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ORIGINAL ARTICLE

Barriers against split-dose bowel preparation for colonoscopy

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ABSTRACT

Objective Although split regimen is associated with higher adenoma detection and is recommended for elective colonoscopy, its adoption remains suboptimal. The identification of patient-related barriers may improve its implementation. Our aim was to assess patients' attitude towards split regimen and patient-related factors associated with its uptake.

Design In a multicentre, prospective study, outpatients undergoing colonoscopy from 8:00 to 14:00 were given written instructions for 4 L polyethylene glycol bowel preparation, offering the choice between split-dose and day-before regimens and emphasising the superiority of split regimen on colonoscopy outcomes. Uptake of split regimen and association with patient-related factors were explored by a 20-item questionnaire.

Results Of the 1447 patients (mean age 59.2 ±13.5 years, men 54.3%), 61.7% and 38.3% chose a split-dose and day-before regimens, respectively. A linear correlation was observed between time of colonoscopy appointments and split-dose uptake, from 27.3% in 8:00 patients to 96% in 14:00 patients ($p<0.001$, χ^2 for linear trend). At multivariate analysis, colonoscopy appointment before 10:00 (OR 0.14, 95% CI 0.11 to 0.18), travel time to endoscopy service >1 h (OR 0.55, 95% CI 0.38 to 0.79), low education level (OR 0.72, 95% CI 0.54 to 0.96) and female gender (OR 0.74, 95% CI 0.58 to 0.95) were inversely correlated with the uptake of split-dose. Overall, the risk of travel interruption and faecal incontinence was slightly increased in split regimen patients (3.0% vs 1.4% and 1.5% vs 0.9%, respectively; p=NS). Split regimen was an independent predictor of adequate colon cleansing (OR 3.34, 95% CI 2.40 to 4.63) and polyp detection (OR 1.46, 95% CI 1.11 to 1.92).

Conclusion Patient attitude towards split regimen is suboptimal, especially for early morning examinations. Interventions to improve patient compliance (ie, policies to reorganise colonoscopy timetable, educational initiatives for patient and healthcare providers) should be considered.

Trial registration number NCT02287051; pre-result.

Significance of this study

What is already known on this subject?

- A split regimen of bowel preparation for colonoscopy has been associated with an improvement of colonic cleansing and adenoma detection.
- A split regimen is strongly recommended by guidelines as routine bowel preparation for elective outpatient colonoscopies.
- The routine adoption of split-dose regimen in clinical practice is suboptimal worldwide.
- Patient-related barriers to split regimen implementation have never been extensively explored.

What are the new findings?

- When offering the choice between a split regime and a day-before regimen, nearly 40% of the study population refused the adoption of a split regimen despite receiving adequate written information on the benefits of such regimen.
- Early timing of colonoscopy (<10:00), female gender and indicators of the socioeconomic status represented the main patient-related barriers against the adoption of a split regimen.
- Primary care physicians and pharmacists had a negative influence on the choice of a split regimen.

How might it impact on clinical practice in the foreseeable future?

- Interventions to improve patient compliance with split-dose regimens, such as policies to reorganise colonoscopy timetable and initiatives to improve either patient or healthcare providers' education, should be encouraged.

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INTRODUCTION

Optimising bowel preparation is critical to increase the effectiveness of colonoscopy in clinical and screening settings. The adoption of a split-dose regimen (ie, the administration of the first half of the bowel preparation the evening before colonoscopy and the second half on the morning of the procedure) has been associated with both a higher quality of bowel preparation[1 2] and a substantial increase in the detection of both (advanced) neoplasia and serrated lesions[3–5] and it is currently recommended by official guidelines.[6 7]

Unexpectedly, the adoption of a split-dose regimen remains suboptimal—especially for morning colonoscopies—in both Europe and USA.[8 9] Main barriers appeared to be related with patient-related factors, such as unwillingness to get up early on the day of colonoscopy and the fear of bowel movements or soiling while travelling to the endoscopy service.[10 11] A few surveys revealed that the vast majority of patients would overcome these potential inconveniences and comply with split-dosing, when appropriately informed on its superiority in terms of colon cleansing and tolerability.[12–14] However, these surveys were generally performed out from a real colonoscopy setting, such as patients undertaking upper endoscopy or other simulated scenarios, generating uncertainty on the real orientation of patients towards a split regimen.

The aim of this multicentre, prospective study was to assess the actual uptake of a split-dose regimen in routine clinical practice and to identify patient-related barriers to its implementation.

METHODS

The study was prospectively performed in 19 open-access endoscopy centres in Italy. The protocol was approved by the Ethics Committee of the participating institutions and it was registered in the http://www.clinicaltrials.gov register (NCT02287051). Written and informed consent was obtained from all subjects enrolled in the study. This was a no-profit study and the investigators had no relationship with the manufacturers of the bowel cleansing agent used in the study; no funding for the study was solicited or accepted.

Study population

The target population included all adult outpatients (aged between 18 and 80 years) presenting for scheduled morning (8:00–14:00) colonoscopy for routine indications during the recruitment period of the study. Exclusion criteria were (1) indication to partial colonic examination, (2) previous colonoscopy, (3) afternoon colonoscopy (after 14:00), (4) patients unable to read, comprehend or consent to their involvement in the study, (5) severe comorbidities, including end-stage cardiovascular, pulmonary, liver or renal diseases (ie, American Society of Anesthesiologists classification system grade III–IV) and (6) pregnancy.

Intervention

For the purpose of this study, patients were freely offered the choice between a 'split-dose' and a 'day-before' regimen, after having been extensively informed about *pros* and *cons* with a dedicated leaflet (see online supplementary figures S1 and S2). According to standard practice in open-access endoscopy centres in Italy, only written instructions for bowel preparation were delivered by secretary staff, so that healthcare providers in the endoscopy centres did not directly influence patients' choice of the preparation regimen. In detail, at the time of colonoscopy scheduling, eligible patients received a standard leaflet highlighting the importance of high-quality bowel preparation and reporting instructions for a 1 day clear liquid diet and for both 'split-dose' and 'day-before' regimens. The leaflet clearly emphasised the superiority of a split-dose regimen (over the 'day-before') in terms of quality of bowel preparation and colonoscopy outcomes, but it also reported the need to get up during the night for early morning procedures and a minimally increased risk of travel interruption for bowel movements during transit to endoscopy centre. To avoid bias related with the type of laxative, patients were required to assume one of the high-volume (ie, 4 L) polyethylene glycol solutions available in Italy (SELG, Alfa Wassermann, Bologna, Italy; SELG-ESSE, Wassermann, Bologna, Italy; ISOCOLAN, Giuliani S.p.A. Milano, Italy)

Data recording

Before colonoscopy, the GI assistant collected, through a 20-item structured questionnaire, data on the characteristics of patients (six items: age, gender, education, working status, transport modality and travel time to get to the endoscopy centre) and bowel preparation (eight items: split regime versus day-before regimen, time of last dose intake, compliance with preparation instruction, main determinants/barriers of preparation regimen choice, need for travel interruption, faecal incontinence or soiling during endoscopy transfer, quality of sleep, willingness to repeat the same preparation in the future). At the end of the procedure, the endoscopist, who was blind to the bowel preparation regimen, reported colonoscopy data (six items: appointment time, indication to colonoscopy, caecal intubation, polyp detection, withdrawal time for diagnostic procedures and quality of bowel preparation, according to the Boston Bowel Preparation Scale (BBPS)).[15]

Outcome measures

Our primary aim was to assess the proportion of patients choosing split-dosing for bowel preparation when undergoing morning colonoscopy and to identify patient-related and procedure-related factors affecting the choice of split-dose preparation. Secondary aims were to evaluate (1) compliance with bowel preparation and its tolerability, (2) procedural outcomes, including caecal intubation and polyp detection rates (PDRs) and the quality of bowel preparation. Colon preparation quality was considered adequate if the BBPS score was ≥6.

Sample size calculation and statistical analysis

The primary aim of the study included two end points: (1) estimating the proportion choosing split-dosing; (2) estimating the OR of independent predictors of selection, by means of multivariable logistic regression. Although the two end points appeared to be correlated, this correlation had no impact on the calculation of the sample size, since the first was an estimate of accuracy and did not imply power issues. The possible rate of split-dosing selection was unknown; therefore, we selected a sample such that under the most restrictive conditions (0.50 select one or the other procedure) it would allow to report the point estimate of the proportion with a 95% accuracy of 0.05 (two-sided) or more. Approximately 1500 patients would allow to report a point estimate of 0.50 with a 95% CI of ±0.025. Any proportion greater (or smaller) than 0.50 would be estimated with a greater accuracy (eg, proportions of 0.300 or 0.700 would be estimated with a 95% accuracy of ±0.023). The same sample would also have 80% power to identify with 95% CI (α error <0.05), an independent predictor of the choice having an OR ≥1.25 (or, conversely, an OR ≤0.75) for an overall proportion of events (choice of split-dosing) of 0.10 or more, on the assumption of a multivariate correlation coefficient among predictors of not more than 0.300.[16] Empirically, under the assumptions of a proportion of events of 0.10 or more (150 events), the sample would allow to correctly estimate the effect size of up to 15 predictors.[17]

Categorical variables were summarised using frequencies and percentages, while quantitative variables were summarised using means and SDsSD. Fisher's exact test and χ^2 test for trend were used to compare categorical variables, whereas Student's t test

was used for continuous variables. A logistic stepwise regression model was used to assess predictors of split-dose acceptance, adequate colon cleansing and polyp detection. We used an automated stepwise procedure as a contribution to model-building; the final set of variables included in the model was defined taking into account both statistical parameters and clinical judgement. All parameters with a $p<0.2$ on univariate analysis were included and those with a $p>0.4$ were removed, according to an automated stepwise procedure. For all comparisons, the OR and 95% CI were given for significant variables. A $p<0.05$ was considered statistically significant.

RESULTS

From June to October 2014, a total of 1469 patients were enrolled in the participating centres; of them, 1447 patients (mean age 59.2±13.5 years, men 54.3%) presented at endoscopy appointment and were included into the analysis. In the study cohort, 892 (61.7%) and 555 (38.3%) patients chose a split-dose and day-before regimen, respectively.

Patient-related and procedure-related features in each group are shown in table 1. Female gender, low education level, working status and a longer travel time to endoscopy unit were inversely associated with the choice of a split-dose regimen (table 1). As concerns procedure-related factors, we observed a linear correlation between split-dose uptake and time of colonoscopy appointment, with higher uptake rates for patients scheduled later in the morning (figure 1). In detail, split-dose uptake ranged from 27.3% in patients scheduled at 8:00 to 96% in those scheduled at 14:00; split-dose regimen was chosen by 33.4% of subjects scheduled from 8:00 to 10:00 and by 78.2% of those scheduled later ($p<0.01$).

Overall, 1123 of 1447 subjects (77.6%) reported the choice of bowel preparation to be exclusively driven by the information provided by the leaflet. In this subgroup, the main drivers of split-dose regimen choice were the higher guarantee of adequate colon cleansing (344/716 patients, 60.6%), better tolerability (31.9%) and less interference with job activity during the day before colonoscopy (7.5%). Among patients who did not choose split-dose regimen, the main barriers were the fear of bowel movements during travelling (199/407 patients, 49.9%) and the refusal to get up early in the morning (47.9%); 13 patients (3.2%) could not specify the reason for their choice.

In the remaining 324 cases (22.4%), the choice was influenced by the advices provided by referring physician (GI specialist or family doctor) or other persons (pharmacist, relatives and friends). In this subgroup, a significantly higher proportion of subjects chose split regimen when advised by GI specialist and, conversely, the day-before regimen when advised by pharmacists (table 2).

At logistic regression analysis, colonoscopy appointment time before 10:00 h (OR 0.14, 95% CI 0.11 to 0.18), distance from home to endoscopy service ≥1 h (OR 0.55, 95% CI 0.38 to 0.79), low education level (OR 0.72, 95% CI 0.54 to 0.96) and female gender (OR 0.74, 95% CI 0.58 to 0.95) were inversely associated with split-dose regimen uptake.

Compliance, satisfaction and tolerability

Compliance with product intake and willingness to repeat the same preparation regimen in the future are shown in table 3. The proportion of patients who were able to take the entire preparation and who would be willing to repeat the same preparation were significantly higher in the split-dose regimen than in the day-before group. The quality of sleep was significantly better in the split-dose group. Overall, the risk of travel interruption and faecal incontinence was small (2.4% and 1.2%, respectively). These risks were slightly increased, although not significantly, in patients adopting split-dose than full dose regimen (table 3).

Table 1 Patient- and procedure-related features in each study group

	Total (n=1447)	Split-dose group (n=892)	Day-before group (n=555)	p Value
Mean age (SD), year	59.2 (13.5)	58.9 (13.5)	59.5 (13.6)	0.30
Males, n (%)	787	511 (64.9)	276 (35.1)	0.005
Education, n (%)				
Less than high-school	602	331 (55.0)	271 (45.0)	0.0001
High-school	563	369 (65.5)	194 (34.5)	
Degree	282	192 (68.1)	90 (31.9)	
Working status, n (%)				
Unemployed/ retired	732	425 (58.1)	307 (41.9)	0.011
Employed	523	336 (64.2)	187 (35.8)	
Self-employed	192	131 (68.2)	61 (31.8)	
Site of colonoscopy scheduling, n (%)				
Endoscopy service	151	102 (67.5)	49 (32.5)	0.48
Single booking centre	1296	790 (60.9)	506 (39.1)	
Distance to endoscopy centre, n (%)				
Less than 1 h	1264	800 (63.3)	464 (36.7)	0.006
From 1 to 2 h	149	83 (55.7)	66 (44.3)	
More than 2 h	32	9 (28.1)	23 (71.9)	
Transport to the endoscopy centre, n (%)				
Car	1312	822 (62.7)	490 (37.3)	0.014
Public transport	135	70 (51.8)	65 (48.2)	
Colonoscopy indication, n (%)				
Screening	826	504 (61.1)	322 (38.9)	0.57
Symptoms	621	388 (62.5)	233 (37.5)	
Time of colonoscopy appointment n (%)				
From 8:00 to 9:00	264	74 (28.0)	190 (72.0)	<0.0001
From 9:00 to 10:00	239	94 (39.3)	145 (60.7)	
From 10:00 to 11:00	319	212 (66.4)	107 (33.6)	
From 11:00 to 12:00	223	166 (74.4)	55 (25.6)	
From 12:00 to 13:00	291	255 (87.6)	36 (12.4)	
From 13:00 to 14:00	111	105 (94.5)	6 (5.5)	

Procedure outcomes

Caecal intubation was achieved in 860/892 and in 530/555 subjects in the split-dose and day-before group, respectively (97.5% vs 95.5%, $p=0.048$). At least one polyp (PDR) was found in 401/892 subjects in the split-dose group and 203/555 subjects in the day-before group (45.0% vs 35.6%, $p=0.002$). At logistic regression analysis, split-dose regimen (OR 1.46, 95% CI 1.11 to 1.92), withdrawal time (OR 1.29, 95% CI 1.23 to 1.36) and patient age (OR 1.04, 95% CI 1.03 to 1.05) were independent predictors of PDR.

The quality of bowel prep was rated as adequate (BBPS ≥6) in 822/892 patients in split-dose group and in 420/555 patients in the day-before group (92.2% vs 75.7%, $p<0.001$). Consistent figures were observed as concerns an adequate proximal colon cleansing in the split-dose and day-before groups (91.1% vs 73.5%, $p<0.001$). Independent predictors of adequate colon cleansing were full compliance with laxative intake (OR 5.51, 95% CI 3.8 to 7.8), split-dosing (OR 3.34, 95% CI 2.40 to 4.63) and screening indication (OR 1.42, 95% CI 1.03 to 1.98)

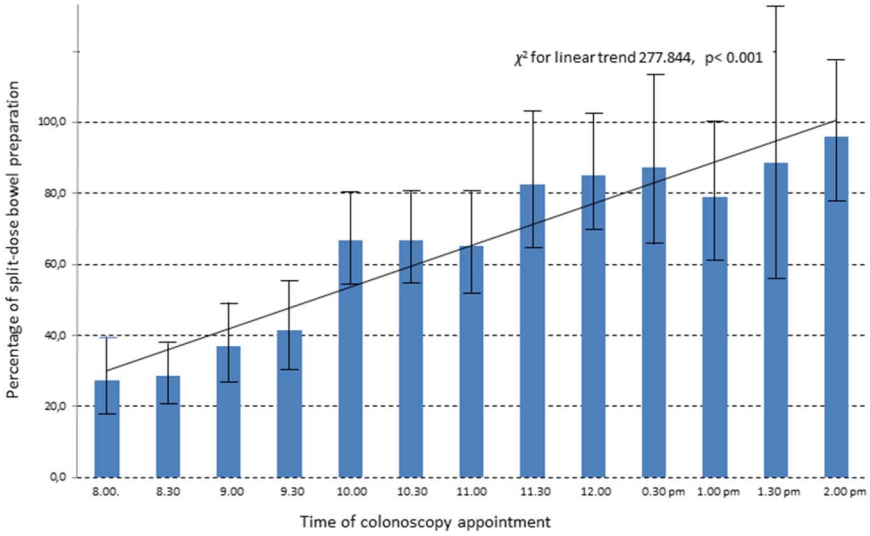

Figure 1 Split-dose regimen uptake (percentage and 95% CI) according to the time of colonoscopy appointment.

DISCUSSION

According to our study, a substantial proportion of patients—corresponding to nearly 40% of the study population—refused the adoption of a split regimen after being adequately informed about the *pros* and *cons* of such regimen. In addition, we showed that simple factors—such as the time of the procedure, female gender and indicators of the socioeconomic status—represented the main patient-related and procedural-related barriers against the adoption of such regimen. We also confirmed a clinically relevant association between the adoption of a split regimen and the main outcomes of colonoscopy.

The results of our study are relevant for several reasons. First, the impact of patient-related barriers is clinically relevant. The adoption of a split regimen has been associated with a 30% higher detection rate of both neoplasia and advanced neoplasia in a high-quality randomised controlled trial,[4] and in turn neoplasia detection rate has been strictly associated with the post-colonoscopy risk of interval cancer.[18 19] Thus, the 38% rate of patients displaced from the split regimen indicated that patient-related barriers severely undermined the efficacy of colonoscopy in preventing colorectal cancer (CRC). Second, we showed that adequate information on the *pros* and *cons* of a split regimen failed to convince a substantial proportion of patients to choose it, indicating patients' failure in appropriately outweighing the potential gain in CRC prevention against the potential disadvantages of a split regimen. Of note, the main reason—that is, 50%—referred by those who refused the split regimen was the fear of bowel movements during travelling, despite this actually occurring only in a tiny fraction of the split group. Thus, it is important for the medical community to address these barriers, irrespectively of how trivial they may appear. In this regard, the very strict relationship between timing of the morning colonoscopy and a favourable attitude towards a split regimen appears as clinically relevant. According to our data, the simple shifting of the timing of the first colonoscopy after 10:00 h (with anticipation of inpatients or upper GI endoscopy patients) would minimise the patient-related resistance to a split regimen by 86%, thus marginalising the unfavourable impact of this barrier in clinical practice. To readapt endoscopy timetable to such cut-off for morning colonoscopy patients would appear extremely more simple and effective than any complex intervention aiming at appropriately orientating the general population on how to outweigh the *pros* and *cons* of a preventive intervention. Similarly, the strict association between the refusal of a split regimen and the duration of patient travelling would suggest the necessity for the healthcare providers to minimise such distance, by scheduling the patient appointment in the nearest endoscopy centre when an individual provider has multiple endoscopic satellites.

Table 2 Factors influencing the choice of bowel preparation regimen

	Total (n=1447)	Split-dose group (n=892)	Day-before group (n=555)	p Value
Leaflet information	1123	716 (63.7)	407 (36.3)	0.002
Advise by referring GI specialist	167	128 (76.6)	39 (23.4)	<0.001
Advise by referring primary care physician	70	45 (64.2)	25 (35.8)	0.64
Advise by pharmacists	37	15 (40.5)	22 (59.5)	0.007
Advise by relatives or friends	50	28 (56.0)	22 (44.0)	0.082

Table 3 Compliance and tolerance

	Split-dose group (n=892)	Day-before group (n=555)	p Value
Compliance with product intake, n (%):			<0.0001
Whole dose (4 L)	797(89.3)	440 (79.3)	
At least 75% of product	74 (8.3)	97 (17.5)	
Less than 75% of product	21 (2.4)	18 (3.2)	
Willingness to repeat the same preparation in the future, n (%)	822 (92.2)	439 (79.1)	<0.0001
Quality of sleep, n (%)			<0.0001
Sleepless night	19 (2.1)	11 (2.0)	
Severe distress	46 (5.5)	43 (7.7)	
Moderate distress	133 (14.8)	160 (28.8)	
Mild/no distress	694 (77.6)	341 (61.5)	
Need for travel interruption, n (%)	27 (3.0)	8 (1.4)	0.08
Faecal incontinence, n (%)	13 (1.5)	5 (0.9)	0.49

Third, we showed that the refusal of a split regimen was associated with patient-related barriers, such as the female sex and a lower educational or socioeconomic status. Despite new, the gender-related barrier against a split regimen was not unexpected. Anecdotally, women reported the impossibility to undertake a split regimen due to interference over early morning domestic or familial activities. Thus, it may appear reasonable to reserve to female patients a priority access to late morning colonoscopies, when required. The inverse association between the low educational and socioeconomic levels is also clinically relevant, since it may help to explain the lower level of bowel cleansing reported in such patients in previous studies.[20–23]

In our study, patients were provided only with written information and instruction. It could be argued that additional oral information on bowel preparation should be provided to patients[6 8]; this is simply impossible in large public health systems, when considering the limitation of resources, as well as the nature of an 'open-access' system and the magnitude of population served by each endoscopy unit. It is conceivable that the combination of written and verbal instructions might enhance split-dose uptake, but this hypothesis needs further evaluation. The written-based methodology of our study allowed for assessing the potential impact by the non-endoscopic medical and para-medical communities. If the favourable effect on the choice of a split regimen by GI physicians was expected, the neutral impact by primary care physicians and the negative influence by pharmacists were disappointing. This shows that an educational campaign, also targeting family doctors and pharmacists, on the irreversible necessity to adopt a split regimen by the GI community is needed.

The results of our study are apparently in conflict with previous surveys, showing that patients overestimated the advantages of a split regimen over the *cons*, marginalising the potential role of patient-related barriers. However, we tested the reliability of these convictions in clinical practice, in contrast with such surveys, which were based on questionnaires provided to oesophagogastroduodenoscopy patients or patients who were scheduled for morning colonoscopy. It is likely that when patients had to practically choose between a split regime and a day-before regimen in real life, they behaved differently than when invited to imagine a possible behaviour in a simulated scenario.

The large sample size of our analysis allowed for confirming the robust association between a split regimen and the main outcomes of colonoscopy. In detail, the caecal intubation rate, the mean level of bowel cleansing and the PDR were significantly increased by the adoption of a split regimen. Similarly, the tolerability of the high-volume solution was improved by the adoption of the split regimen.

The multicentre design of the study provided highly generalisable results. However, we acknowledge certain limitations First, although the study targeted all patients booking colonoscopy in a definite time-period, the delivery of the leaflet was performed by secretary personnel, so that we cannot guarantee the enrolment of all patients meeting the inclusion criteria. In spite of that, we believe that a selection bias was unlikely, as the secretary staff simply delivered the leaflet containing written instructions for colonoscopy preparation and were ultimately unaware of the study purposes. Second, we can neither definitely exclude the possibility of reporting and observer biases. For reporting bias (the participant report the desired response), it seems unlikely that patients could misreport the type of preparation to please the researcher and the interviewers could anyway eventually verify if the type of preparation declared could be consistent with other procedural steps included in the questionnaire (ie, timing of the preparation). As concerns the observer bias, this should have been minimised by the fact that the endoscopist performing the procedure and assessing the quality of bowel cleansing was blind to the preparation regimen. Actually, data on bowel prep (including the type of regimen and timing of last dose intake) were collected by the GI assistant before the procedure. We should also consider that both the quality of bowel cleansing and PDR were not the main outcome of the study. We already know, from randomised experimental studies that the quality of bowel prep is indeed superior with split dose in terms of quality of bowel prep and detection rate of neoplastic lesions.[4]

Third, compliance with bowel preparation, secondary outcome of the study, was self-reported instead of formally checked, for example by asking patients to bring back the original package. However, given that we were conducting the study within routine clinical activity this was not feasible. Fourth we considered plausible factors associated with split-dose uptake, but we cannot exclude to have missed some unknown factors. Last but not least, present study included patients receiving high volume bowel prep and results may not be necessarily transferable to the low volume setting.

In conclusion, our study showed the existence of patient-related barriers against a spli-regimen of preparation, especially for early morning examinations, that are clinically relevant and deserve to be addressed. When considering the strict association between early morning colonoscopy and refusal of the split regimen, policies directed to reorganise colonoscopy timetable should be considered (ClinicalTrials.gov: NCT 02287051).

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Contributors FR, SP, CH and AR: study concept and design; interpretation of results and drafting of the manuscript. FR, CH, SP and CS: acquisition of data and statistical analysis. All the authors: data collection, critical revision of the article for important intellectual content and final approval of the article.

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