Effective bowel cleansing before colonoscopy: a randomized study of split-dosage versus non-split dosage regimens of high-volume versus low-volume polyethylene glycol solutions (CME)

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Background: Adequate bowel cleansing is essential for a high-quality, effective, and safe colonoscopy.

Objectives: To evaluate the degree of colon cleansing comparing split-dosage versus non-split-dosage intake of two different polyethylene glycol (PEG) volumes (low-volume PEG + ascorbic acid vs standard-volume PEG-electrolyte solution) and to identify predictors of poor bowel cleansing.

Design: Single-blind, active control, randomized study.

Setting: Tertiary-care institutions in Italy.

Patients: This study involved adult patients undergoing elective colonoscopy.

Intervention: Colonoscopy with different bowel preparation methods.

Main Outcome Measurements: Degree of bowel cleansing.

Results: We randomized 895 patients, and 868 patients were finally included in intention-to-treat (ITT) analysis. Overall compliance was excellent (97%) for both preparation methods. No difference in tolerability was recorded. Palatability was superior with low volume compared with high volume (acceptable or good 58% vs 51%, respectively, $P < .005$), independently of intake schedule. PEG plus ascorbic acid produced the same degree of cleansing as standard-volume PEG-electrolyte solution (77% vs 73.4%, respectively, within the split-dosage group and 41.7% vs 44.3%, respectively, within the non-split-dosage group). Independently of PEG volumes, the split-dosage regimen produced markedly superior cleansing results over the same-day method (good/excellent 327/435, 75.2% vs 186/433, 43.0%, $P = .00001$). Maximum cleansing was observed in colonoscopies performed within 8 hours from the last fluid intake versus over 8 hours from the last fluid intake ($P < .001$). The degree of bowel cleansing affected both cecal intubation (failed intubation 11.7% with fair/poor preparation vs 1.2% with good/excellent preparation, $P = .00001$) and polyp detection rates (12.2% with fair/poor vs 24.6% with good/excellent preparation, $P = .001$). Aborted procedures were significantly more frequent in the non-split-dosage arm (21.2% vs 6.9%, odds ratio [OR] 3.60 [2.29-5.77], $P < .0001$). Independent predictors of poor bowel cleansing were male sex (OR 1.45 [1.08-1.96], $P = .014$) and a non-split-dosage bowel preparation schedule (OR 2.08 [1.89-2.37], $P = .0001$).

Conclusion: Low-volume PEG plus ascorbic acid is as effective as high-volume PEG-electrolyte solution but has superior palatability. A split-dosage schedule is the most effective bowel cleansing method. Colonoscopy should be performed within 8 hours of the last fluid intake. (Gastrointest Endosc 2010;72:313-20.)

Abbreviations: ITT, intention to treat; PEG, polyethylene glycol.

DISCLOSURE: *All authors disclosed no financial relationships relevant to this publication.*

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0016-5107/$36.00
doi:10.1016/j.gie.2010.02.048

Received December 30, 2009. Accepted February 25, 2010.

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Diagnostic accuracy and therapeutic safety of colonoscopy depend on the quality of colon cleansing. Inadequate bowel preparation can result in missed lesions, aborted procedures, and increased discomfort as well as a potential increase in complication rates.[1-8] The ideal preparation for colonoscopy would reliably and rapidly empty the colon of all fecal material, with no gross or histologic alteration of the colonic mucosa. It also would not cause any patient discomfort or shifts in fluid or electrolyte balances, and it would be inexpensive.[1,2,9] Polyethylene glycol (PEG) is a nonabsorbable solution that should pass through the bowel without net absorption or secretion. Significant fluid and electrolyte balance shifts are therefore avoided. Large volumes (4 L) are required to achieve a cathartic effect.[1,10,11] When taken in divided doses, a standard 4-liter PEG volume was demonstrated to be as effective as, and better tolerated than, the bolus dose given 1 day before the procedure.[12-15] A new cleansing agent consisting of high molecular weight PEG plus ascorbic acid has been developed. The cathartic effects of ascorbic acid are thought to be due to its absorption mechanism, which becomes saturated at high doses.[16,17] Excess ascorbic acid, which cannot be absorbed, remains in the bowel, where it exerts an osmotic effect, acting synergistically with PEG. The combination of PEG plus ascorbic acid reduces the volume patients have to drink without compromising efficacy or safety.[18-21] No data are available as to the role of split-dosage intake for low-volume PEG solutions or as to the optimal duration of the interval between the completion of bowel preparation with low-volume preparations nor as to how long the split-dosage preparation remains effective.

Aims of the study were (1) to evaluate the degree of colon cleansing in patients undergoing colonoscopy, comparing the modality of administration (split vs non-split dosage) of two different volumes of PEG (low vs high); and (2) to identify predictors of poor bowel cleansing.

Take-home Message

- This study demonstrates that a split-dosage intake regimen provides the best colon cleansing, independent of the volume of polyethylene glycol (standard or low dose) and that optimal timing of colonoscopy is within 8 hours of the last fluid intake. Male patients are at higher risk of poor bowel cleansing. Procedures might be better scheduled in late morning or in the afternoon to allow for split-dosage bowel preparation, especially for male patients.

METHODS

Design of the study

This was a single-blind, active control, prospective, randomized study of adult patients undergoing routine elective colonoscopy. All patients with an appropriate indication to colonoscopy were considered eligible. Exclusion criteria were pregnant or lactating women, age less than 18 years, significant gastroparesis or gastric outlet obstruction or ileus, known or suspected bowel obstruction or perforation, phenylketonuria or glucose-6-phosphate dehydrogenase deficiency, severe chronic renal failure (creatinine clearance <30 mL/minute), severe congestive heart failure (New York Heart Association [NYHA] class III or IV), dehydration, severe acute inflammatory disease, compromised swallowing reflex or mental status, uncontrolled hypertension (systolic blood pressure ≥170 mm Hg, diastolic blood pressure ≥100 mm Hg), toxic colitis, or megacolon. These exclusion criteria are consistent with contraindications of currently approved bowel preparations; therefore, the results of this study may be generalized to the entire target population of patients undergoing colonoscopy, including the elderly.

The two products used in the study differ in components: the standard PEG solution (SELG 1000; Promefarm, Italy) is a solution of PEG 4000 plus electrolytes (sodium sulphate, sodium bicarbonate, sodium chloride, potassium chloride) and is taken diluted into 4 L of plain water (high volume), whereas the low-volume solution (Moviprep; Norgine Ltd, Harefield, UK) is composed of macrogol 3350 plus electrolytes (sodium sulphate, sodium chloride, potassium chloride) and 4.700 g ascorbic acid and is taken diluted into 2 L of plain water (low volume). The quantity per interval was 8 ounces every 15 minutes. In cases of the non-split-dosage schedule, the entire dose was administered in the evening of the day before the planned colonoscopy, taken 2 hours apart in the evening before the planned colonoscopy, starting at around 18:30 hours (that is, 1 L every 2 hours for low volume and 2 L every 2 hours for high volume). For the low-volume solution, patients were encouraged to drink at least 1 L of additional clear fluid. In cases of the split-dosage-intake schedule, half the dose (1 L of Moviprep or 2 L of SELG) was taken the afternoon before and half the dose early in the morning on the day of the colonoscopy.

The preparations were dispensed by a nurse endoscopist who carefully explained how they should be taken, emphasizing the importance of complete intake of the solution in order to ensure a safe and effective procedure. Apart from instructions, the nurse also informed the patients as to potential side effects of the preparation solution as well as the drawbacks of an aborted procedure or missed lesion.

The following dietary advice was given to patients: no fruit, legumes, or vegetables for 3 days before the procedure; on the day before colonoscopy have a light breakfast and lunch but a semiliquid dinner (clear soup, yoghurt, or compote) before taking the bowel preparation solution. For both types of preparation, no solid food was allowed from the start of the bowel preparation. All patients were

instructed to take nothing by mouth from midnight, on, before the procedure.

Randomization and blinding

Patients were enrolled by the medical personnel of the endoscopy units after assessment of appropriate indications and ruling out of any contraindications to the procedure or to the use of PEG solutions. Patients were randomly allocated to receive one of the 4 different bowel preparation regimens (split-dosage vs non-split-dosage and low vs high volume), using a centralized, computer-generated, random-number list with a permutation block size of 4, 8, 12, and 16. Patients were stratified for bowel habits (with or without constipation) by using consecutive blocks. In each block, there were serially numbered, sealed, opaque envelopes. Each patient received the next pack stored in the center, following ascending order of the labels.

Assessment of bowel preparation–scoring system

Bowel cleansing was assessed by colonoscopists who were unaware of the preparation method. For each anatomical segment of the colon, the degree of bowel cleansing was rated on a segmental scoring scale of 1 to 4 by using an inverted Ottawa scale: 4 (excellent), colon empty and clean; 3 (good), presence of clear liquid in the colon easy to aspirate; 2 (fair), presence of brown liquid or small amounts of semisolid residual stool, partially removable by suction to adequately visualize the underlying colonic mucosa; and 1 (poor), large amounts of fecal residue, not removable, with hampered visualization of the underlying mucosa. We adopted an ordinal scale directly correlated to the level of cleansing where 4 was given to the best bowel cleansing and 1 to the worst (equivalent to the "inadequate" and "poor" of the original Ottawa scale[22]).

The maximum score was, therefore, 24, and the minimum score was 6. Patients unable to tolerate their preparations or those who were not examined because of lack of bowel cleansing were considered as failures.

In order to have a satisfactory concordance (kappa index $\geq$0.60) among the personnel involved in the assessment of the degree of bowel cleansing, prior to study initiation designated observers performed a calibration exercise on 30 colonoscopies by using the scoring system adopted in the study.

Colonoscopy and endpoint measurement

On the morning of colonoscopy, immediately before the procedure, a nurse questioned each patient about his/her experience by using a standardized questionnaire composed of a set of questions with yes/no answers. Patients were asked about compliance, tolerance, additional fluid intake, acceptability, and willingness to repeat the same type of bowel preparation if necessary. The endoscopist was not allowed to listen to the questioning or to see the questionnaire at any time before colonoscopy and assessment of the degree of bowel cleansing. Colonoscopies were performed by experienced endoscopists unaware of the treatment allocation. The primary endpoint was the degree of colon cleansing. Data on palatability were collected with a 1 to 10 visual analogue scale, which was then re-coded into 4 categories (poor, fair, acceptable, or good taste) because we thought that an overall clinical judgement on the taste of the preparation would have better expressed the patients' opinions than would a numerical value. Any adverse events related to bowel preparation (nausea, vomiting, bloating, abdominal pain, headache, etc) were recorded by the questioning nurse, and all participants were monitored for adverse events during colonoscopy.

Sample size calculation and statistical analysis

We assumed that the percentage of patients with an overall good/excellent grade of cleansing in both preparation types would be 70%[12] and that 90% of patients would be evaluable. With an alpha error of 5%, a power of 90%, and an expected 10% difference in efficacy (split-dosage vs non-split-dosage) or a 5% difference in equivalency (low vs high volume), the continuity-corrected sample size would be 824 patients.

Statistics. Unpaired *t* tests and variance analysis were used for multiple comparisons for continuous data; Mann-Whitney *U* or Kruskal-Wallis tests were used for ordinal data. Categorical variables were tested by using corrected chi-square or 2-sided Fisher exact tests when appropriate. The criterion for statistical significance was $P < .05$. All calculations were made with the STATA package 10.1 (StataCorp LP, College Station, Tex). The Bonferroni correction method was used in view of multiple testing. All variables showing a significance of $< .10$ at univariate analysis were placed in a backward stepwise logistic regression model in order to identify independent predictors of poor bowel cleansing. Intention-to-treat analysis was performed.

Ethics

Ethical approval for the study was granted by the institutional review boards of participating institutions. In addition, all eligible patients were asked to sign written, informed-consent documents.

RESULTS

Study participant allocation is recorded in Figure 1. Of the 926 patients assessed for eligibility, 31 were excluded for contraindications (9 for severe chronic renal failure, 6 for age <18 years, 2 for dementia, 6 for cerebrovascular disease, and 8 for severe hypertension). A total of 895 patients were included and randomized to the split-dosage schedule (N = 448) or to the non-split-dosage schedule (N = 447). Nine patients had a major protocol deviation (2

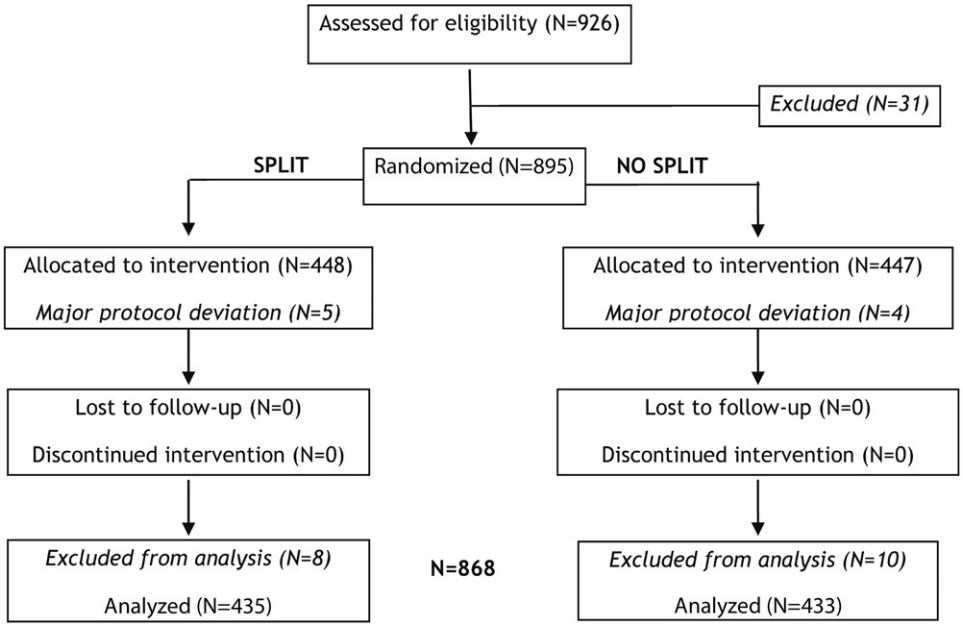

Figure 1. Study flow diagram.

patients had a double dose of PEG solution, 1 patient had his bowel preparation ended 1 day earlier than indicated, 1 patient took two different types of bowel preparation, and 5 patients drank the solution in small, fractioned doses over 24 hours). Furthermore, an additional 18 patients were excluded from analysis for incomplete data report forms as to the type of preparation used. Therefore, a total of 868 randomized patients were finally analyzed (435 in the split-dosage group and 433 in the non-split-dosage group). Study demographics are shown in Table 1.

Efficacy

Study compliance was excellent in both groups, independently of the intake schedule: complete preparation, that is, drinking of the full amount of fluid indicated, was accomplished by 96.3% of low-volume-group patients and 95.8% of high-volume-group patients in the non-split-dosage group and by 97.2% and 98.6% for both volumes, respectively, in the split-dosage group (Pearson chi-square, $P = .245$).

The split-dosage regimen produced markedly superior cleansing results over the non-split-dosage regimen (Table 2). Overall, a good/excellent degree of bowel cleansing was recorded in 75.2% of patients allocated to the split-dosage regimen versus 43.0% of patients allocated to the non-split-dosage regimen ($P = .00001$). The overall cleansing score was 20.4 (95% confidence interval [CI], 17.0-23.5) in the split-dosage group and 16.4 (95% CI, 14.2-17.7) in the non-split-dosage group ($P = .00001$). The split-dosage regimen provided a significantly superior degree of bowel cleansing in all colon segments, although the difference was highest in proximal colon segments (Fig. 2). The superiority of the split-dosage intake schedule was independent of the volume of PEG solutions. In fact, both low-volume and high-volume PEG solutions produced the same degree of cleansing: 77% versus 73.4%, respectively, within the split-dosage group ($P = .431$) and 41.7% versus 44.3%, respectively, within the non-split-dosage group ($P = .217$) (Fig. 3). The timing of bowel preparation, that is, the time elapsed between the last fluid intake and the colonoscopy, was an important factor affecting the degree of bowel cleansing. As depicted in Figure 4, the cleansing score decreased significantly after 6 to 8 hours from the last fluid intake (Fig. 4).

Tolerability

Both preparations were well-tolerated, with 511 of 868 patients (58.9%) reporting no side effects. Preparation-related symptoms of cramping, bloating, nausea, and vomiting were generally mild and infrequent. No difference in incidence and type of side effects was seen between low or high volume PEG solutions nor between split-dosage or non-split-dosage intake schedules (Table 3).

Patients randomized to the low-volume PEG plus ascorbic acid group reported a significantly superior palatability of the solution. Taste was rated as good or acceptable by 54% of patients versus 47% of those allocated to the standard PEG solution group ($P = .04$). Such a difference in the perceived taste of the preparations remained also when the split-dosage and non-split-dosage intake regimens were compared.

Other endpoints

Overall, a complete colonoscopy was achieved in 94.6% of cases (821/868). Cecal intubation failed in 47

TABLE 1. Demographic and clinical features of the study population

Feature	Split-dosage group (N = 435)		Non-split-dosage group (N = 433)		Total (N = 868)
	High volume (N = 218)	Low volume (N = 217)	High volume (N = 215)	Low volume (N = 218)	
Age, years, mean ± SD	58.2 ± 15.9	59.2 ± 14.8	57.9 ± 14.8	57.5 ± 13.8	58.3 ± 14.8
Male sex,* no. (%)	107 (49.8)	130 (54.8)	117 (54.4)	142 (65.1)	496 (57.5)
Outpatients,* no. (%)	157 (72.0)	182 (83.9)	192 (89.3)	198 (90.8)	729 (84.0)
Constipation, no. (%)	41 (19.2)	40 (18.8)	40 (18.6)	41 (18.8)	162 (19.1)
Laxative use, no. (%)	7 (3.2)	9 (4.1)	13 (6.0)	9 (4.1)	38 (4.4)
Previous abdominal surgery, no. (%)	82 (37.6)	103 (47.5)	92 (42.8)	111 (50.9)	387 (44.6)
Diabetes, no. (%)	8 (3.7)	16 (7.4)	12 (5.6)	5 (2.3)	41 (4.7)
More frequent indications to colonoscopy, no. (%)					
Symptoms (pain, hematochezia, diarrhea)	98 (44.9)	81 (37.3)	91 (42.3)	91 (41.7)	356 (41.0)
Screening	33 (15.1)	33 (15.2)	28 (25.2)	17 (15.3)	111 (12.8)
Surveillance	32 (14.6)	31 (14.2)	40 (18.6)	34 (15.6)	137 (15.8)
Polypectomy/resection	15 (6.9)	19 (8.8)	13 (6.0)	22 (10.1)	69 (7.9)

*$P < .05$ in the 4 groups.

TABLE 2. Overall frequency of excellent/good versus fair/poor bowel cleansing in patients undergoing split-dosage versus non-split-dosage intake schedules

Degree of cleansing	Split-dosage group No. (%)	Non-split-dosage group No. (%)	*P* value
Fair/poor in all segments	38 (8.7)	106 (24.4)	.00001
Fair/poor in some segments and good/excellent in other segments	70 (16.1)	141 (32.6)	
Good/excellent in all segments	327 (75.2)	186 (43.0)	

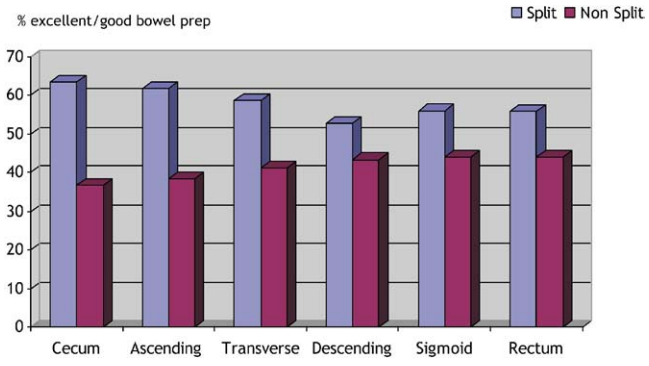

Figure 2. Frequency of excellent/good bowel cleansing in different colon segments according to the split-dosage versus non-split-dosage intake schedule. $P = .0001$ for all comparisons.

patients (5.4%). The degree of bowel cleansing was clearly associated with the cecal intubation rate. Failed intubation to the cecum was recorded in 41 of 354 patients (11.7%) with fair/poor bowel cleansing and in 6 of 513 patients (1.2%) with good/excellent bowel cleansing ($P = .00001$). The reasons for failed cecal intubation in those 6 patients with good/excellent bowel cleansing were diverticulitis (1), a large groin hernia (1), visceral adhesions (1), stenosing cancer (2), and dolichocolon (1).

Inadequate bowel preparation was responsible for an aborted procedure with a consequent need to repeat the colonoscopy in 121 cases (14.0%). These included the 47 patients with failed cecal intubation (see previous) as well as those patients in which the cecum was actually reached despite suboptimal cleansing, but the endoscopist judged the bowel preparation clinically inadequate, that is, the endoscopist did not feel confident to assure the patient about the absence of lesions, albeit the evidence was minimal. Aborted procedures were significantly more frequent in patients randomized to the non-split-dosage group (91/430 [21.2%] vs 30/432 [6.9%] of the split-dosage group, OR 3.60 [95% CI, 2.29-5.77], $P < .0001$).

Colorectal polyps were detected in 201 of 868 patients (23.1%). The polyp detection rate was significantly higher

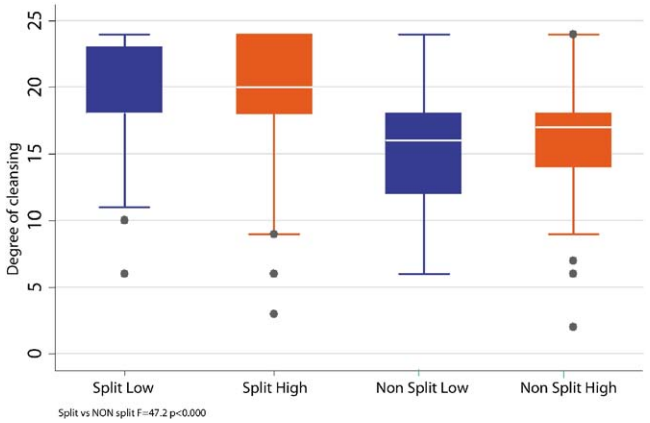

Figure 3. Degree of colon cleansing according to the volume of PEG and intake schedules. The blocks represent the 25th to 75th percentiles (*blue blocks* are low-volume PEG solutions; *orange blocks* are high-volume PEG solutions). Grey dots are the outliers, the bars are interquartile ranges (5th-95th percentiles), the white line in the middle of the main block is the median value. $P = .0001$ split-dosage versus non-split dosage.

TABLE 3. Tolerability of the low-volume and high-volume polyethylene glycol solutions

Symptom	Low-volume PEG + AA group No. (%)	High-volume PEG group No. (%)	Total No. (%)
No adverse events	251 (28.9)	260 (29.9)	511 (58.8)
Nausea	90 (10.3)	85 (9.8)	175 (20.1)
Abdominal discomfort	17 (1.9)	15 (1.8)	32 (3.7)
Vomiting	33 (3.8)	44 (5.1)	77 (8.9)
Bloating	21 (2.4)	19 (2.1)	40 (4.5)
Headache/ confusion	4 (0.5)	6 (0.7)	10 (1.2)
Tachycardia	7 (0.8)	1 (0.1)	8 (0.9)
Lipotimia	5 (0.6)	2 (0.2)	7 (0.8)
Other	5 (0.6)	3 ((0.3)	8 (0.9)

PEG, Polyethylene glycol; *AA,* ascorbic acid.
P = not significant for all comparisons.

in patients with bowel cleansing rated as fair/good (57/209, 27.3%) or good/excellent (126/512, 24.6%) compared with those with bowel cleansing rated as poor/fair (18/147, 12.2%) ($P = .001$).

At logistic regression analysis, independent predictors of poor bowel cleansing were male sex (OR 1.45 [95% CI, 1.07-1.96], $P = .014$) and the non-split-dosage intake schedule (OR 2.08 [1.89-2.37], $P = .0001$). Constipation was not an independent predictor of poor bowel cleansing (OR 1.12 [95% CI, 0.93-2.15], $P = 1.65$).

DISCUSSION

The results of our study add to the generalizability of the finding that the low-volume PEG plus ascorbic acid solution is as effective as the standard 4 L PEG solution, with equivalent degrees of colon cleansing.[18,20] Efficacy was coupled with an excellent safety profile. Adverse events were infrequent and of minor clinical relevance. Compliance to complete preparation was surprisingly high in our study, with no difference among volumes or intake schedules. Possible explanation resides in the continuative efforts made by study nurses to clearly explain the importance of drinking the full amount of solution in order to achieve a proper cleansing, thus conferring to the patient a strong motivation toward an effective and safe colonoscopy.

Some 5% to 15% of patients do not complete the preparation because of poor palatability and/or large volume of fluids.[1,2] The taste of the preparation may well be an important driving force to improved compliance. In this context, the low-volume PEG plus ascorbic acid preparation was significantly more acceptable to patients, independently of the intake schedule, potentially improving effectiveness in routine practice.

The present study is the first to demonstrate that the advantage of split-dosage intake is true also for low-volume solutions. Preparation with split-dosage PEG provided significantly better quality colon cleansing than preparation with whole-dose PEG, irrespective of the fluid volumes (2 or 4 L), with no significant impact on patient tolerability and side effects.

Furthermore, our data confirm that the sooner the procedure is performed from the last fluid intake, the higher the chance of finding an adequate degree of bowel cleansing. Colonoscopies performed within 6 to 8 hours of the end of preparation were associated with significantly better bowel cleansing than endoscopic examinations performed more than 8 hours after the end of preparation. Beyond this time limit, the cleansing advantages of the split dosage also vanished. This may have relevant implications in terms of daily practice. According to our data, colonoscopies should be scheduled in late morning or in the afternoon to allow patients to drink the second half of the dose on the day of the planned procedure. This is certainly true for outpatients, especially those living away from the endoscopy center. Inpatients might be scheduled also at the beginning of the work day because they can drink their half dose very early in the morning.

Also, because our data show that the non-split-dosage intake regimen and, to a minor extent, male sex are the only independent predictors of poor bowel cleansing, we think it would be wise to schedule male patients for afternoon colonoscopies in order to take maximum advantage of the split-dosage schedule. Unlike results found in other studies,[23] the procedural indication of constipa-

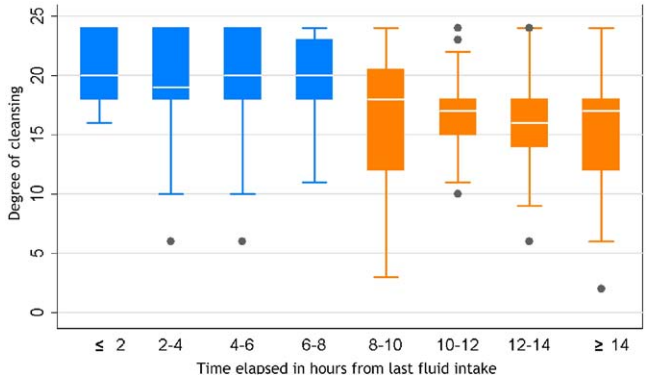

Figure 4. Degree of colon cleansing according to the time elapsed from the last fluid intake and colonoscopy (2-hour intervals). The blocks represent the 25th to 75th percentiles. Blue blocks represent patients whose colonoscopies were performed within the time limit of 8 hours, and orange blocks represent patients having their colonoscopies beyond this time cut-off, independently of the volume and intake schedule. Grey dots are the outliers, the bars are interquartile ranges (5th-95th percentiles), the white line in the middle of the main block is the median value. $P = .001$ for every blue box versus every orange box; $P =$ not significant for every comparison within blue boxes or every comparison within orange boxes (1-way analysis for multiple comparison with the Bonferroni method).

tion was not a significant predictor of poor bowel cleansing in our study.

In terms of quality indicators, our study confirmed that completion of the colonoscopy, that is, intubation to the cecum, is strongly associated with the degree of bowel cleansing. Incomplete colonoscopy was rare (5.4%) but significantly more frequent in patients with fair/poor bowel cleansing. Also, aborted procedures were more frequent in patients inadequately prepared, adding to the direct and indirect costs of colonoscopy, a major issue in times of constrained budgets for health care systems. Overall, the rate of poor bowel preparation that absolutely precluded an examination (14%) was similar to recently reported data.[24]

Last, but not least, the polyp detection rate is considered another key quality indicator for colonoscopy.[2-4] Yet, poor bowel preparation also heavily influenced the ability to detect precancerous colon lesions. Our data showed a significantly lower detection rate in patients with poor bowel cleansing as compared with those with good/excellent cleansing (12% vs 24%). In terms of effective secondary prevention of colorectal cancer, the implications of this endpoint are self-evident.

In conclusion, our large, randomized study demonstrated that a split-dosage intake schedule provides the most effective bowel cleansing, especially in the right colon segments, irrespective of the PEG volume (low or high). The split-dosage intake schedule likely enhances the cecal intubation and polyp detection rates. Low-volume PEG plus ascorbic acid is as effective and is tolerated as well as high-volume PEG, but it has improved palatability. Colonoscopies should be performed within a maximum of 6 to 8 hours of the last fluid intake.

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Registration of Human Clinical Trials

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