Randomized controlled trial comparing efficacy and acceptability of split- and standard-dose sodium picosulfate plus magnesium citrate for bowel cleansing prior to colonoscopy

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Bibliography
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Background and study aim: Sodium picosulfate plus magnesium citrate (PMC) is a very effective, safe, and tolerated low-volume preparation for colon cleansing. This study evaluates whether split dosing is associated with a further increase in efficacy and acceptability compared with the standard dosing regimen.

Patients and methods: This was a multicenter, randomized, single-blind study. Adult outpatients undergoing colonoscopy received PMC either in the standard dosing (two sachets taken the day before endoscopy) or in split dosing (the second sachet taken on the morning of colonoscopy). Bowel cleansing was assessed using the Boston Bowel Preparation Scale (BBPS) and was rated as adequate when BBPS was ≥ 2 in each segment. Patient acceptance, satisfaction, and related symptoms were recorded.

Results: A total of 862 patients were included in the study (577 in the standard group and 285 in the split-dose group). Preparation was adequate in only 69.8% of patients in the standard group compared with 85.8% of those in the split-dose group ($P=0.0001$). Mean BBPS scores for the whole colon and the right colon were also statistically significantly higher in the split-dose group ($P=0.0001$). Both regimens were well tolerated, and only 8.0% of patients reported discomfort. Compliance was better with the split regimen (0.7% vs. 7.1% unable to take 75% of the preparation; $P<0.0001$), and willingness to repeat the preparation was similar. Performing colonoscopy within 6 hours after preparation was associated with better colon cleansing. Other predictors of poor cleansing at multivariate analysis were constipation, obesity, and discomfort during preparation.

Conclusions: The split-dose regimen of PMC was superior to the standard regimen in terms of effective colon cleansing and compliance.
ClinicalTrial.gov (NCT01909219)

Introduction

The implementation of colon cancer screening programs and the consequent increase in the number of colonoscopies in recent years have intensified the need for optimum colon cleansing regimens [1]. The ideal preparation should be able to clean the colon without damaging the mucosa or causing fluid or electrolyte imbalance; moreover, it should minimize patient discomfort [2,3], a crucial issue for colonoscopy acceptance.

Several colon cleansing agents with different characteristics are currently available, and their efficacy, safety, and tolerability have been evaluated in a number of studies [3]. The recent European Society of Gastrointestinal Endoscopy (ESGE) guidelines have been developed with the aim of providing caregivers with a review of the various regimens available and practical advice on bowel preparation.

The ESGE recommends a split-dose regimen of 4 L polyethylene glycol (PEG) solution for routine preparation, but also suggests that a split-dose regimen of 2 L PEG plus ascorbate or of sodium picosulfate plus magnesium citrate (PMC) may represent a valid alternative [4]. Moreover, the ESGE emphasizes that the delay between the last dose of preparation and the colonoscopy should be minimized and should be no longer than 4 hours in order to obtain maximum result [4]. These statements are supported by several studies, most of which have used 4 L PEG [5,6] and 2 L PEG plus ascorbate [7]; the volume of data on PMC is significantly lower.

PMC is a very low-volume agent, which combines stimulant (sodium picosulfate) and osmotic (magnesium oxide and citric acid) laxatives. This agent has been available in the United Kingdom and Australia for several years, and it has been recently adopted in Canada and several European

countries, including Italy. PMC has been shown to be very well tolerated and to be at least as effective as other cleansing products [8–14]. The significant advantage of the split-dose regimen over the standard single-dose regimen in terms of adequate cleansing for the PEG-based preparations is likely to be also true for PMC. However, only a few studies are available on the role of split-dose PMC regimens [11, 15], and no study has yet addressed the optimal duration of the interval between the completion of PMC bowel preparation and colonoscopy. This information is likely to be very important as the bowel preparation market shifts towards very low-volume products, and as the use of PMC increases.

The aims of the current study were to compare the efficacy, tolerability, and acceptability of two PMC dosing regimens, the standard regimen (whole dose taken the day before endoscopy) and the split-dose regimen (the first half dose taken the day before endoscopy and the second half taken on the day of endoscopy) in adult outpatients undergoing colonoscopy. The optimal interval between PMC preparation and colonoscopy in order to achieve adequate bowel cleansing was also evaluated.

Patients and methods

This was an endoscopist-blinded, prospective, multicenter study, involving adult outpatients, aged 18–85 years, undergoing elective colonoscopy in 15 Italian tertiary Endoscopy Services from January 2012 to June 2012.The protocol was approved by the Ethics Committee of each hospital (number CE ICH-40/12), and the study was registered at ClinicalTrials.gov (NCT01909219). Patients provided written, informed consent to take part in the study.

Exclusion criteria were: previous colon resection, ileus, intestinal obstruction, toxic megacolon, severe heart failure (New York Heart Association Class III or IV), acute cardiovascular disease, uncontrolled arterial hypertension (systolic pressure >170 mmHg, diastolic pressure>100 mmHg), severe liver cirrhosis (Child–Pugh score C) or renal failure (creatinine clearance<30 mL/minute), ascites, phenylketonuria, and glucose-6-phosphate dehydrogenase deficiency. Pregnant or breastfeeding women were excluded.

Treatment allocation and masking

Patients were randomly assigned to either the standard PMC-based preparation or the split-dose PMC-based regimen, in a 2:1 ratio using a computer-generated sequence. The treatment allocation was concealed and revealed by nonresearch medical personnel at the screening visit.

Colon cleansing preparations

PMC (Citrafleet; Ibi Lorenzini, Aprilia, Italy) consists of two sachets, each containing 10 mg of sodium picosulfate, 3.5 g light magnesium oxide, and 10.97 g citric acid anhydrous. Patients were provided with detailed verbal and written instructions about dietary measures and how to administer the investigational treatment. All patients were advised to consume a low-fiber diet for 3 days before the procedure. They had a normal breakfast and a light lunch on the day before the procedure, but then only a semi-liquid dinner was allowed until after colonoscopy.

Patients in the standard regimen group were instructed to take the two sachets diluted in a glass of water 2–4 hours apart, starting at 17:00 hours on the day before colonoscopy. Those in the split-dose group were instructed to take the first sachet at 19:00 hours the day before colonoscopy and the second one at 06:00 hours on the morning of the day of colonoscopy. Patients in both groups were also encouraged to drink 3–4 L of clear fluids.

Assessment

Before colonoscopy, patients completed a nurse-administered questionnaire describing their experience with the bowel preparation, which included two major items, patient tolerance and patient acceptance of the preparation. The overall tolerance of the preparation and the severity of symptoms during the bowel preparation period were rated on a scale ranging from 0 (no discomfort) to 3 (severe discomfort). Patient acceptance of the preparation was evaluated by a questionnaire with a 5-point scale ranging from 1 (worse) to 5 (best), and assessed interference with daily activity, palatability, ease of taking the product and the adjunctive clear fluid, and the taste of the product. The nurse also asked the patient whether s/he had completed the prescribed regimen: compliance was defined as poor for patients who consumed less than 75% of the product. Willingness to repeat the same preparation in the future was also recorded.

All endoscopic procedures were performed between 11:00 and 16:00 under conscious sedation by two endoscopists at each center who were blinded to the preparation regimen. To guarantee endoscopist blindness, endoscopists entered the endoscopy suite only after the nurse and patient had completed the abovementioned questionnaire. Patients were instructed not to discuss their preparation with the endoscopist. The investigators recorded demographic and clinical data, as well as indications for colonoscopy, procedure start time, depth of colonoscope insertion, time to cecal intubation, total procedure time, reasons for failure of cecal intubation, endoscopic diagnosis, and any therapeutic procedures.

The endoscopist rated the quality of cleansing for each segment of the colon (right, transverse, and left colon) using the Boston Bowel Preparation Scale (BBPS) as described previously [16, 17]: 0=inadequate, 1=fair, 2=good, 3=excellent. If the endoscopist was unable to reach the colon segment due to poor quality of bowel preparation, the segment was automatically rated as inadequate.

The overall quality of colonic cleansing was based on the sum of scores for each segment, and ranged from 0 to 9. Patients who did not take the study product or did not follow the prescription (major protocol violations) were excluded from the analysis, according to a per protocol approach, as discussed below.

End point measurement

The primary end point of the study was the quality of overall colon cleansing, as assessed by the endoscopist. Colon cleansing quality was dichotomized as “adequate” (score≥2 in each colon segment) or “inadequate” (score<2 in one or more colon segments). Secondary end points included the quality of cleansing in the right colon, the number of polyps detected, patient acceptance, tolerability and compliance with the cleansing regimen, and the assessment of safety based on the severity of adverse events.

Sample size and statistics

Based on results from previous studies with PMC [11], a success rate of about 75% was assumed, and with 2:1 randomization of groups, at least 528 and 264 patients were required for the two arms, respectively, in order to detect a 9% increase in success

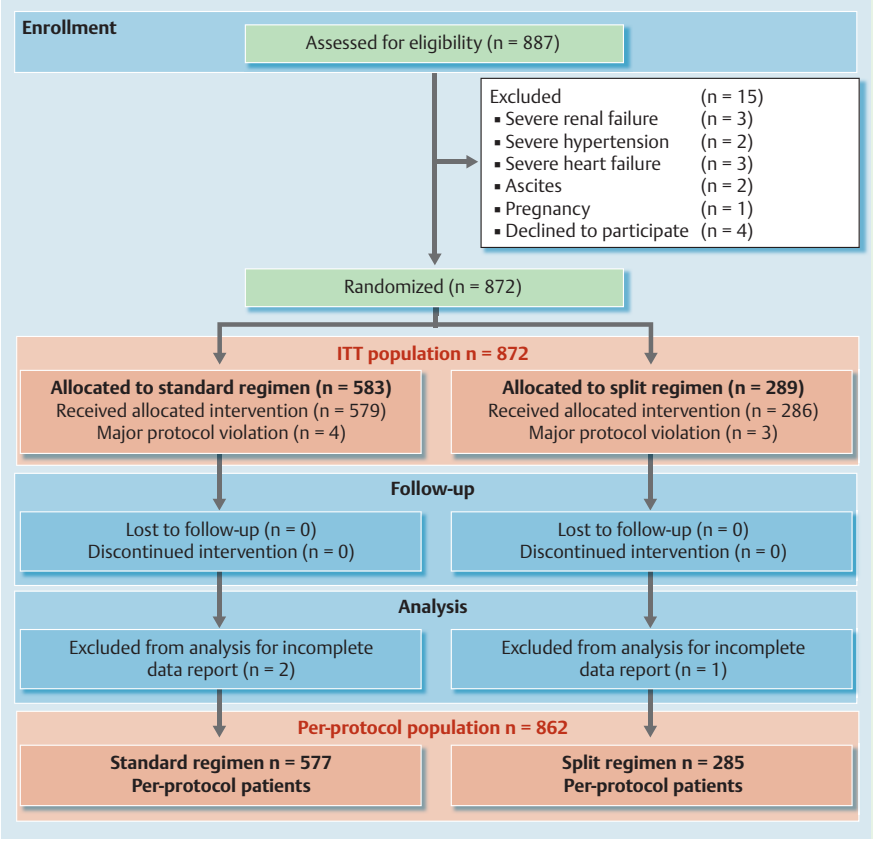

Fig. 1 Flow diagram of patients through the study.

rate between the groups (i.e. from 75% to 84% of adequate colon preparation, $\alpha = 5\%$, $\beta = 80\%$).

The primary analysis was conducted on both the intention-to-treat (ITT) and per-protocol populations [18]. For univariate analysis, comparisons between groups were performed using the Student's t test, the chi-squared test, or Fisher's exact test, as appropriate. The Mann–Whitney rank sum test was used to compare nonpaired, nonparametric variables. Multivariate analysis was used for the primary outcome variables, in a logistic stepwise regression model. All variables with a P value of < 0.2 at univariate analysis were included, and those with a P value > 0.4 were removed, according to an automated backward stepwise procedure. A P value of < 0.05 was considered to be significant. Statistical analysis was performed using SPSS statistical software version 13 (SPSS Inc., Chicago, Illinois).

Results

The patient flow through the study is reported in **Fig. 1**. Of the 887 patients screened for the study, 11 were excluded for severe renal failure (n = 3), severe hypertension (n = 2), severe heart failure (n = 3), ascites (n = 2), and pregnancy (n = 1); 4 further patients declined to participate in the study. The remaining 872 patients represented the ITT population, with 583 randomized to the standard regimen group and 289 to the split-dose regimen group. Seven patients were excluded after enrollment due to major protocol violations (one doubled the dose of preparation, one took the preparation 1 day early, one presented for colonoscopy but had not taken the study product, and four took a different preparation from that prescribed for the study). Three further patients were excluded from analysis for incomplete data reporting.

All 10 excluded patients were included in the ITT analysis of efficacy as failures. A total of 862 patients (577 in the standard and 285 in the split-dose group) were included in the per-protocol analysis. The two groups were comparable with respect to demographics, clinical features, indications for colonoscopy, and procedure start time, but were significantly different with regard to the time between the end of preparation and the colonoscopy procedure (14.1 ± 2.6 vs. 4.49 ± 1.9, respectively; $P < 0.0001$) (**Table 1**).

Efficacy of bowel preparation

In the ITT analysis, colon cleansing was adequate (score ≥ 2 in each colon segment) in only 655/872 patients (75.1%); the rate of adequate preparation was significantly higher in the split-dose group (248/289; 85.8%) than in the standard group (407/583; 69.8%; $P = 0.0001$; odds ratio [OR] 2.61, 95% confidence interval [CI] 1.79–3.80). The BBPS scores were significantly higher in the split-dose group than in the standard group for both the whole colon (7.25 ± 1.67 vs. 6.33 ± 2.19; $P = 0.0001$) and the right colon (2.15 ± 0.75 vs. 1.78 ± 0.94; $P = 0.0001$). Superiority of the split-dose regimen was also shown in the per-protocol analysis, where the rates of adequate preparation were 87.0% and 70.5%, respectively ($P < 0.0001$).

Compliance

Compliance was significantly influenced by the preparation regimen. The full amount of product and adjunctive fluids were taken by 225/285 patients (78.9%) in the split-dose group and by 406/577 patients (70.4%) in the standard group. The difference was significant ($P = 0.008$; OR 1.57, 95%CI 1.12–2.21). Compliance was poor (< 75% solution intake) in 2/285 patients (0.7%) in the split-dose group and 41/577 patients (7.1%) in the standard group ($P < 0.0001$; OR 10.8, 95%CI 2.6–45.1).

Table 1 Demographic and clinical characteristics of the study population.

	Standard regimen	Split regimen
Number	577	285
Male sex, n (%)	284 (49.2)	148 (51.9)
Age, mean ± SD, years	58.5 ± 14.4	59.8 ± 14.5
BMI > 30 kg/m^2, n (%)	81 (14.0)	37 (13.0)
Grade of education, n (%)		
Elementary or middle school	261 (45.2)	118 (41.4)
High school	232 (40.2)	119 (41.8)
University	84 (14.6)	48 (16.8)
Constipated patients, n (%)	37 (6.4)	20 (7.0)
Bristol stool scale, mean ± SD	3.5 ± 1.6	3.9 ± 1.5
Main indications for colonoscopy, n (%)		
Screening	173 (30.0)	91 (31.9)
Polyps follow-up	150 (26.0)	68 (23.9)
Symptoms (bleeding, pain, diarrhea)	167 (28.9)	88 (30.9)
Others	87 (15.1)	38 (13.3)
Previous colonoscopy, n (%)	220 (33.2)	104 (36.5)
Time between preparation and colonoscopy, mean ± SD, hours	14.1 ± 2.6	4.49 ± 1.9

BMI, body mass index.

Tolerability and safety

The standard and split-dose regimens were both well tolerated, as demonstrated by the similar rate of patients who reported discomfort of any level from the preparation (44/577 [7.6%] vs. 25/285 [8.8%], respectively; P=n.s.) (**Table 2**). Discomfort was related to dietary restriction for 13 patients (7 in the standard group and 6 in the split-dose group), to the volume of liquid required for 31 (22 and 9, respectively), to the taste of the product for 8 (6 and 2, respectively), and to preparation-related symptoms for 29 (16 and 13, respectively). Discomfort was reported as mild for the majority of patients (42/49), with only 6 patients defining discomfort as severe. No severe adverse events were recorded in the two groups. The mean symptom severity score for each group is shown in **Fig. 2**. No significant difference was observed between the two groups with regard to dizziness, headache, abdominal pain, bloating, belching, insomnia, nausea, hunger, and thirst. Patients who received the split-dose preparation experienced significantly less anal irritation.

Acceptance

Patient acceptance of the preparation was similar for the two regimens in terms of general palatability of the preparation, ease in taking the product and the adjunctive clear fluid, and taste of the product. Patients in the split-dose group reported lower interference with daily activities (**Fig. 3**). Willingness to repeat the same preparation for future endoscopies was reported by 95.8% of patients in the standard group (553/577) and 96.5% of patients in the split-dose group (275/285; P=n.s.).

Predictors of poor bowel cleansing

The rate of adequate colon cleansing changed according to the time between the end of bowel preparation and the colonoscopy procedure (**Fig. 4**). In particular, colon cleansing was adequate in 228/264 patients (86.4%) when the time was ≤6 hours and in 427/598 (71.4%) when the time was >6 hours (P<0.0001; OR 2.53, 95%CI 1.71–3.76).

At univariate analysis, factors inversely related to the quality of colon cleansing were nonsplit schedule, time from preparation to colonoscopy>6 hours, poor patient compliance (<75% intake), any degree of discomfort during preparation, diabetes, BMI>30 kg/m^2, limited mobility, constipation, Bristol stool scale 1 or 2, and low school education (elementary or middle school) (**Table 2**). At logistic regression analysis, independent predictors of poor bowel cleansing were nonsplit dose (OR 2.3, 95%CI 1.5–3.6; P<0.001), discomfort during preparation (OR 2, 95%CI 1.06–3.73; P=0.03), constipation (OR 2.17, 95%CI 1.16–4; P=0.01), and obesity (BMI>30 kg/m^2; OR 1.78, 95%CI 1.04–2.78; P=0.03).

Table 2 Factors related to inadequate preparation at univariate analysis.

	Adequate (n=655)	Inadequate (n=207)	OR [95%CI]	*P* value
Male sex, n (%)	332 (50.7)	102 (49.3)	0.94 [0.69–1.29]	0.77
Age<60 years, n (%)	314 (47.9)	101 (48.8)	1.03 [0.76–1.41]	0.88
BMI>30 kg/m^2, n (%)	80 (12.2)	38 (18.4)	1.61 [1.05–2.4]	0.003
High school education, n (%)	381 (58.2)	97 (46.9)	0.63 [0.46–0.87]	0.005
Previous colonoscopy, n (%)	237 (36.2)	87 (42.0)	1.2 [0.9–1.7]	0.13
Standard dose, n (%)	407 (62.1)	170 (82.1)	2.80 [1.90–4.13]	<0.001
Poor compliance to product instruction, n (%)	11 (1.7)	32 (15.5)	10.7 [5.3–21.7]	<0.001
Any degree of discomfort during preparation, n (%)	44 (6.7)	25 (12.1)	1.91 [1.14–3.20]	0.019
Patient history, n (%)				
Parkinson's disease	10 (1.5)	2 (1.0)	0.62 [0.14–2.89]	0.7
Stroke/dementia	11 (1.7)	3 (1.4)	0.86 [0.24–3.11]	1
Depression	21 (3.2)	7 (3.4)	1.06 [0.44–2.52]	0.9
Diabetes	40 (6.1)	22 (10.6)	1.82 [1.05–3.15]	0.04
Renal failure	13 (2.0)	2 (1.0)	0.48 [0.11–0.15]	0.5
Liver cirrhosis	10 (1.5)	2 (1.0)	0.62 [0.14–2.89]	0.7
COPD	18 (2.7)	7 (3.4)	1.23 [0.53–3.0]	0.8
IBD	34 (5.2)	15 (7.2)	1.42 [0.76–2.67]	0.1
Limited mobility, n (%)	15 (2.3)	11 (5.3)	2.39 [1.1–5.3]	<0.05
Diarrhea, n (%)	96 (14.7)	29 (14.0)	0.95 [0.6–1.48]	0.9
Constipation, n (%)	37 (5.6)	20 (9.7)	1.78 [1.01–3.15]	0.03
Bristol stool scale 1–2	158 (24.1)	77 (37.2)	1.86 [1.33–2.6]	0.0003

BMI, body mass index; OR, odds ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; IBD, inflammatory bowel disease.

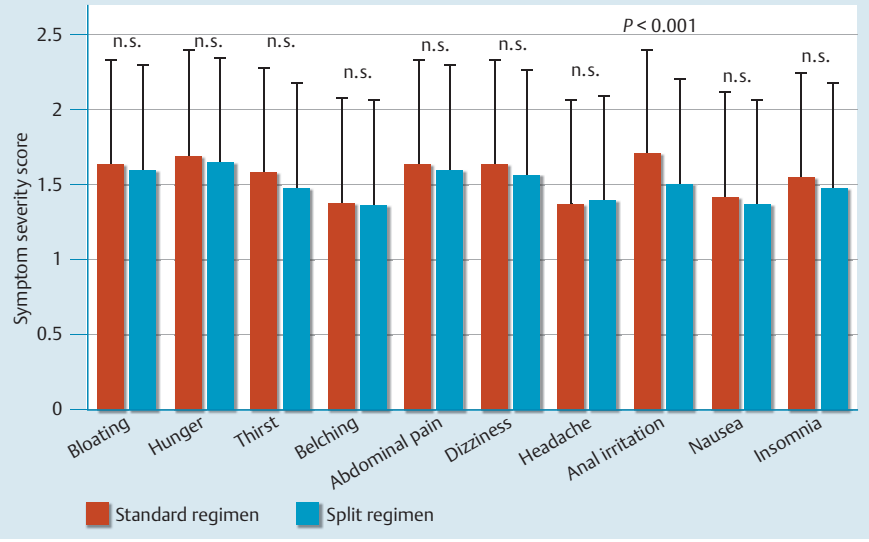

Fig. 2 Preparation-related symptom scores in the two groups. Symptoms were rated from 0 to 3 (0 = absent, 1 = mild, 2 = moderate, 3 = severe) and are described as mean ± SD.

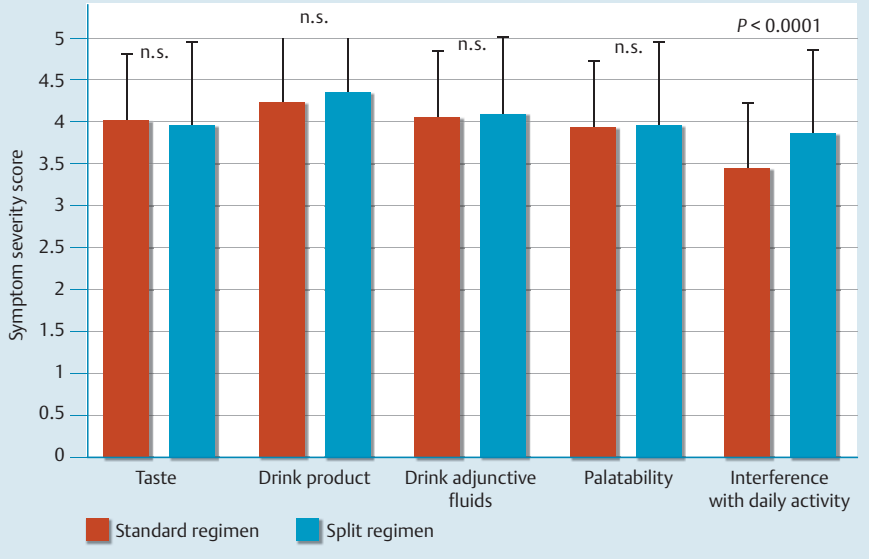

Fig. 3 Factors related to patient acceptance of the two study preparations. Factors were rated on a 5-point scale ranging from 1 (worse) to 5 (best) and are described as mean ± SD.

Endoscopic outcomes

A complete colonoscopy was achieved in 782/862 cases (90.7%). Failure of cecal intubation occurred in 10/285 patients (3.5%) in the split-dose group and 70/577 patients (12.1%) in the standard group (OR 3.79, 95%CI 1.92–7.48; $P<0.001$). Overall, failure of cecal intubation was associated with inadequate preparation in 71/80 patients (88.5%), 2 in the split-dose group and 69 in the standard group. Time to reach the cecum was 12.6 ± 6.03 vs. 9.96 ± 5.24 minutes ($P=0.0002$) in adequately and inadequately prepared patients, respectively, and was also significantly different according to the preparation schedule (10.68 + 5.46 minutes in the standard group vs. 9.77 + 5.4 minutes in the split-dose group; $P=0.02$).

Overall, 203 polyps were found in 862 patients. At least one polyp was observed in 173 patients, with no difference between preparation regimens (114/577 patients [19.8%] in the standard group and 59/285 patients [20.7%] in the split-dose group). The mean number of polyps per patient was 0.69 ± 1.2 in the standard group and 0.64 ± 1.05 in the split-dose group (P = n.s).

Discussion

Extensive research has been conducted in recent years with the aim of improving methods of colon cleansing. Failure to follow prescribed preparation instructions is the most commonly cited reason for inadequate colon preparation, and the primary reasons for this noncompliance are patient discomfort and inability to ingest the required fluid volume [19, 20]. Another factor affecting the quality of colon cleansing is the timing of bowel preparation, with better results being achieved when the preparation regimen is completed in the morning of the procedure, a few hours before colonoscopy [5, 7].

Several studies, involving high- and low-volume PEG solutions or very low-volume oral sodium phosphate, have demonstrated that the split dosage provides significantly better quality colon cleansing than a nonsplit schedule, and that the sooner the procedure is performed after the last preparation intake the higher is the chance of finding a clean bowel [5, 7,21]. The combination of a stimulant laxative, (picosulfate) with an osmotically active agent (magnesium citrate) is likely to represent an effective and very acceptable low-volume preparation without the safety problems associated with the use of sodium phosphate. Our

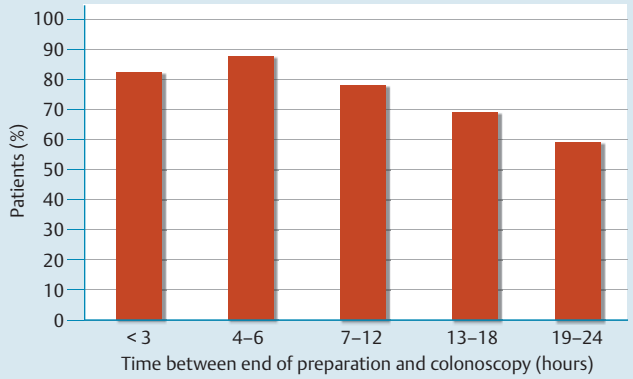

Fig. 4 Rate of effective colon cleansing according to the time between the end of preparation and the colonoscopy procedure.

group and others have demonstrated that PMC is at least as effective as high- and low-volume PEG solutions, and sodium phosphate [8, 10, 11, 16] but with the significant advantage of being more acceptable to patients. Moreover, it has been suggested that a split-dose regimen of PMC represents a valid alternative to PEG in preparation of the bowel for routine colonoscopy [4], but only a few data are available on its use in this setting.

Flemming et al. have recently demonstrated that use of the PMC split-dose regimen results in significantly better colon cleansing compared with the standard regimen [15]. In this study, however, the PMC preparation was enhanced by bisacodyl tablets taken on the previous 2 days [15]. Rex et al. compared a PMC split-dose preparation with 2 L PEG plus bisacodyl tablets administered in the standard fashion; results demonstrated the superiority of the PMC regimen in terms of cleansing quality and tolerability [12]. In a previous study, designed to compare PMC and 2 L PEG plus ascorbate in a small subgroup of patients, the PMC split-dose regimen resulted in better colon cleansing than a standard PMC regimen [11].

The present study confirms, in a large, multicenter series of adult patients undergoing elective colonoscopy, the significant advantage of the split dosage over the standard single dosage in terms of effective colon cleansing. This result was evident both for the whole colon and for the right-sided colon, an issue which is likely to be very important as cleansing is typically least effective in the right-sided colon. Moreover, the current data confirm that the quality of colon cleansing significantly affects the quality of colonoscopy [22 – 26], with standard dosage resulting in a prolonged procedure time and a lower cecal intubation rate. In the current study, the cecal intubation rate in the standard dosage group was less than 90 %, a rate that is lower than that stated in quality criteria for colonoscopy [23] and similar to that reported by other authors for nonsplit regimens [27]. Interestingly, in the current study, nearly 90 % of incomplete colonoscopies were determined by inadequate preparation, a finding that confirms the importance of bowel preparation for an effective colonoscopy.

According to the current data, the time between the last fluid intake and the endoscopy significantly affected the quality of preparation. Colonoscopies performed within 6 hours of the end of bowel preparation were associated with significantly better bowel cleansing than examinations performed more than 6 hours after the end of preparation. A similar finding has been reported with other products [5, 7, 21], and this is the first time it has been reported for PMC. In the study by Flemming et al. [15], all patients included in the split-dose regimen group were instructed to take the second PMC dose 4 hours before colonoscopy, making it impossible to evaluate the optimum time interval between solution intake and colonoscopy. The authors found that the benefit of the split-dose regimen was not restricted to the afternoon investigations but was also evident with procedures conducted in the morning, thus suggesting that using a PMC split dose is associated with a real significant improvement in efficacy [15]. The current study confirms these data and further emphasizes the concept that shortening the time interval between solution intake and colonoscopy is the most important way to improve colon cleansing, irrespective of the dosing regimen: even within the split-dose group, patients undergoing colonoscopy more than 6 hours after the end of preparation showed a trend toward worse preparation in the right-sided colon (BBPS 1.96 ± 0.6 vs. 2.16 ± 0.76; $P = 0.1$).

PMC, with its very low volume and good palatability, is a very well accepted and tolerated regimen. Overall, about 96.1 % (828 / 862) of patients expressed their willingness to repeat the same preparation in future endoscopies, and only 43 / 862 patients (5.0 %) were not able to drink the prescribed amount of product. Compliance with the preparation was, however, significantly better with the split-dose regimen, and this is likely to be related to the fact that taking the preparation over 2 days was described by patients as having less of an impact on daily activities. Overall tolerability was similarly good between the two regimens, with only 8.0 % of patients reporting discomfort from preparation. However, anal irritation was described to be more severe in the standard regimen group, and this is likely to be related to the fact that shortening the time for preparation intake would result in a more severe diarrhea within a shorter time.

The issue of compliance and tolerability, the main drawbacks of the high-volume preparations [2 – 4], seems therefore to be less relevant for both PMC-based preparations evaluated in the current study. However, the current study also showed that low tolerability was an independent predictor of poor cleansing. Comorbidities, such as diabetes, obesity, and constipation represented further independent factors associated with poor preparation. These findings have been demonstrated previously for PMC and other products [2 – 4], and have been confirmed in the current study.

When using hypertonic products such as PMC, some concerns may exist with regard to the safety profile. The effects of the two regimens on intravascular volume and electrolyte balance were not addressed in the current study, but previous studies have demonstrated that PMC is safe if high risk patients are excluded [12]. In the current study, no severe adverse events were reported, and symptoms related to preparation intake were generally mild to moderate in intensity and mainly gastrointestinal in nature.

The current study design deserves some discussion. First, patients were randomized to the two study groups in a 2:1 ratio. This ratio was likely to reflect the usual practice in Italian endoscopy units, where the majority of patients are prescribed the standard preparation [28]. Second, study endoscopies were performed after 11:00, a fact which is likely to introduce a bias in favor of the split-dose regimen, as the patients in the standard regimen group were examined at a time even later after their final dose of bowel cleansing agent. In addition, this factor could theoretically limit the applicability of the current results to early morning colonoscopies. This timing was adopted to increase patient compliance, as some concern may exist that patients would

not be willing to wake up early in the morning to take the second dose. Moreover, it is likely to reflect more closely the real life practice of most Italian (and probably European and American) endoscopy services, where the split-dose regimen is considered impractical for morning colonoscopies and is prescribed mainly for the late morning and afternoon investigations [28,29]. Poor endoscopist awareness about the advantages of split-dose regimens over standard ones and concern about the risk that patients would not accept waking up early in the morning to take the second dose or may suffer from uncontrollable diarrhea during the trip to the endoscopy unit have limited the adoption of split-dose regimens into routine endoscopy practice. The advantages of the split over the nonsplit regimens are, however, so dramatic that every effort should be made to abandon standard preparation and to promote adoption of the split-dose regimens in endoscopy units by re-organizing the endoscopy schedule, postponing all colonoscopies to the late morning, and discussing the issue of split dosing with patients before prescribing a preparation.

In conclusion, this large, multicenter study demonstrated that the PMC split-dose regimen provided the most effective bowel cleansing and resulted in effective and easier colonoscopy. The split-dose regimen with PMC is likely to increase patient compliance and tolerability of bowel preparation. The most effective cleansing is obtained when colonoscopy is performed within 6 hours after the end of preparation. As quality of colon cleansing significantly affects the quality of colonoscopy, application of these concepts should be strongly recommended as an important driving force to improve results of colonoscopy.

The MAGIC-P (Magnesium Citrate-Sodium Picosulfate) study group includes the following authors:

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