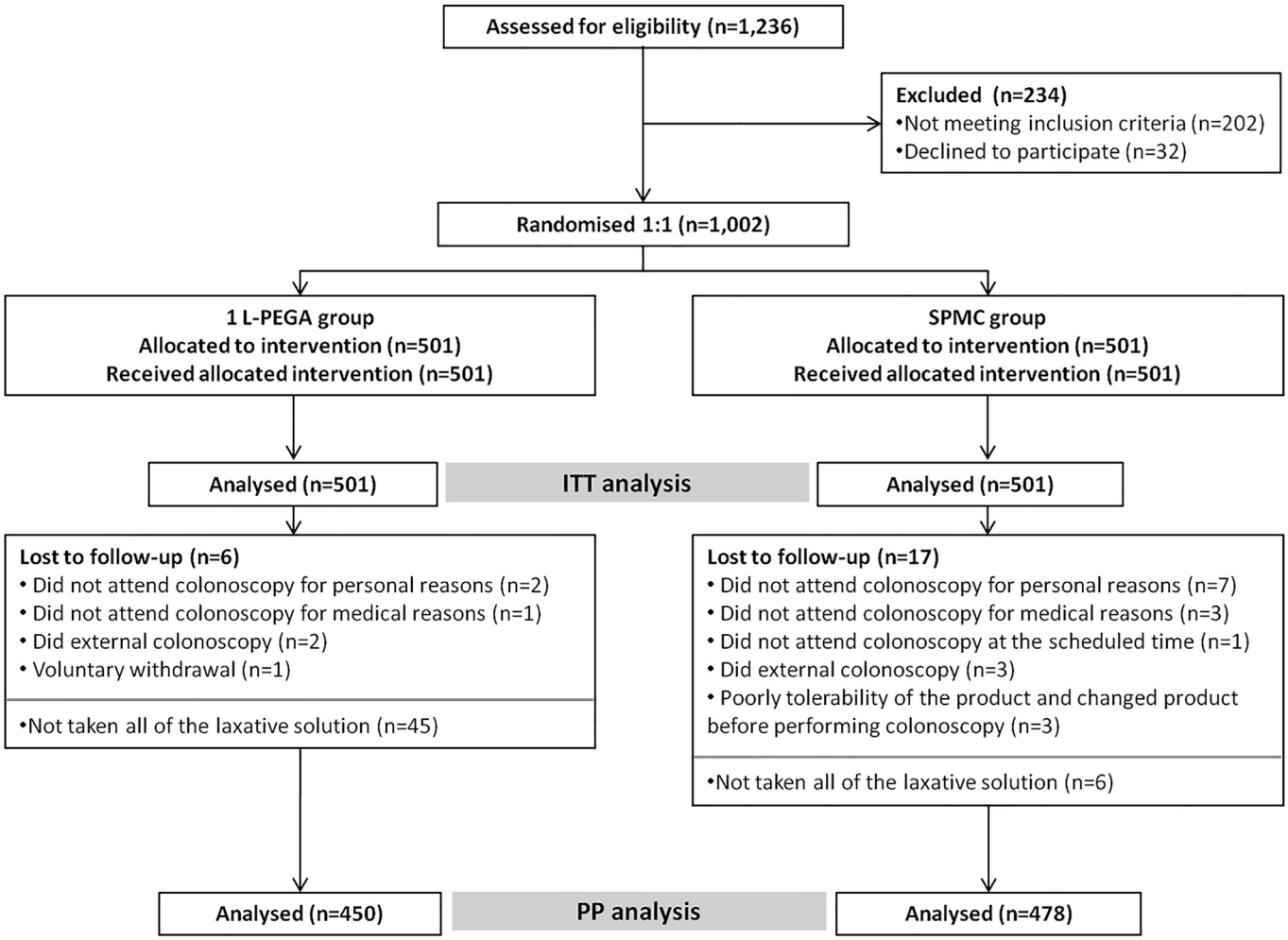

Figure 1. Study flowchart. 1L-PEGA, 1 L of polyethylene glycol plus ascorbate; *SPMC*, Sodium picosulfate with magnesium citrate; *ITT*, intention-to-treat; *PP*, per-protocol.

adverse events significantly impacted the subjects' ability to ingest the entire dose, thus leading to incomplete consumption.

In the first dose, 27.2% of participants (131/481) in the 1L-PEGA group and .2% (1/475) in the SPMC group indicated that the taste of the laxative solution was bad or very bad ($P < .001$). These data increased considerably in the second dose, with 46.9% of participants (223/475) in the 1L-PEGA group and .6% (3/472) in SPMC group ($P < .001$).

Almost 1 of 5 individuals (87/448; 19.4%) in the 1L-PEGA group indicated that they would not be willing to repeat with the same product, whereas in the SPMC group only 2.2% (10/462) provided that same answer ($P < .001$). Moreover, 22.5% of participants (106/471) in the 1L-PEGA group and .9% (4/463) in the SPMC group ($P < .001$) indicated the solution was very difficult or difficult to drink.

DISCUSSION

To our knowledge, this is the first randomized controlled trial comparing 1L-PEGA and SPMC administered in split doses in a population-based, organized, iFOBT-based CRC screening program and considering ADR as the main endpoint. According to our results, both ultra-low-volume bowel preparation products had similar clinical efficiency in detecting neoplastic lesions. However, 1L-PEGA showed advantages in terms of bowel preparation quality, with a higher proportion of adequate and excellent preparations compared with SPMC. On the other hand, 1L-PEGA was associated with more nonserious TEAEs and lower individual satisfaction compared with SPMC.

Although adequate bowel preparation serves as a surrogate marker for lesion detection during colonoscopy, the primary goal of a screening program is to prevent CRC, not solely to achieve excellent bowel preparation. A high-quality bowel preparation enhances the likelihood of detecting lesions, but ADR directly correlates with the program's effectiveness in identifying precancerous lesions, guiding future policy decisions and resource allocation. Therefore, prioritizing ADR as our primary outcome measure provides robust evidence on the screening program's effectiveness in preventing CRC. Although higher rates of

TABLE 1. Baseline demographic and clinical characteristics of participants

	1 L Polyethylene glycol plus ascorbate (n = 501)	Sodium picosulfate with magnesium citrate (n = 501)
Male	262 (52.3)	269 (53.7)
Female	239 (47.7)	232 (46.3)
Age, y	60.0 (55.0-65.0)	60.0 (55.0-65.0)
Body mass index, kg/m^2	26.0 (23.0-29.0)	26.0 (23.0-30.0)
Previous colonoscopy with inadequate bowel preparation	18 (3.6)	11 (2.2)
Diverticulosis at study colonoscopy	190 (37.9)	182 (36.3)
Any comorbidities	230 (45.9)	239 (47.7)
Hypertension	93 (40.4)	84 (35.1)
Diabetes	10 (4.3)	6 (2.5)
Stroke	0 (.0)	6 (2.5)
Cirrhosis	0 (.0)	1 (.4)
Abdominal/pelvic surgery	75 (32.6)	71 (29.7)
Any medical treatment	94 (18.8)	101 (20.2)
Opioids	9 (9.6)	4 (4.0)
Tricyclic antidepressants	24 (25.5)	15 (14.9)
Calcium antagonists	24 (25.5)	32 (31.7)
Calcium supplements	19 (20.2)	26 (25.7)
Oral iron supplements	3 (3.2)	4 (4.0)
Antiepileptics	1 (1.1)	5 (5.0)
Antipsychotics	4 (4.3)	1 (1.0)
Use of laxatives	66 (13.2)	64 (12.8)
Frequency of laxatives use		
Every day	39 (59.1)	29 (45.3)
Al least once a week	11 (16.7)	17 (26.6)
Al least once a month	5 (7.6)	10 (15.6)
Very occasionally	11 (16.7)	8 (12.5)
Bristol stool form scale		
Types 1-2	42 (8.4)	45 (9.0)
Types 3-4	400 (79.8)	405 (80.8)
Types 5-6	54 (10.8)	50 (10.0)
Type 7	5 (1.0)	1 (.2)
Any Rome IV criteria		
Presence of ≥2 criteria	33 (6.6)	38 (7.6)
Presence of <2 criteria	468 (93.4)	463 (92.4)

Values are median (interquartile range) or n (%). The Bristol stool form scale is a validated tool that assesses stool consistency on a spectrum of 7 types: type 1, separate hard lumps; type 2, lumpy and sausage-like; type 3, sausage shape with cracks in the surface; type 4, like a smooth, soft sausage or snake; type 5, soft blobs with clearcut edges; type 6, mushy consistency with ragged edges; type 7, liquid consistency with no solid pieces. Rome IV criteria is used to diagnose functional constipation, and subjects must have had ≥2 of the following symptoms in the last 3 months (with onset at least 6 months prior): straining >25% of defecations, lumpy or hard stools (Bristol stool form scale type 1 or 2) >25% of defecations, sensation of incomplete evacuation more than one-fourth (25%) of defecations, sensation of anorectal obstruction/blockage more than one-fourth (25%) of defecations, manual maneuvers to facilitate more than one-fourth (25%) of defecations, or <3 spontaneous bowel movements.

adequate bowel preparation may theoretically enhance lesion detection and reduce CRC incidence, the magnitude of this effect and its clinical significance remain uncertain.[17] Factors such as lesion characteristics, patient demographics, and procedural expertise also influence CRC prevention outcomes. In that sense, it has been shown that a BBPS score of 2 per bowel segment was noninferior to segmental cleansing scores of 3 in the detection of lesions > 5 mm, whereas a higher level of cleansing (overall BBPS score 7 to 9 or individual segmental score of 3; stool-free) was needed to improve the detection of sessile serrated lesions.[18] On the contrary, in a post-hoc combined

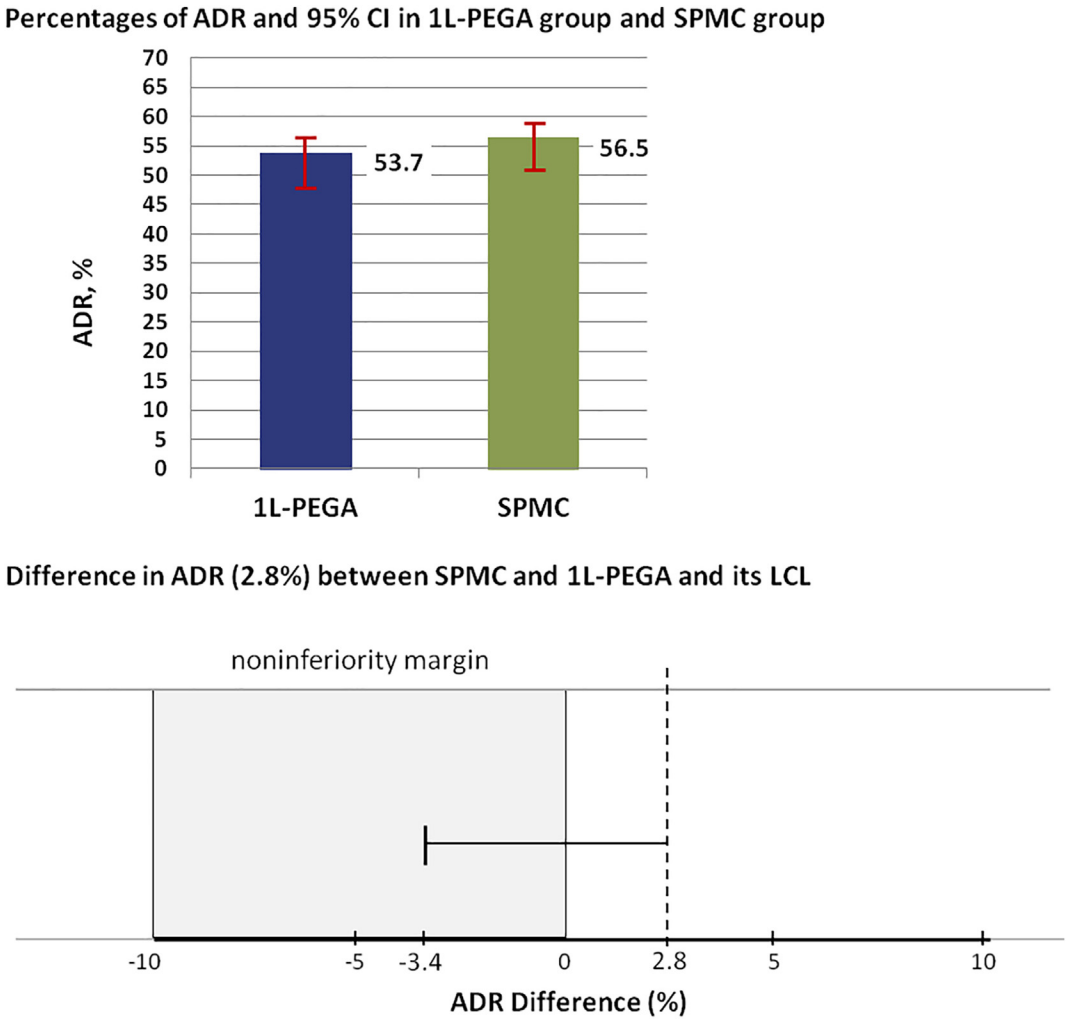

Figure 2. In the intention-to-treat analysis, the pooled adenoma detection rate (ADR) tended to be higher in the sodium picosulfate with magnesium citrate (SPMC) group compared with the 1 L of polyethylene glycol plus ascorbate (1L-PEGA) group, and SPMC showed noninferiority in ADR compared with 1L-PEGA because the LCL of the 2-sided 95% CI for the ADR difference between SPMC and 1L-PEGA met the criteria for noninferiority (at least –10%). *LCL*, Lower confidence limit; *CI*, confidence interval.

analysis of 3 randomized trials, it was shown that high-quality cleansing, in comparison with an adequate level, was associated with an increased ADR.[19] Therefore, further research is warranted to elucidate the precise relationship between bowel preparation quality and CRC prevention, particularly in the context of incremental improvements beyond the 90% threshold.

Our study found no significant differences in the detection of adenomas irrespective of size, morphology, or location in both the ITT and PP analyses. However, as previously shown,[18] we identified a higher number of proximal serrated lesions in the 1L-PEGA group, suggesting that excellent bowel preparation might have a clinical impact in the detection of flat and subtle polyps. Interestingly, the rate of adequate bowel preparation and ADR in our study was much higher than those reported in previous randomized controlled trials.[10,14] This is probably because the study was performed inside an organized, population-based screening program that has been running for more than 10 years and where a dedicated nurse does a precolonoscopy visit where she explains the bowel preparation. In this sense, the results from previous studies summarized in a recent meta-analysis[10] and showing adequate bowel preparation in only 75.2% and 82.9% of individuals using SPMC and 1L-PEGA, respectively, might not be applicable in the setting of a screening program that complies with all quality standards of care.

Interestingly, despite a high cecal intubation rate that was similar in both groups, the absolute numbers of incomplete colonoscopies in both groups (2 in the 1L-PEGA group and 10 in the SPMC group) were surprisingly different. Of note, 8 of the 10 incomplete colonoscopies in the SPMC group were related to poor bowel preparation, whereas none was related to poor bowel preparation in the 1L-PEGA group. We ruled out possible confounding factors such as age, medication, difficult colon, diverticulum, and so on that

TABLE 2. Mean number of lesions per patient

	1 L Polyethylene glycol plus ascorbate (n = 501)	Sodium picosulfate with magnesium citrate (n = 501)	*P* value
Total polyps	2.18 ± 3.02 (1.91-2.44)	2.18 ± 3.79 (1.85-2.51)	.865
Adenomas	1.39 ± 2.15 (1.20-1.58)	1.42 ± 2.24 (1.22-1.61)	.773
Advanced adenomas	.29 ± .63 (.24-.35)	.32 ± .00 (.25-.38)	.628
Flat adenomas*	.53 ± 1.18 (.43-.63)	.42 ± 1.24 (.31-.53)	.100
Proximal† adenomas	.68 ± 1.28 (.26-.50)	.77 ± 1.74 (.26-.50)	.631
Serrated lesions	.60 ± 1.57 (.47-.74)	.59 ± 2.16 (.40-.78)	.100
Advanced serrated lesions	.07 ± .33 (.04-.09)	.11 ± .71 (.05-.17)	.409
Proximal† advanced serrated lesions	.05 ± .28 (.02-.07)	.06 ± .34 (.03-.09)	.732
Proximal† serrated lesions	.32 ± 1.00 (.22-.41)	.23 ± .82 (.16-.31)	.034
Serrated lesions ≥5 mm	.33 ± 1.00 (.23-.42)	.35 ± 1.55 (.21-.48)	.381
Sessile serrated polyps	.20 ± 1.17 (.10-.30)	.20 ± 1.23 (.09-.30)	.740
Hyperplastic polyps	.40 ± .97 (.32-.48)	.38 ± 1.38 (.26-.50)	.176
Hyperplastic polyps ≥10 mm located in rectosigmoid colon	.00 ± .04 (–.00 to .01)	.02 ± .37 (–.01 to .06)	.101

Values are mean ± standard deviation (95% confidence interval).
*Morphology 0-IIa, 0-IIb, or 0-IIc according to the Paris classification.
†Proximal to the splenic flexure.

TABLE 3. Bowel preparation according to the BBPS

	1 L Polyethylene glycol plus ascorbate (n = 501)	Sodium picosulfate with magnesium citrate (n = 501)	Relative risk (95% confidence interval) of 1 L polyethylene glycol plus ascorbate vs sodium picosulfate with magnesium citrate	*P* value
Adequate bowel preparation (BBPS ≥2 of each segment)	482 (96.2)	447 (89.2)	1.08 (1.04-1.12)	<.001
Adequate bowel preparation (by segments)				
Right-sided colon	487 (97.2)	458 (91.4)	1.06 (1.03-1.10)	<.001
Transverse colon	486 (97.0)	463 (92.4)	1.05 (1.02-1.08)	<.01
Left-sided colon	487 (97.2)	459 (91.6)	1.06 (1.03-1.09)	<.001
High-quality bowel preparation (BBPS = 3 of each segment)	287 (57.3)	170 (33.9)	1.69 (1.46-1.95)	<.001
High-quality bowel preparation (by segments)				
Right-sided colon	346 (69.1)	221 (44.1)	1.57 (1.40-1.76)	<.001
Transverse colon	365 (72.9)	254 (50.7)	1.44 (1.30-1.59)	<.001
Left-sided colon	343 (68.5)	219 (43.7)	1.57 (1.40-1.76)	<.001

Values are n (%) unless otherwise defined.
BBPS, Boston Bowel Preparation Scale.

could explain those differences (data not shown). Although the numbers remain marginal, we consider this finding clinically meaningful because up to 6% of individuals with a positive iFOBT might have CRC, and incomplete colonoscopy would delay the diagnosis and increase costs because of rescheduling the examination.[4,5]

On the other hand, with respect to nonserious TEAEs, 1L-PEGA caused significantly more nausea, abdominal bloating and gas, dizziness, sleep interruption, dry mouth, and bad taste than SPMC. When analyzing separately the second dose, these differences were more pronounced, and, in fact, up to 45% of individuals presented nausea and 14.7% did vomit. Indeed, the second dose of 1L-PEGA contains high concentrations of ascorbic acid, which is a compound that can produce undesirable GI effects such as nausea and vomiting. Efforts in the posology have been made to improve the tolerability and reduce the TEAEs of this second dose (eg, ingesting the product

TABLE 4. Laxative nonserious treatment-emergent adverse events observed in the treatment groups and in each dose

	1L-PEGA (n = 486)*	SPMC (n = 476)*	Relative risk (95% CI)		1L-PEGA (n = 486)*	SPMC (n = 476)*	Relative risk (95% CI)	
	First dose		1L-PEGA vs SPMC	*P* value	Second dose		1L-PEGA vs SPMC	*P* value
Nausea	134/464 (28.9)	42/464 (9.1)	3.19 (2.31-4.40)	<.001	208/462 (45.0)	57/452 (12.6)	3.57 (2.75-4.64)	<.001
Vomiting	10/460 (2.2)	3/463 (.7)	3.36 (.93-12.11)	<.05	66/450 (14.7)	8/450 (2.0)	7.38 (3.73-14.63)	<.001
Abdominal pain	139/467 (29.8)	117/464 (25.2)	1.18 (.96-1.46)	.120	125/459 (27.2)	70/452 (15.5)	1.76 (1.35-2.29)	<.001
Abdominal bloating or gas	235/468 (50.2)	188/466 (40.3)	1.25 (1.08-1.44)	<.01	219/460 (47.6)	141/453 (31.1)	1.53 (1.29-1.81)	<.001
Dizziness	35/468 (7.5)	34/463 (7.3)	1.02 (.65-1.60)	.937	88/458 (19.2)	31/452 (6.9)	2.80 (1.90-4.13)	<.001
Headache	62/466 (13.3)	66/463 (14.3)	.93 (.68-1.29)	.674	96/459 (20.9)	81/451 (18.0)	1.17 (.89-1.52)	.260
Interrupted the night's rest	141/439 (32.1)	210/449 (46.8)	.69 (.58-.81)	<.001	105/420 (25.0)	129/424 (30.4)	.82 (.66-1.02)	.078
Shaking chills	105/465 (22.6)	93/462 (20.1)	1.12 (.88-1.44)	.363	127/458 (27.7)	82/451 (18.2)	1.53 (1.19-1.95)	<.01
Dry mouth	139/464 (30.0)	97/462 (21.0)	1.43 (1.14-1.79)	<.01	199/464 (42.9)	98/452 (21.7)	1.98 (1.61-2.43)	<.001
Bad mouth taste	141/464 (30.4)	55/461 (11.9)	2.55 (1.92-3.39)	<.001	189/464 (40.7)	61/450 (13.6)	3.01 (2.32-3.89)	<.001

Values are n/N (%) unless otherwise defined.
1L-PEGA, 1 L Polyethylene glycol plus ascorbate; *SPMC*, sodium picosulfate with magnesium citrate; *CI*, confidence interval.
*Values in parentheses represent the number of responders to the safety, tolerability, and satisfaction questionnaire shown in Appendix 1.

slowly, in small volumes combined with clear fluids). However, when asking about solution taste, almost half of those who took the second dose of 1L-PEGA rated it as bad or very bad. Furthermore, almost one-fourth of subjects in the 1L-PEGA group defined the solution as very difficult or difficult to drink compared with <1% in the SPMC group, and individuals in the 1L-PEGA group would not choose the same laxative product for further colonoscopy 10 times more frequently than those in the SPMC group. Unfortunately, the higher incidence of nonserious TEAEs and the poor palatability of the laxative product might interfere in the compliance with screening and postpolypectomy surveillance. Therefore, considering the excellent profile of 1L-PEGA in terms of quality preparation, it would be worth investing in improving the palatability and tolerance of the second dose.[20]

Overall, in view of our results, whereas 1L-PEGA may be preferred for maximizing lesion detection and ensuring a complete examination during a patient's first screening colonoscopy, SPMC may be the product of choice for those prioritizing tolerance, given our findings indicating it is not associated with a lower ADR. However, when both products demonstrate good ADR and overall effectiveness, decision-making becomes challenging, especially considering individual patient factors. Healthcare providers, like nurses, play a crucial role in gathering comprehensive patient information, tailoring bowel preparation choices to each patient's specific needs and characteristics. It is important to acknowledge the potential for bias in decision-making based solely on patient factors, necessitating a balanced approach. Ongoing monitoring and evaluation of patient outcomes can guide future refinements in protocol, whereas transparent communication between healthcare providers and patients is essential for promoting trust and satisfaction in the screening process.

Limitations of our study include that it was carried out in a single center with high quality standards and a precolonoscopy visit by a specialized nurse, which might not be generalizable to other settings. However, most organized, population-based iFOBT screening programs have very similar characteristics, thus rendering the information provided in our study especially valuable in this setting.

In conclusion, split-dosing SPMC showed noninferiority in ADR compared with split-dosing 1L-PEGA. Moreover, although bowel preparation quality was significantly better with 1L-PEGA both overall and per colon segments, participant safety, tolerability, and satisfaction were higher with SPMC.

DISCLOSURE

The following authors disclosed financial relationships: A. Serradesanferm: Research support from Beca d'Intensificació Clínic. R. Moreira: Research support from Programa d'impuls del talent i de l'ocupabilitat del PERIS 2016-2020, Generalitat de Catalunya, Departament de Salut, SLT017/20/000179. A. Castells: Research support from Fundación Científica de la Asociación Española contra el Cáncer and Universal Diagnostics; consultant for Goodgut, Amadix, and iVascular; speaker for Medial EarlySign and Abbvie. M. Pellisé: Research support from Fujifilm Spain, ZiuZ, and Casen Recordati; speaker for Fujifilm, Olympus, Medtronic, Norgine, Alphasigma, Mayoli, and Casen Recordati. All other authors disclosed no financial relationships. Research support for this study was provided by Casen Recordati. Research support for this study was provided by Casen Recordati, S.L., Spain.

ACKNOWLEDGMENT

We thank our GI service nurses, endoscopy nurses, and medical staff who have helped with data collection.

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Abbreviations: 1L-PEGA, 1 L of polyethylene glycol plus ascorbate; ADR, adenoma detection rate; BBPS, Boston Bowel Preparation Scale; CI, confidence interval; CRC, colorectal cancer; iFOBT, immunochemical fecal occult blood test; ITT, intention-to-treat; LCL, lower confidence limit; PEG, polyethylene glycol; PP, per-protocol; RR, relative risk; SED, standard error of the difference; SPMC, sodium picosulfate with magnesium citrate; TEAE, treatment-emergent adverse event.

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0016-5107
https://doi.org/10.1016/j.gie.2024.07.007

Received February 16, 2024. Accepted July 5, 2024.

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APPENDIX 1

Safety, tolerability, and satisfaction questionnaire

CLÍNIC BARCELONA Hospital Universitari

LOWOL STUDY
Código de identificación del participante: _____

Eficacia y tolerabilidad de dos productos de volumen reducido para la colonoscopia de cribado de cáncer colorrectal: Ensayo comparativo paralelo aleatorizado. Lowol Study.

1

1ª TOMA DE SOLUCIÓN LAXANTE (noche anterior a la colonoscopia)

Una vez finalizada la 1ª toma de la solución laxante, conteste el cuestionario referente a la **1ª toma** marcando con una cruz (x) la respuesta que crea más oportuna.

FECHA EN LA QUE RELLENA ESTA PARTE DEL CUESTIONARIO: ____/____/_____

1) ¿Ha tomado toda la solución laxante?

☐ Sí ☐ No

2) ¿En caso de NO haber tomado toda la solución laxante, indique cuál ha sido el motivo? (puede *marcar varias opciones*):

☐ Náuseas ☐ Vómitos ☐ Dolor abdominal ☐ Hinchazón abdominal

☐ Mareos ☐ Escalofríos ☐ Boca seca ☐ Dolor de cabeza

☐ Otros: _____

3) ¿Cuánta cantidad de solución laxante NO se ha podido tomar?

_____ mL (un vaso lleno equivale a 250 mL)

4) ¿En cuánto tiempo se ha tomado la solución laxante? _____

5) Una vez terminada la solución laxante, ¿cuánto tiempo ha tardado en empezar a ir de vientre? _____

6) Tipo de líquido adicional bebido después de la 1ª toma de la solución laxante:

☐ Caldos colados ☐ Agua ☐ Zumos colados ☐ Té/Infusiones

☐ Bebidas isotónicas (Isostar®/Aquarius®) ☐ Otros líquidos claros

7) Cantidad de líquido adicional que ha tomado después de la 1ª toma de la solución laxante:

☐ Menos de medio litro

☐ Medio litro

☐ De medio litro a 1 litro

☐ 1 litro

☐ De 1 litro a 1'5 litros

☐ 1'5 litros

☐ Más de 1'5 litros

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8) Valore el sabor del producto:

☐ Pésimo ☐ Malo ☐ Aceptable ☐ Bueno ☐ Excelente

9) Valore la disolución del producto, es decir, la facilidad con que el polvo se ha mezclado con el agua:

☐ Pésima ☐ Mala ☐ Aceptable ☐ Buena ☐ Excelente

10) Marque con una cruz si ha experimentado alguno de los siguientes efectos adversos:

- **Náuseas**
  ☐ No ☐ Leve ☐ Bastante ☐ Intenso
- **Vómitos**
  ☐ No ☐ Leve ☐ Bastante ☐ Intenso
- **Dolor abdominal**
  ☐ No ☐ Leve ☐ Bastante ☐ Intenso
- **Hinchazón abdominal, distensión abdominal o gases**
  ☐ No ☐ Leve ☐ Bastante ☐ Intenso
- **Mareos**
  ☐ No ☐ Leve ☐ Bastante ☐ Intenso
- **Dolor de cabeza**
  ☐ No ☐ Leve ☐ Bastante ☐ Intenso
- **El efecto de la solución laxante ha interrumpido mi descanso nocturno**
  ☐ No ☐ Leve ☐ Bastante ☐ Intenso
- **Escalofríos**
  ☐ No ☐ Leve ☐ Bastante ☐ Intenso
- **Boca seca**
  ☐ No ☐ Leve ☐ Bastante ☐ Intenso
- **Mal sabor de boca**
  ☐ No ☐ Leve ☐ Bastante ☐ Intenso

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2ª TOMA DE SOLUCIÓN LAXANTE (mismo día de la colonoscopia)

2

Una vez finalizada la 2ª toma de la solución laxante, conteste el cuestionario referente a la **2ª toma** y la **Valoración global de todo el proceso**.

FECHA EN LA QUE RELLENA ESTA PARTE DEL CUESTIONARIO: _____/_____/_____

1) ¿Ha tomado toda la solución laxante?

☐ Sí ☐ No

2) ¿En caso de NO haber tomado toda la solución laxante, indique cuál ha sido el motivo? *(puede marcar varias opciones)*:

☐ Náuseas ☐ Vómitos ☐ Dolor abdominal ☐ Hinchazón abdominal

☐ Mareos ☐ Escalofríos ☐ Boca seca ☐ Dolor de cabeza

☐Otros: _____

3) ¿Cuánta cantidad de solución laxante NO se ha podido tomar?

_____ mL (un vaso lleno equivale a 250 mL)

4) ¿En cuánto tiempo se ha tomado la solución laxante? _____

5) Una vez terminada la solución laxante, ¿cuánto tiempo ha tardado en empezar a ir de vientre? _____

6) Tipo de líquido adicional bebido después de la 2ª toma de la solución laxante:

☐ Caldos colados ☐ Agua ☐ Zumos colados ☐ Té/Infusiones

☐ Bebidas isotónicas (Isostar®/Aquarius®) ☐ Otros líquidos claros

7) Cantidad de líquido adicional que ha tomado después de la 2ª toma de la solución laxante:

☐ Menos de medio litro

☐ Medio litro

☐ De medio litro a 1 litro

☐ 1 litro

☐ De 1 litro a 1'5 litros

☐ 1'5 litros

☐ Más de 1'5 litros

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8) **Valore el sabor del producto:**

☐ Pésimo ☐ Malo ☐ Aceptable ☐ Bueno ☐ Excelente

9) **Valore la disolución del producto, es decir, la facilidad con que el polvo se ha mezclado con el agua:**

☐ Pésima ☐ Mala ☐ Aceptable ☐ Buena ☐ Excelente

10) **Marque con una cruz si ha experimentado alguno de los siguientes efectos adversos:**

- **Náuseas**
  ☐ No ☐ Leve ☐ Bastante ☐ Intenso
- **Vómitos**
  ☐ No ☐ Leve ☐ Bastante ☐ Intenso
- **Dolor abdominal**
  ☐ No ☐ Leve ☐ Bastante ☐ Intenso
- **Hinchazón abdominal, distensión abdominal o gases**
  ☐ No ☐ Leve ☐ Bastante ☐ Intenso
- **Mareos**
  ☐ No ☐ Leve ☐ Bastante ☐ Intenso
- **Dolor de cabeza**
  ☐ No ☐ Leve ☐ Bastante ☐ Intenso
- **El efecto de la solución laxante ha interrumpido mi descanso nocturno**
  ☐ No ☐ Leve ☐ Bastante ☐ Intenso
- **Escalofríos**
  ☐ No ☐ Leve ☐ Bastante ☐ Intenso
- **Boca seca**
  ☐ No ☐ Leve ☐ Bastante ☐ Intenso
- **Mal sabor de boca**
  ☐ No ☐ Leve ☐ Bastante ☐ Intenso

Página 4 de 5

VALORACIÓN GLOBAL DE TODO EL PROCESO

1) **¿Ha tomado Primperan® para evitar los vómitos durante la preparación?**

   ☐ Sí

   ☐ No

2) **En caso de haber tomado Primperan®, ¿cuándo lo ha tomado?**

   ☐ Antes o una vez empezada la 1ª toma de la solución laxante

   ☐ Antes o una vez empezada de la 2ª toma de la solución laxante

3) **¿Cómo valora la toma de la solución laxante?**

   ☐ Muy difícil ☐ Difícil ☐ Aceptable ☐ Fácil

4) **Basado en su experiencia actual: si tuviera que realizarse una colonoscopia en el futuro, ¿repetiría la misma solución laxante?**

   ☐ Sí

   ☐ No

   Especificar el motivo: _____

MUCHAS GRACIAS POR SU COLABORACIÓN

- **NOTA IMPORTANTE:**

  Entregue este cuestionario al personal de enfermería que le atienda en el Servicio de Endoscopia el mismo día de la colonoscopia.

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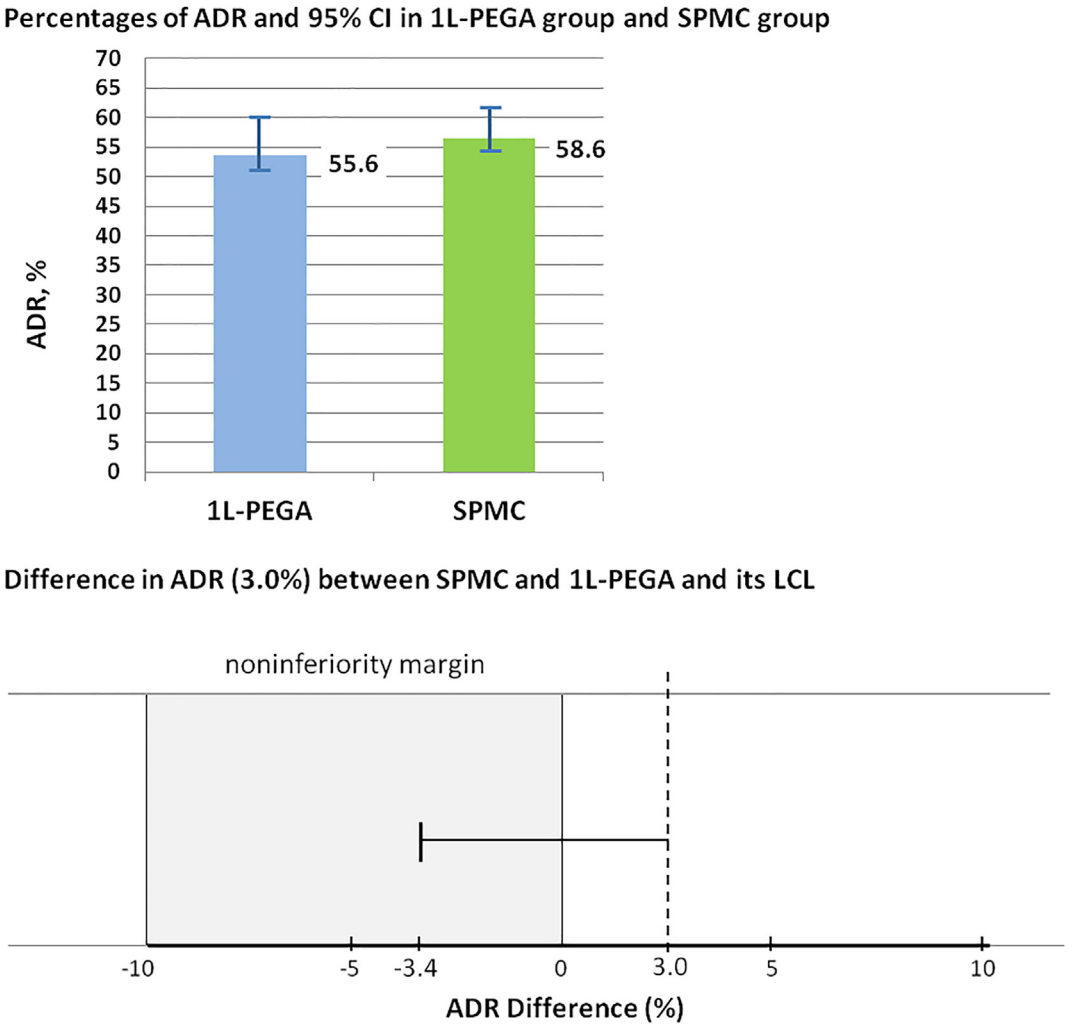

Supplementary Figure 1. In the per-protocol analysis, the pooled adenoma detection rate (ADR) tended to be higher in the sodium picosulfate with magnesium citrate (SPMC) group compared with the 1 L of polyethylene glycol plus ascorbate (1L-PEGA) group, and SPMC showed noninferiority in ADR compared with 1L-PEGA because the LCL of the 2-sided 95% CI for the ADR difference between SPMC and 1L-PEGA met the criteria for noninferiority (at least −10%). *LCL*, Lower confidence limit; *CI*, confidence interval.

SUPPLEMENTARY TABLE 1. Preparation bowel according to the BBPS in the per-protocol analysis

	1 L Polyethylene glycol plus ascorbate (n = 450)	Sodium picosulfate with magnesium citrate (n = 478)	Relative risk (95% confidence interval) of 1 L polyethylene glycol plus ascorbate vs sodium picosulfate with magnesium citrate	*P* value
Adequate bowel preparation (BBPS ≥2 of each segment)	440 (97.8)	441 (92.3)	1.06 (1.03-1.09)	<.001
Adequate bowel preparation (by segments)				
Right-sided colon	443 (98.4)	451 (94.4)	1.04 (1.02-1.07)	<.01
Transverse colon	443 (98.4)	457 (95.6)	1.03 (1.01-1.05)	<.05
Left-sided colon	443 (98.4)	452 (94.6)	1.04 (1.02-1.07)	<.01
High-quality bowel preparation (BBPS = 3 of each segment)	262 (58.2)	167 (34.9)	1.67 (1.44-1.93)	<.001
High-quality bowel preparation (by segments)				
Right-sided colon	312 (69.3)	216 (45.2)	1.53 (1.37-1.72)	<.001
Transverse colon	331 (73.6)	250 (52.3)	1.41 (1.27-1.56)	<.001
Left-sided colon	314 (69.8)	215 (45.0)	1.55 (1.38-1.74)	<.001

Values are n (%) unless otherwise defined.
BBPS, Boston Bowel Preparation Scale.