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Superiority of a Split-dose Regimen of Sodium Picosulfate/ Magnesium Citrate (SPMC) in Comparison to a Prior-day Schedule (AM/PM) for Colonoscopy Preparation. A Randomized Single-blinded Study

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ABSTRACT

Background & Aims: Split-dose regimens are generally recommended for bowel cleansers. However, other regimens still remain in the summary of product characteristics of some bowel cleansers in Europe. The aim of this study is to compare the efficacy and safety of a split-dose regimen of sodium picosulfate/magnesium citrate (SPMC) with a prior-day schedule (AM/PM).
Methods: Multicenter, randomized (EudraCT no. 2013-001620-20), endoscopist-blinded, parallel study, carried out in subjects 18 years or older undergoing elective colonoscopy. The primary endpoint was the bowel cleansing assessment using a binary transformation (adequate/inadequate) of the Global Preparation Assessment (GPA) scale. Additional parameters analyzed were the segmental assessment of bowel cleansing (RSS), the adenoma detection rate and safety evaluations.
Results: 315 subjects comprised the ITT set. A significantly higher proportion of patients in the split-dose regimen had an adequate bowel preparation (AM/PM: 30.8% vs split-dose: 79.9%; p<0.0001). The mean global RSS was significantly lower in the split-dose group (AM/PM: 5.0 [SD: 2.91] vs split-dose: 2.6 [SD: 2.14]; p<0.0001). Flat polyps were detected in a higher proportion of subjects in the split-dose group compared with the AM/PM group (AM/PM: 16.0% vs split-dose: 22.0%). Both regimens were equally safe and well tolerated, with no serious treatment-emergent adverse events or discontinuations due to adverse events.
Conclusion: A split-dose regimen of SPMC is superior to the AM/PM regimen administered the day before colonoscopy. Split regimen of SPMC should be considered the standard of use.

Key words: sodium picosulfate magnesium citrate – colon cleansing – split regimen – colonoscopy – bowel preparation.

Abbreviations: CTCAE: Common Terminology Criteria for Adverse Events; eGFR: Glomerular filtration rate; mITT: modified intent-to-treat; RSS: Residual Stool Score; SA: safety analysis; SAE: serious adverse event; SmPC: summary of product characteristics; SPMC: sodium picosulfate-magnesium citrate.

INTRODUCTION

Colonoscopy is the method of choice for the detection and prevention of colorectal cancer [1]. The effectiveness of any endoscopic-based colorectal cancer screening program is dependent on adequate bowel preparation [2]. Suboptimal bowel preparation is associated with decreased adenoma detection rate and increased costs due to repetitive colonoscopies [3, 4].

Sodium picosulfate-magnesium citrate (SPMC) is a low-volume bowel cleansing powder packed in a sachet for oral solution. Recently published clinical studies on SPMC have shown a successful bowel cleansing rate in 73% to 93% of subjects [5, 6].

According to the currently approved summary of product characteristics (SmPC), the first sachet of SPMC should be taken before 08:00 AM on the day before performing the diagnostic procedure, followed by the second sachet 6-8 hours later (AM/PM schedule). Split administration of doses of bowel cleansers on the evening prior to colonoscopy and the morning of the colonoscopy has evolved over the last years into the standard of care for preparing the colon for colonoscopy with polyethylene glycol preparations, rendering improved effectiveness for bowel cleansing [7-10].

Studies from Canada [11, 12], Australia [13] and the United States [14] have reported on the use of a split-dose SPMC bowel preparation and a split-dose SPMC product has been approved for use in the United States [15]. Recently, the European Society of Gastrointestinal Endoscopy (ESGE) published guidelines for bowel preparation that recommend split-dosing bowel preparations where feasible and suggest limiting the delay between the last dose of bowel preparation and the start of colonoscopy [7].

The present phase III clinical trial aimed at comparing a split-dose administration schedule of SPMC with the currently approved regimen of this formulation.

METHODS

This study was a randomized, multicenter, single-blind, parallel, phase III study conducted in five colonoscopy sites in Germany and sponsored by Casen Recordati S.L. The study was approved on 26th August 2013 by the Ethics Committee of each participant site and performed in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines. All patients provided their written informed consent before any study-specific procedure was implemented. The trial was registered at www.clinicaltrialsregister.eu (EudraCT no. 2013-001620-20).

Subject population

Subjects were included if they were 18 years or older and were undergoing elective colonoscopy. Pregnant and lactating women were excluded as well as people with severe chronic renal disease, congestive heart failure, gastrointestinal and other conditions contraindicating the administration of the product. Subjects were also required to be capable of following their assigned low-residue diet and hydration regimen and complying with dosing instructions, diary completion and other study requirements, such as providing with their hand-signed and dated informed consent form.

Randomization, blinding and treatment regimens

Subjects who met the selection criteria were randomly allocated to receive one of two regimens of SPMC in a ratio 1:1. A computer-generated randomization schedule was centrally prepared to achieve the balance between treatment regimens among sites. One randomization list was prepared for all sites using a block size of 2 without stratification, containing 400 entries. For each treatment number, one randomization envelope was prepared. Eligible subjects were randomized to either treatment group according to the next available envelope.

Endoscopists performing colonoscopies and bowel cleansing assessments were kept blind to treatment allocation. At each site, a coordinator responsible for the management of investigational product, allocation of subjects to treatment groups and training of study subjects was appointed.

All subjects were required to take two sachets of SPMC prior to colonoscopy. Description of both treatment regimens is provided in Table I. The subjects had to follow a low-residue diet on the day prior to colonoscopy and were encouraged to drink plenty of clear fluids before, during and after taking SPMC. Following the first dose of SPMC, subjects were instructed to drink at least 250 ml/hr of clear liquids until the effect of the investigational product had stopped and to observe a nil-by-mouth period during at least 3 hours before the scheduled time of colonoscopy.

Study assessments

Clinical assessments were performed during four study visits: screening, randomization, colonoscopy and follow-up (four days after colonoscopy). Subjects registered the amount of liquids taken in a diary, together with the occurrence and severity of 12 frequent adverse events. Blood and urine specimens were collected at screening, before colonoscopy and at follow-up visit.

Endoscopists performing colonoscopy assessed segmental bowel cleansing at each of the five colon segments (rectum, sigmoid/descending, transverse, ascending and cecum), through the evaluation of three parameters: amount and consistency of stools, assessed before suctioning, and the percentage of the wall visualized, assessed after suctioning. The most proximal level reached was also collected (Table II). From this segmental assessment, a segmental Residual Stool Score (RSS) is calculated as the sum of the scores for each parameter (amount, consistency and percentage of wall visualized) within each segment, and the global RSS is estimated as the average of all available segmental RSS. RSS ranges from 0 to 12, being 0 the best.

Once segmental cleansing was evaluated, endoscopists were required to perform the Global Preparation Assessment (GPA) developed by Fleet Laboratories, using the definitions provided in Table II.

Additional efficacy assessments were the number, morphology, location and size of the polyps detected during colonoscopy.

Table I. Description of the treatment regimens

Administration schedule	First dose[1]	Interval (hrs)	Second dose[1]	Colonoscopy[2]
SmPC (AM/PM)	Day -1 Before 08:00	6 – 8	Day -1 6 – 8 hrs after the first dose	Day 0 10:00 – 14:00
Split-dose	Day -1 18:00 – 20:00	9 – 12	Day 0[3] 05:00 – 06:00	Day 0[3] 10:00 – 14:00

[1] Day 1 = day before colonoscopy; Day 0 = day of colonoscopy; [2] Start time of examination to be no earlier than 10:00 and no later than 14:00; [3] Time elapsed between the 2nd dose and the colonoscopy should be at least 4 hours, allowing for 3 hours of full fasting conditions.
SmPC: summary of product characteristics.

Table II. Segmental assessment of preparation and Global Preparation Assessment definitions

Segmental assessment				
Segment	Most proximal level reached	Residual stool (before suctioning and washing)		After suctioning and washing
		Amount	Consistency	% wall visualized
Rectum				
Sigmoid/ Descending				
Transverse				
Ascending				
Cecum				
		0 = None 1 = Minimal 2 = Small 3 = Moderate 4 = Large	0 = None 1 = Clear yellow liquid 2 = Muddy liquid 3 = Particulate Stool 4 = Solid Stool	0 = >95% 1 = 85% - 94% 2 = 75% - 84% 3 = 50% - 74% 4 = <50%

Global Preparation Assessment (GPA) definitions	
Category	Definition
Excellent	Clean colon or small volume of clear liquid
Good	Moderate to large volume of clear to semi-clear liquid
Fair	Some semi-solid stool suctioned or washed away
Poor	Semi-solid or solid stool unable to be suctioned or washed away

Subjects rated their acceptability to the study drug (ease of drink and taste) and to the study procedure (overall tolerance to the bowel cleansing regimen and willingness to repeat the regimen in the future) on a questionnaire. Subjects also rated their tolerability to 12 expected adverse reactions (nausea, vomiting, abdominal bloating, abdominal cramps, anal irritation, weakness/dizziness/faint feeling, chills, headache, hunger, thirst, indigestion and overall physical discomfort).

The following parameters were analyzed as part of the laboratory assessments at screening, before colonoscopy and at follow-up visit: sodium (Na), potassium (K), albumin, calcium (Ca), magnesium (Mg), bicarbonate (CO_3H), creatinine (Cr) and urea (BUN). Calculated calcium, BUN/Cr ratio and glomerular filtration rate (eGFR) per the Modification of Diet in Renal Disease (MDRD) equation were also assessed. If available, each laboratory assessment was assigned a Common Terminology Criteria for Adverse Events version 4.03 (CTCAE) grade. Abnormal test results CTCAE grade 3 or more were considered adverse events, except those that were determined to be an error. Abnormal test results CTCAE grade 2 or less were considered adverse events if they were medically significant, according to the investigator's judgement.

Adverse events were assessed during the colonoscopy and the follow-up visits. Neither colonoscopy pathological findings nor the 12 expected adverse reactions, unless classified as serious, were considered adverse events.

Statistical analysis

Statistical analyses have been performed using the software SAS, version 9.1.

The primary endpoint of this study was based on the binary transformation of the GPA: "excellent" and "good" grades were transformed into adequate, and "fair" and "poor" grades were transformed into inadequate. The analysis of the primary outcome so designed followed a superiority model.

The null hypothesis of this study was the lack of difference between both treatment groups with regards to the percentage of adequate preparations. It was estimated that 142 subjects per treatment group were needed in order to detect an absolute difference of 15% in the percentage of adequate preparations between the treatment groups (70% for the AM/PM and 85% for the split-dose), considering a power of 80% and a type I error of 5% for a two-sided test. Considering 10% of lost-to-follow-up subjects, 160 subjects were to be randomized per treatment regimen. No corrections for multiplicity have been applied for the secondary analyses.

The primary analysis used a logistic regression model with factors of regimen, site, gender and age group. Poor ratings have been compared between treatment groups using Chi-square or Fisher exact tests, as appropriate. Segmental evaluations and acceptability and tolerability assessments have been analyzed using ANOVA with factors of regimen, site, gender and age group.

In order to detect any treatment group imbalance for categorical baseline characteristics, a Cochran-Mantel-Haenszel test stratified by the center was performed.

RESULTS

A total of 326 subjects were screened and 321 subjects were eligible and randomized. Five of the randomized subjects were excluded from the safety analysis (SA) set (n=316): 4 did not take SPMC and 1 had a critical informed consent violation. One subject was excluded from the modified intent-to-treat (mITT) set (n=315) since colonoscopy was not performed. Twenty subjects were excluded from the per-protocol (PP) set (n=295) due to protocol violations. A total of 308 subjects completed the

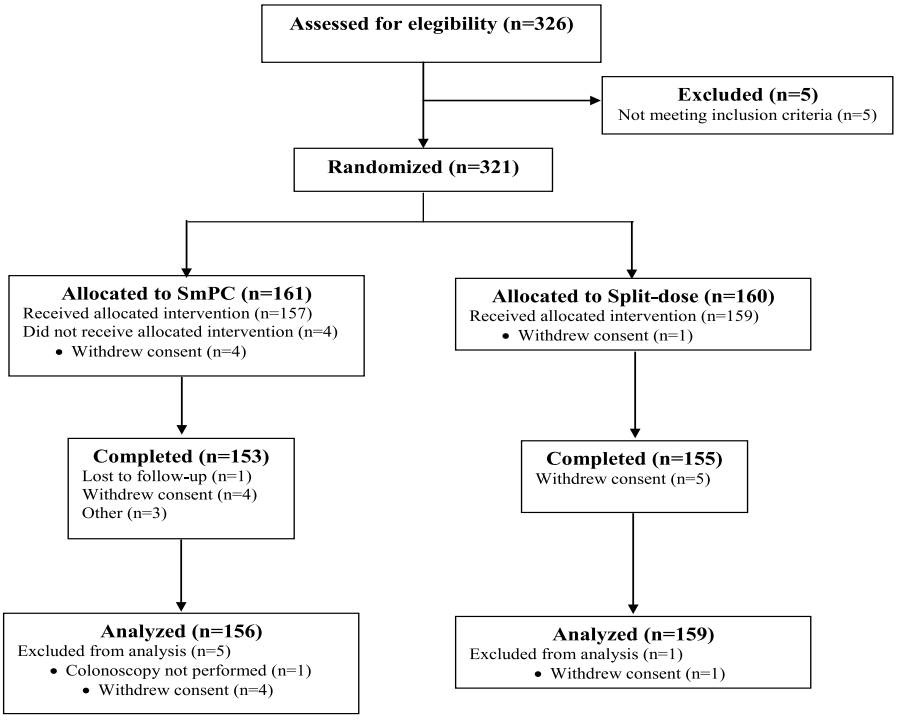

Fig. 1. Subjects flow diagram. SmPC: summary of product characteristics.

study. From those subjects who were randomized, 9 subjects withdrew consent due to personal reasons, 1 subject was lost to follow-up and 3 subjects terminated the study prematurely due to other reasons (Fig. 1).

Treatment groups were comparable regarding demographic characteristics (Table III). In addition, no relevant differences between treatment groups were found for primary reasons for colonoscopy (Table IV).

Efficacy parameters

A significantly higher proportion of patients in the split-dose regimen demonstrated an adequate bowel preparation (AM/PM: 30.8% vs split-dose: 79.9%; p<0.0001) (Table V). Subjects with a medical history of constipation, colon resection, diabetes and/or inflammatory bowel disease were more likely to have a bowel preparation rated as inadequate (Fig. 2). The difference between both groups in the percentage of subjects rendering an adequate bowel preparation was consistent in both age and sex groups, although elderly (≥ 65 yrs) men were somewhat less likely to get an adequate bowel preparation.

When the rating of bowel cleansing was assessed in four categories, there was also a significant difference between both treatment regimens favoring the split-dose schedule (p<0.0001) (Table VI). The proportion of patients with poor bowel preparation was significantly higher in the AM/PM group compared to the split-dose group (AM/PM: 62.2% vs split-dose: 10.7%; p<0.001). The cecum was visualized in a significantly higher proportion of subjects in the split-dose group (AM/PM: 78.8% vs split-dose: 91.8%; p=0.001).

The mean global RSS was significantly lower in the split-dose group (AM/PM: 5.0 [SD: 2.91] vs split-dose: 2.6 [SD: 2.14]; p<0.0001). Segmental RSS results by treatment group are displayed in Fig. 3: the more proximal the segment, the larger the difference between treatment groups.

The overall polyp detection rate was higher in the split-dose group (26.4%) compared to the AM/PM group (21.2%). Flat polyps were detected in a higher proportion of subjects in the split-dose group compared with the AM/PM group (AM/PM: 16.0% vs split-dose: 22.0%).

Acceptability parameters

The majority of subjects considered treatment with SPMC as easy or very easy to take, regardless of the regimen (AM/PM: 96.2% vs split-dose: 93.7%). The taste was also found very or somewhat pleasant by the majority of subjects (AM/PM: 76.9% vs split-dose: 78.0%). An overall good or very good tolerance was observed in 87.2% of subjects in the AM/PM group and in 84.9% of subjects in the split-dose group. Most subjects in both groups were willing to retake the treatment in the future (AM/PM: 96.8% vs split-dose: 96.2%).

Safety parameters

Both regimens were safe and well tolerated. With regards to tolerability to the 12 expected adverse reactions, physical discomfort and nausea were significantly more frequent in subjects receiving the split-dose regimen, while hunger was significantly more frequent in subjects receiving AM/PM regimen (Table VII).

There were four drug-related adverse events (AEs) in each treatment group (Table VIII). There were two subjects with laboratory abnormalities in the AM/PM group, but both laboratory values returned to normal after colonoscopy. One serious adverse event (SAE) was reported in a subject in the AM/PM group before taking the investigational product. There

Table III. Demographic parameters (SA set)

		AM/PM	Split-dose	Total	p-value
		N=157	N=159	N=316	
Age (years)	Mean ± SD	57.6 ± 14.01	56.5 ± 15.56	57.1 ± 14.80	0.811[1]
	Min-Max	19-83	19-86	19-86	
	n	157	159	316	
Height (cm)	Mean ± SD	171.2 ± 9.32	170.6 ± 9.24	170.9 ± 9.27	0.488[1]
	Min-Max	150-192	144-193	144-193	
	n	157	159	316	
Weight (kg)	Mean ± SD	78.0 ± 14.22	76.6 ± 14.50	77.3 ± 14.35	0.611[1]
	Min-Max	41-135	46-137	41-137	
	n	157	159	316	
BMI (kg/m²)	Mean ± SD	26.6 ± 4.56	26.3 ± 4.19	26.4 ± 4.37	0.804[1]
	Min-Max	15-50	18-44	15-50	
	n	157	159	316	
		Nnumber of subjects (% of subjects)			
Gender	male	80 (51.0)	72 (45.3)	152 (48.1)	0.331[2]
	female	77 (49.0)	87 (54.7)	164 (51.9)	
Age group	<65 years	103 (65.6)	106 (66.7)	209 (66.1)	0.825[2]
	≥65 years	54 (34.4)	53 (33.3)	107 (33.9)	
Ethnicity	Caucasian	154 (98.1)	157 (98.7)	311 (98.4)	0.278[2]
	Black or African American	0 (0.0)	2 (1.3)	2 (0.6)	
	Asian	3 (1.9)	0 (0.0)	3 (0.9)	
	Other	0 (0.0)	0 (0.0)	0 (0.0)	

[1] p-value from ANOVA with factors treatment, centre and treatment-by-centre interaction; [2] p-value from Cochran-Mantel-Haenszel test; SA: safety analysis.

were no serious AEs in subjects who received the split-dose regimen. None of the AEs led to study discontinuation.

Eleven patients (AM/PM n=5, split-dose n=6) reported 12 grade 3 or 4 CTCAE abnormal laboratory values, 7 of them occurring in elderly subjects (AM/PM n=1, split-dose n=6). Eight of those reactions were considered artifacts by the investigator, 5 of them in elderly subjects. One of these adverse events concerned an elderly patient in the split-dose group who reported a Na value of 119 mmol/l, suffering

Table IV. Primary reasons for colonoscopy (SA set)

	AM/PM	Split-dose
	N=157	N=159
Screening (no personal history of polyps or cancer)	58 (36.9)	63 (39.6)
History of polyps	26 (16.6)	21 (13.2)
Change in bowel habits	26 (16.6)	21 (13.2)
Inflammatory bowel disease	22 (14.0)	23 (14.5)
Rectal bleeding	4 (2.5)	9 (5.7)
Family history of colon cancer	5 (3.2)	4 (2.5)
Cancer surveillance (follow-up evaluation)	4 (2.5)	5 (3.1)
Anaemia	2 (1.3)	2 (1.3)
Abnormal imaging (barium enema, CT, MRI)	0 (0.0)	0 (0.0)
Other	10 (6.4)	11 (6.9)

SA: safety analysis.

Table V. Results for the primary efficacy parameter (mITT set)

	AM/PM (n=156)	Split (n=159)	Odds Ratio (Split vs AM/PM) 95% exact CI[1]	p value[2]
	N (%)	N (%)		
Bowel cleansing adequacy				
Adequate	48 (30.8)	127 (79.9)	12.92 (7.14 – 23.40)	<0.0001
Inadequate	108 (69.2)	32 (20.1)		

[1] OR and CI derived from logistic regression model with factors for treatment, site, gender and age group; [2] p value for treatment effect.

Table VI. Rating of bowel cleansing according to four categories in the GPA (mITT set)

	AM/PM (n=156)	Split (n=159)	Odds Ratio (Split vs AM/PM) (95% exact CI)	p value[2]
	N (%)	N (%)		
Bowel cleansing rating (GPA)				
Excellent	9 (5.8)	59 (37.1)	13.95 (8.36 – 23.30)	<0.0001
Good	39 (25.0)	68 (42.8)		
Fair	11 (7.1)	15 (9.4)		
Poor	97 (62.2)	17 (10.7)		

[1] OR and CI derived from ordinal logistic regression model with factors for treatment, site, gender and age group,[2] p value for treatment effect; GPA: Global Preparation Assessment; mITT: modified intend-to-treat.

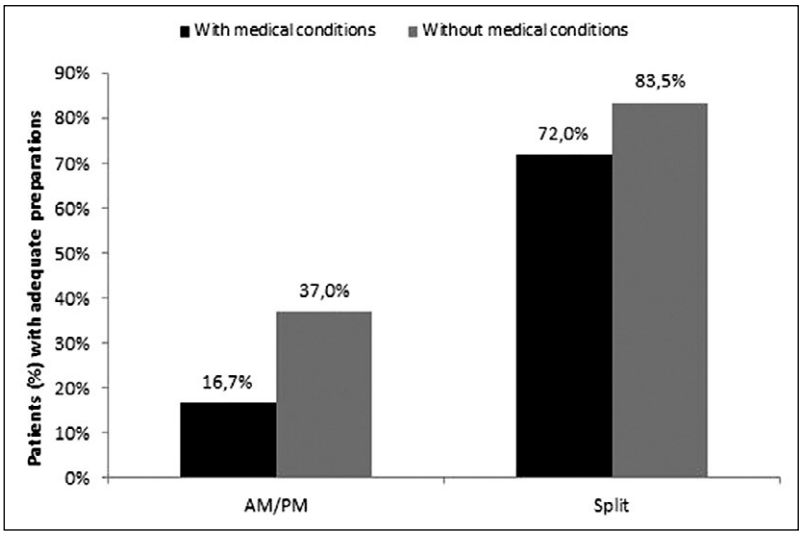

Fig. 2. Bowel cleansing adequacy by treatment group and presence of specific medical condition (mITT set). Medical conditions considered were constipation, colon resection, diabetes and/or inflammatory bowel disease.

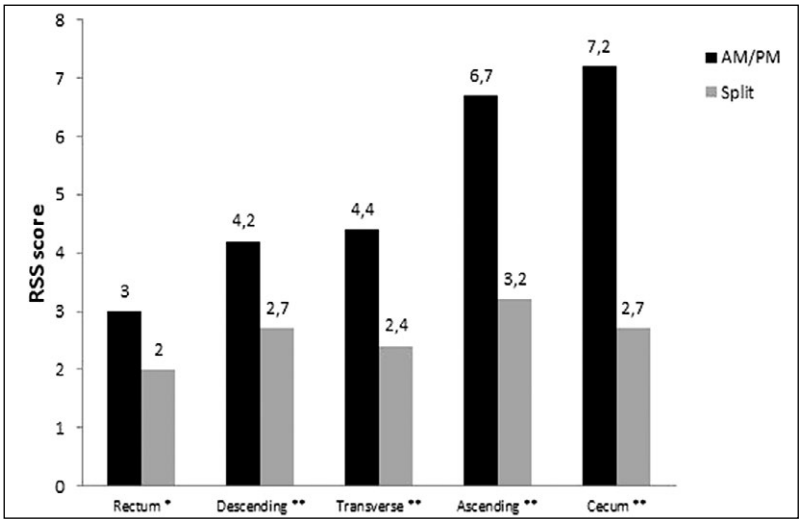

Fig. 3. Segmental Residual Stool Score (RSS) by treatment group (mITT). RSS score: from 0 (best) to 12 (worst) *p=0.0008; **p<0.0001

from moderate overall physical discomfort, which returned to normal at follow-up visit. Another elderly patient in the split-dose group who already suffered from a compensated renal failure at study entry reported a grade 4 CTCAE GFR value during the follow-up visit (29 ml/min/1.73m^2). Another young patient in the AM/PM group reported grade 3 CTCAE

Table VII. Tolerance: expected side-effects (mITT set)

	SmPC (AM/PM) n=156 number (%) of subjects	Split-dose (PM/AM) n=159 number (%) of subjects	Odds ratio (split vs SmPC) (95%CI)	p value
Nausea	21 (13.5)	37 (23.3)	1.92 (1.06-3.49)	0.034
Vomiting	4 (2.6)	4 (2.5)	0.94 (0.23-3.87)	0.930
Stomach bloating	38 (24.4)	44 (27.7)	1.16 (0.7-1.94)	0.560
Stomach cramps	22 (14.1)	24 (15.1)	1.13 (0.60-2.14)	0.706
Anal irritation	62 (39.7)	58 (36.5)	0.84 (0.52-1.33)	0.448
Weakness, dizziness or faint feeling	23 (14.7)	26 (16.4)	1.09 (0.59-2.04)	0.779
Chills	18 (11.5)	20 (12.6)	1.03 (0.52-2.06)	0.935
Headache	45 (28.8)	43 (27.0)	0.88 (0.53-1.45)	0.608
Hunger	72 (46.2)	51 (32.1)	0.53 (0.33-0.86)	0.009
Thirst	51 (32.7)	45 (28.3)	0.81 (0.49-1.32)	0.389
Indigestion	13 (8.3)	14 (8.8)	1.12 (0.50-2.52)	0.782
Overall physical discomfort	27 (17.3)	47 (29.6)	2.04 (1.19-3.50)	0.010

mITT: modified intend-to-treat.

Table VIII. Safety: drug-related adverse events (SA set)

	AM/PM (n=157)	Split (n=159)
	no. subjects (% subjects) no. events	
Feeling cold	1 (0.6) 1	3 (1.9) 3
Fatigue	1 (0.6) 1	0 (0.0) 0
Hypercreatininaemia	1 (0.6) 1	0 (0.0) 0
Hypocalcaemia	1 (0.6) 1	0 (0.0) 0
Dysgeusia	0 (0.0) 0	1 (0.6) 1

hyperkalaemia (6.2 mmol/l) at the colonoscopy visit which returned to normal in the follow-up visit. Finally, one young patient in the AM/PM group reported an asymptomatic grade 4 CTCAE hyperkalaemia (8.5 mmol/l) at the follow-up visit.

Most of the remaining laboratory parameter changes occurring in both study groups with similar frequencies, were transient and returned to pre-treatment levels. Hyponatraemia was slightly more frequent in the split-dose group (AM/PM n=6, 3.8%; split-dose n=10, 6.3%), but all except one (commented above) were mild and asymptomatic.

DISCUSSION

The results of this clinical trial demonstrate the superiority of the split-dose regimen of SPMC compared to the AM/PM-regimen in terms of efficacy. This superiority of the split-dose regimen has been consistent through all parameters of efficacy, such as global bowel cleansing assessed using a binary transformation of a categorical scale, a segmental scale, bowel cleansing in the right colon, cecal intubation rates and detection of polyps.

This is, to our knowledge, the first study comparing head-to-head a split-dose regimen of SPMC with the AM/PM regimen of the product. There are several previous reports confirming the good efficacy results of the split-dose SPMC regimen for bowel cleansing. When both prior-evening and split-dose regimens of SPMC added bisacodyl, the split-dose schedule achieved a significantly better bowel cleansing [12]. Similar findings were obtained when prior-evening and split-dose regimens of SPMC were compared [16]. The split-dose regimen of SPMC has also been shown superior for bowel cleansing to a prior-evening schedule of PEG-2L plus bisacodyl [14].

The efficacy of the split-dose regimen in this study is not surprising. Parra-Blanco et al. showed that same-morning regimens (preparations administered during the morning of colonoscopy), compared to prior-evening ones, of either PEG3L or oral sodium phosphate solution, rendered significantly better bowel cleansing and a significantly higher number of flat polyps were detected [17]. Other reports have shown that split-dose schedules are significantly better than previous-day ones or alternative regimens [18, 19]. These results stress the importance of reducing the time from the end of the preparation until the colonoscopy in order to improve the quality of bowel cleansing. In line with this, Hassan et al. recommended the split-dose regimen as the preferred one in the European Society of Gastrointestinal Endoscopy (ESGE) Guideline [7].

In our study, only 31% of patients allocated to the AM/PM treatment group achieved an adequate bowel cleansing. This result differs from the results published in earlier reports with this regimen. In general, between 50% and 80% of patients receiving the AM/PM regimen of SPMC for colonoscopy rendered a satisfactory bowel cleansing [5, 20, 21]. We identified several reasons for such poor results for the AM/PM treatment group in this study. Firstly, the GPA scale used in this study is more demanding than other scales because, for a preparation to be classified as adequate, no semi-solid stool in the colon is allowed, regardless of whether residues are washable or not; additionally, in contrast with other scales, amount and consistency of residues are assessed prior to any washing effort. Secondly, a significant percentage of patients in this study (31%) suffered from conditions known to make bowel cleansing more difficult (constipation, colon resection, diabetes or inflammatory bowel disease). In fact, these subjects were more likely to have a bowel preparation rated as inadequate. Finally, patients were allowed to have lunch during the day prior-to-colonoscopy, which may have had adversely affected the efficacy of the AM/PM group too.

The administration of both bowel preparation schedules was safe. However, for both regimens temporary shifts in electrolytes and decrease of renal function were observed in single patients. Especially in elderly patients with pre-existing chronic renal insufficiency, monitoring of kidney function and electrolytes should be considered.

This study has some limitations. Firstly, it was a single blinded study due to the differences in the administration schedules. However, in order to avoid bias, commonly accepted measures to ensure that endoscopists remain blinded were implemented. Secondly, the scale used to evaluate bowel cleansing is not fully validated. However, this scale has been subjected to construct validity and inter-observer reliability assessments [22, 23]. Additionally, using pooled data from 477 subjects in three separate studies, colon polyps were detected in 48.7% of adequate preparations versus 37% of inadequate preparations (p=0.055).

CONCLUSION

In conclusion, the split-dose regimen of SPMC has shown a superior efficacy for bowel cleansing compared to the AM/PM one in patients preparing for colonoscopy. This study supports that split-dose schedule is the preferential method of bowel preparation for colonoscopy.

Conflicts of interest: No conflict to declare.

Authors contribution: C.B. and C.S. made a substantial contribution to the analysis and interpretation of the data, drafted the manuscript together and revised it critically, and gave approval to the submitted and final version. C.B., C.S., S.M., J.M. and J.S. contributed to the study design. C.S., J.M., J.S., S.M. and C.S. performed the study and collected data. D.H. and P.M. supervised the study. C.S. and P.M. performed a critical revision of the manuscript. All authors approved the final version of the manuscript.

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Superioritatea unui regim cu doză divizată de picosulfat de sodium/citrat de magneziu (SPMC) pentru pregătirea colonului, comparativ cu regimul de administrare în ziua premergătoare examinării (AM/PM). Studiu randomizat simplu orb

ABSTRACT / REZUMAT

Premize și Scop: Regimurile cu administrare divizată a dozei sunt în general recomandate pentru curățirea colonului. Cu toate acestea, alte regimuri rămân în continuare incluse în sumarul caracteristicilor unor produse utilizate în Europa pentru pregătirea colonului. Scopul acestui studiu este de a compara eficacitatea și siguranta unui regim utilizând doza divizată de picosulfat de sodium/citrat de magneziu (SPMC) cu cea a regimului de administrare a SPMC în ziua premergătoare examinării.

Metodă: Un studiu multicentric, randomizat (EudraCT no. 2013-001620-20), paralel, simplu orb (endoscopistul) a fost efectuat unor subiecți (≥ 18 ani) programați pentru colonoscopie electivă. Obiectivul primar a fost evaluarea curățirii colonului utilizând o functie binară (adecvat/inadecvat) a scalei Global Preparation Assessment (GPA). Parametrii adiționali analizați au fost evaluarea pe segmente a gradului de curățare a colonului (RSS), rata de detectare a adenoamelor și siguranța administrării.

Rezultate: 315 subiecți au fost incluși în grupul inițial (ITT, intention to treat). O proporție semnificativ mai mare de pacienți pregătiți în regimul cu doză divizată (seara premergătoare și dimineața examinării) au avut o pregătire adecvată a colonului comparative cu cei cu doza administrate în ziua premergătoare examinării (AM/PM: 30.8% vs doza divizată: 79.9%; p<0.0001). Scorul mediu global RSS a fost semnificativ mai redus la grupul cu doză divizată (AM/PM: 5.0 [SD: 2.91] vs doza divizată: 2.6 [SD: 2.14]; p<0.0001). Polipii plați au fost detectați în proporție mai mare la subiecții cu doza divizată (AM/PM: 16.0% vs split-dose: 22.0%). Ambele regimuri au fost la fel de sigure și de bine tolerate, fără reacții adverse serioase la preparat sau întrerupere datorită reacțiilor adverse.

Concluzie: Regimul de administrare divizată a SPMC este superior regimului AM/PM administrat în ziua premergătoare examinării, și ar trebui să fie considerat ca standard de pregătire pentru colonoscopie.