

Bowel Preparation for Colonoscopy: The Patient Point of View

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Keywords

Colonoscopy · Bowel preparation · Patient-reported outcomes · BOCLIR · Oral mannitol

Abstract

Introduction: Colonoscopy is a common procedure that requires adequate bowel preparation. Polyethylene glycol (PEG) is widely used but commonly associated with patient complaints, including the split-dose administration schedule. Mannitol could be an attractive alternative as it acts quickly, requires low volumes, and is palatable. A recent Phase III international, multicenter, randomized study (SATISFACTION) compared the efficacy and safety of bowel preparation using same-day oral mannitol or a split-dose regimen of 2L PEG-ASC. This study investigated the effects of the two laxatives on the Bowel Cleansing Impact Review (BOCLIR), a questionnaire exploring the degree of satisfaction of patients undergoing preparation for a colonoscopy. **Methods:** The BOCLIR measures the acceptability and tolerability of bowel cleansers on three unidimensional scales (satisfaction, symptoms, and activity limitations). The total score is the sum of the three sub-scores and ranges from 0 to 110, with higher scores representing worse patient experiences. **Results:** This analysis included 476 patients

who completed the BOCLIR questionnaire: 236 in the mannitol group and 240 in the PEG-ASC group. The difference in the least square means of the total score was -8.01 (95% CI: -10.70 to -5.31), with a highly significant difference in favor of mannitol ($p < 0.0001$). **Conclusion:** This analysis of the SATISFACTION study shows that bowel preparation with mannitol was far preferable to PEG-ASC in terms of acceptability and tolerability. Based on these results, mannitol may be close to an ideal preparation from the patient's point of view.

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Introduction

Colonoscopy is a widespread procedure for screening, diagnostic confirmation, interventional maneuver, or prognostic follow-up of intestinal diseases. Proper colon cleansing is the main prerequisite for reliable results [1]. Indeed, optimal cleansing assures maximal diagnostic accuracy and safe endoscopy, including operative procedures. Inadequate colon cleansing invalidates the process and results in repeat examinations [2].

The bowel preparation procedure uses laxatives, usually with an osmotic mechanism of action. Several

products are available, mainly based on polyethylene glycol (PEG), and are effective in 75–95% of cases [3, 4]. However, they require that the patients take significant amounts of fluids at two separate times (split dose), the evening before and the morning of the colonoscopy. This schedule implies considerable discomfort for the patient as it causes nocturnal evacuations that disturb sleep as well as protracted digestive complaints. In addition, PEG preparations have an unpleasant taste that can lead to nausea and vomiting. All these features make colonoscopy preparation particularly unpleasant or even unbearable. In theory, the ideal medication for bowel preparation should be effective, safe, and easy to take (e.g., single dose), and have a rapid onset (for same-day preparation), good patient acceptance, and low cost [2].

For this reason, the use of mannitol for colonoscopy preparation has recently been re-evaluated. Indeed, oral mannitol has several advantages: it has a pleasant taste, requires relatively modest amounts of water to dissolve, and acts quickly so that it can be administered in a single dose on the morning of the colonoscopy.

In this regard, an international study tested the safety and efficacy of oral mannitol in terms of non-inferiority compared with a commercial reference preparation [5]. Since the patient's point of view plays a crucial role in this context, the study paid special attention to certain patient-related aspects. In particular, a special focus was directed toward patients' responses to bowel cleansing preparation.

The satisfaction perceived by the patient presently has huge relevance in assessing treatment results [6]. However, the concept of patient satisfaction is complex and depends on personal characteristics and clinical settings. In addition, the expectation of treatment outcomes is highly relevant to satisfaction [7, 8], meaning that patients will be satisfied with treatment if they achieve their expectations.

One issue is how to measure satisfaction from the patient's point of view; the appropriate measurement of subjective issues is critical in clinical trials. In this regard, patient-reported outcome measures (PROMs) are currently a cornerstone in assessing clinical trials. PROMs can measure different aspects of health (including symptom severity perception, quality of life, functional status, and wellness) as well as treatment satisfaction and are therefore a valuable parameter in clinical trials. In particular, PROMs consider the clinical course [9], measure treatment outcomes [10], and improve communication between patients and doctors [11].

The word PROM is an umbrella term that covers a wide range of potential endpoints measuring direct patient out-

comes without the need for interpretation by clinicians or others [8, 9]. Standardized questionnaires can properly collect PROMs provided they meet certain requirements, including psychometric and scale standards [12]. The Bowel Cleansing Impact Review (BOCLIR) meets all of these standards [13]. The BOCLIR stemmed from the need to acquire a range of information regarding the degree of satisfaction of patients undergoing preparation for a colonoscopy. Evidence shows that the BOCLIR accurately assesses the patient's response to bowel preparation [13]. Based on this background, Phase III of the SATISFACTION study investigated the efficacy, safety, and PROMs of two medications (oral mannitol and PEG-ASC) for bowel preparation.

Materials and Methods

Study Design

The SATISFACTION study was an international, multicenter, randomized, parallel-group, endoscopist-blinded trial conducted in 30 centers in Italy, Germany, France, and Russia. The Ethics Committee (EC) of the primary center approved the study on 12 February 2020 (Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; EC MI-AREA 3 No.: 62-12022020), followed by the ECs of the other centers. The trial protocol was registered with ClinicalTrials.gov (<https://clinicaltrials.gov/ct2/show/NCT04759885>) and with EudraCT (eudract_number: 2019-002856-18). The study's design is summarized in Figure 1.

The inclusion criteria were the patient's ability to consent and provide signed informed consent, age ≥ 18 , males and females scheduled for elective (screening, surveillance, or diagnostic) colonoscopy to be prepared and performed according to ESGE guidelines, and willingness and ability to complete the entire study and comply with instructions. Written informed consent was obtained from participants prior to the study. The patients enrolled were randomized in a 1:1 ratio to one of the following treatment groups:

- Mannitol powder 100 g dissolved in 750 mL water to be drunk in 30 min on the day of the colonoscopy, with administration completed at least 4 h before the colonoscopy
- 2 L PEG-ASC administered according to a split-dose regimen: the first liter over 1–2 h the evening before colonoscopy and the second liter the morning of the procedure, with administration completed at least 4 h before the colonoscopy

The complete methods were reported in detail in recent publications [5, 14–16]. This analysis evaluated

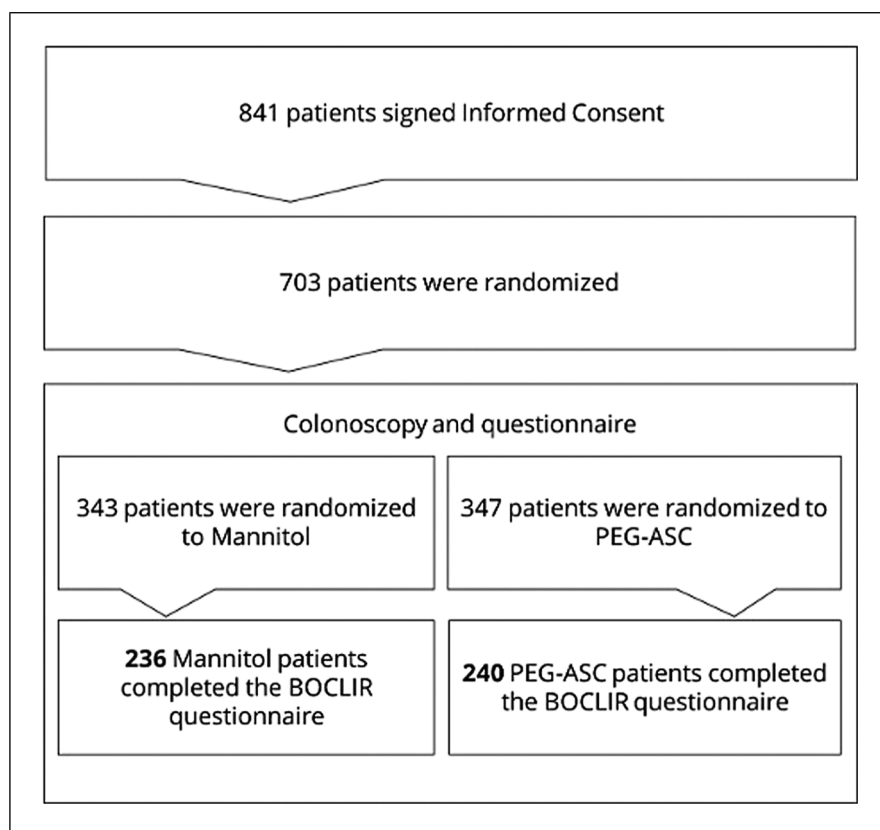


Fig. 1. Study design.

the BOCLIR outcomes. The present study included only the patients who completed the BOCLIR questionnaire. The full list of participating sites and ECs can be found at reference 16.

Bowel Cleansing Impact Review

The BOCLIR measures the acceptability and tolerability of bowel cleansers on three unidimensional scales (satisfaction, symptoms, and activity limitations) with good psychometric and scaling properties. Item responses are summed to provide scale scores. The original version of BOCLIR questionnaire is in English language; the Italian version has been validated (see the online suppl. Fig. 1; for all online suppl. material, see <https://doi.org/10.1159/000547968>). The satisfaction scale contains eight items (each using a 5-point scale), and the score ranges from 0 (highly satisfied) to 32 (highly dissatisfied). The symptoms scale includes 14 items (each using a 4-point scale), and the score ranges from 0 (no symptoms) to 42 (severe symptoms). The activity limitations scale is made up of 12 items (each using a 4-point scale from 0 to 3), and the score ranges from 0 (no effect on activities) to 36 (activities greatly affected). The total

score is the sum of the three scales and ranges from 0 to 110, with higher scores representing a worse experience. The BOCLIR allows accurate assessment of patient response to bowel cleansing preparations [13].

Only patients in Italy completed the BOCLIR questionnaire, at visit 4 following completion of the study drug self-administration and before colonoscopy. This is because only the Italian language version of the BOCLIR, and not the language versions of the other countries in which the SATISFACTION trial was carried out (France, Germany, and Russia), was validated for use in the trial.

Statistical Analysis

Statistical analysis was performed using an ANOVA model, with BOCLIR total score as the dependent variable and treatment group as the independent variable, to assess the mean difference in BOCLIR scores between study treatments.

Results

A total of 476 patients enrolled in the SATISFACTION trial in Italy, out of the 703 patients enrolled globally, completed the BOCLIR questionnaire: 236 from

Table 1. Demographic data of participants

	Mannitol (N = 236)	PEG-ASC (N = 240)	Total (N = 476)
Age at study entry, n			
Mean (SD)	54.0 (13.12)	53.6 (12.63)	53.8 (12.86)
Median	54.0	55.0	54.5
Sex, n (%)			
Male	92 (38.98)	112 (46.67)	204 (42.86)
Female	144 (61.02)	128 (53.33)	272 (57.14)

the mannitol group and 240 from the PEG-ASC group. The demographic data are reported in Table 1.

Table 2 and Figure 2 summarize the BOCLIR results. The scores range from 0 to 102; the lower the score, the better.

Mean satisfaction total scores for mannitol and PEG-ASC were 5.8 ± 3.37 and 8.7 ± 3.93 , respectively; the intergroup comparison was significant ($p < 0.0001$).

Mean symptoms total scores for mannitol and PEG-ASC were 9.8 ± 4.87 and 11.5 ± 5.94 , respectively; the intergroup comparison was significant ($p < 0.0008$).

Mean activity limitations total scores for mannitol and PEG-ASC were 7.8 ± 9.43 and 11.3 ± 10.02 , respectively; the intergroup comparison was significant ($p < 0.0001$).

Mean BOCLIR total scores for mannitol and PEG-ASC were 23.5 ± 13.48 and 31.5 ± 16.26 , respectively. The difference in the least square means of the total score was -8.01 (95% CI: -10.70 to -5.31), with a significant difference in favor of mannitol ($p < 0.0001$).

Discussion

The Phase III RCT demonstrated that mannitol preparation was not inferior than PEG-ASC. This relative equivalence should be implemented with some advantages offered by a better tolerated preparation. This outcome underlines the compliance issue: crucial for guaranteeing the quality of bowel preparation and consequently the adherence to colonoscopy exam and, in general, to screening programs [17]. Indeed, cleaning the colon lumen guarantees diagnostic adequacy and allows safe and effective operative procedures during colonoscopy [18, 19]. Inadequate bowel cleansing is consistently associated with an increased risk of endoscopic complications and implies the repetition of the procedure with significant patient discomfort, diagnostic delay, and increased costs. In addition, the morning single-dose regimen is more advantageous and acceptable than split dose.

Several preparations are available for bowel cleansing, with different procedures in terms of liquid volumes, schedules (split dose), and restricted diets. In addition, many medications have an unpleasant taste. The occurrence of adverse events, the inability to comply with restrictions, complaints (nausea, vomiting, abdominal cramps), sleep disturbance, and unpleasant taste contribute to the dissatisfaction of patients undergoing bowel preparation. Therefore, bowel preparation per se is a relevant factor in discouraging patients from colonoscopy attendance [20].

Thus, the ideal bowel preparation choice should seriously consider these issues. PROMs allow for the identification of reliable medications, and the BOCLIR questionnaire has adequate psychometric properties and fulfills the necessary requirements to be appropriately applied in clinical trials [13].

The advantage of the BOCLIR is its ease of compilation and understanding as the patient takes about 5 min to complete the questionnaire, acts independently, and can complete it at any time. As a result, the BOCLIR is a helpful tool for considering the patients' response to bowel preparation for colonoscopy. For this reason, Phase III of the SATISFACTION study included BOCLIR in the outcomes.

Because a validated version of the BOCLIR was available only for the Italian language, in the SATISFACTION study only patients enrolled in Italy completed the survey. The BOCLIR scores comprehensively analyzed the patients' experience of bowel preparation in terms of satisfaction, impact on symptoms, and limitations on social, work, and family activities. The observed results consistently favored mannitol and agreed with the abovementioned assessments.

Mean scores (the lower the score, the better) for mannitol and PEG-ASC were 5.8 and 8.7 for satisfaction, 9.8 and 11.5 for symptoms, 7.8 and 11.3 for activities, and 23.5 and 31.5 for the total score, respectively. Notably, the differences for all three single scores were statistically significant in favor of mannitol ($p < 0.0001$). The

Table 2. BOCLIR score in the two study groups

	Mannitol (N = 236)	PEG-ASC (N = 240)
Satisfaction total score, <i>n</i>		
Mean (SD)	5.8 (3.37)	8.7 (3.93)
Median	6.0	8.0
ANOVA model: satisfaction total score		
<i>p</i> value from type III effect ^a		<0.0001
Least square means (95% CI)	5.8 (5.4, 6.3)	8.7 (8.2, 9.2)
Difference of least square means (95% CI), <i>p</i> value	2.84 (−3.50, −2.18), <0.0001	Reference
Symptoms total score, <i>n</i>		
Mean (SD)	9.8 (4.87)	11.5 (5.94)
Median	9.00	11.0
ANOVA model: symptoms total score		
<i>p</i> value from type III effect ^a		0.0008
Least square means (95% CI)	9.8 (9.2, 10.5)	11.5 (10.8, 12.2)
Difference of least square means (95% CI), <i>p</i> value	−1.69 (−2.67, −0.71), 0.0008	Reference
Activities total score		
Mean (SD)	7.8 (9.43)	11.3 (10.02)
Median	4.0	10.0
ANOVA model: activities total score		
<i>p</i> value from type III effect ^a		0.0001
Least square means (95% CI)	7.8 (6.6, 9.1)	11.3 (10.1, 12.5)
Difference of least square means (95% CI), <i>p</i> value	−3.48 (−5.23, −1.72), 0.0001	Reference
BOCLIR total score		
Mean (SD)	23.5 (13.48)	31.5 (16.26)
Median	20.0	29.0
ANOVA model: activities total score		
<i>p</i> value from type III effect ^a		<0.0001
Least square means (95% CI)	23.5 (21.6, 25.4)	31.5 (29.6, 33.4)
Difference of least square means (95% CI), <i>p</i> value	−8.01 (−10.70, −5.31), <0.0001	Reference

^a*p* value from type III effect refers to the *p* value of the overall model.

difference in the least square means of the total score was −8.01 (95% CI: −10.70 to −5.31; *p* < 0.0001); the upper limit of the 95% CI is 5.31 points lower than zero (i.e., equivalence); therefore, even considering the less favorable limit of the 95% CI, the difference between the two groups is greater than 16%; this makes the difference between the two groups highly significant from both a statistical and clinical point of view. Moreover, the BOCLIR score obtained by mannitol in this study compares favorably to that obtained by other drugs for bowel preparation evaluated in other reports. Indeed, although data from different studies should be compared with caution, in a recent randomized controlled Phase III trial, the mean total BOCLIR score was 39.9 (±17.7) for patients prepared with NER1006 and 39.6 (±17.5) for those prepared with trisulfate [21], quite a bit higher than the mannitol score of 23.5 ± 13.48. Interestingly, mannitol

also showed far better results for all three sub-scores, i.e., satisfaction, symptoms, and activity limitation.

As such, oral mannitol is the lowest-scoring drug of all preparations tested by BOCLIR scores thus far, resulting in the highest degree of perceived satisfaction. For the satisfaction item in particular, oral mannitol achieved a low overall score, with a mean value of 5.8. The patient satisfaction items included general satisfaction, volume, taste, drinking full volume/keeping it down, preparation instructions, adhering to a diet and fast, certainty of the thoroughness of cleansing, speed of effect, and comparison to other previous preparations (if any).

Likewise, patients taking oral mannitol experienced a lower impact on symptoms. The list of considered symptoms included bloating, cramps/gurgling/stomach pains, nausea/dizziness, energy/fatigue/concentration problems, sleep disturbance, headache, need to urinate, bowel

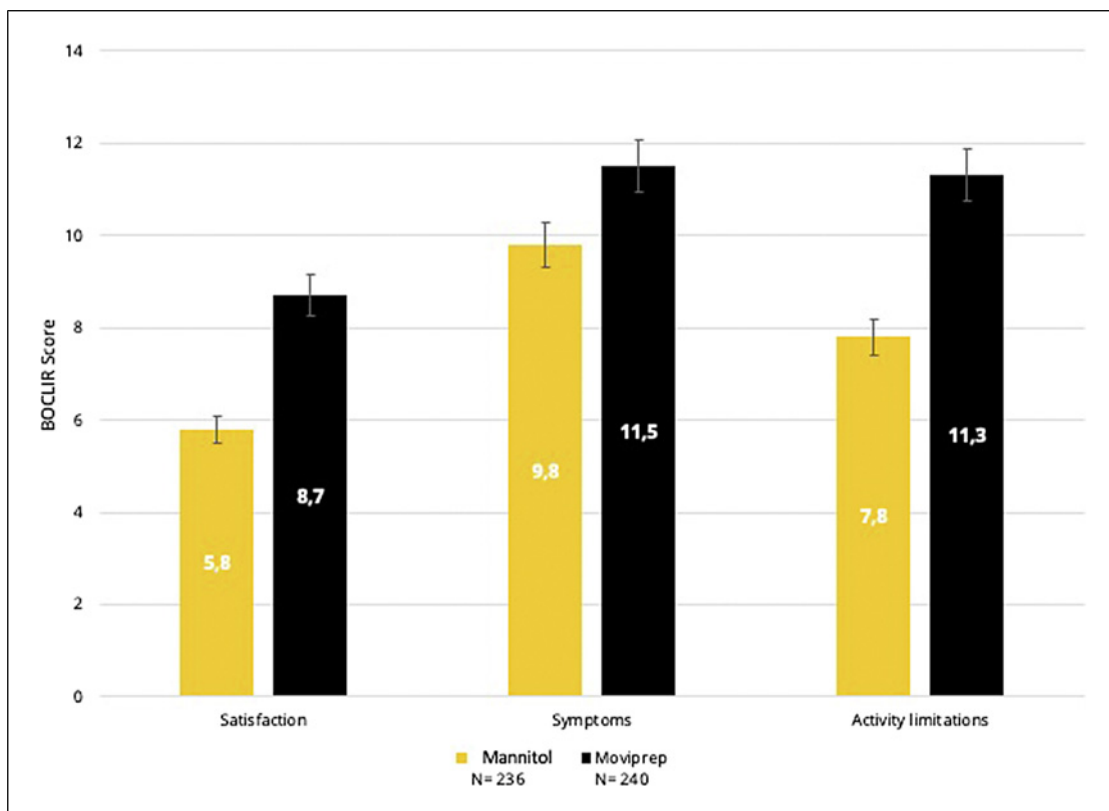


Fig. 2. BOCLIR scores. Data are reported as means \pm standard deviations.

evacuation (mainly concerning urgency/control, frequency, leakage, and pain/soreness), hunger, dry mouth/thirst, and irritability. It is important to note that assessing the impact of patient-described symptoms using a validated questionnaire such as the BOCLIR provides different and clinically more relevant information than the simple numerical proportion of patients who presented symptoms, which is the only data generally reported in clinical studies. In fact, it is possible, as occurred in the SATISFACTION study, that the simple numerical incidence of symptoms is significantly higher for one of the two drugs being compared, while the impact of the same symptoms assessed by the patients is lower precisely in the treatment group that had a higher numerical incidence. Consequently, the symptom impact area of the BOCLIR goes into meticulous detail about the effects of preparation on the patient. The results obtained with mannitol therefore emphasize the high degree of tolerability, especially when compared with other medications.

Finally, the area of activity limitations explored the effects of preparations on the general ability to perform one's usual activities, in terms of household chores (e.g., cooking), family impact, social impact, and work impact. Therefore, even for

these more "social" aspects, mannitol is confirmed to be the preparation that causes less inconvenience to patients.

Generally speaking, of course, efficacy and safety are two indispensable requirements in evaluating any drug. Yet increasing attention is being paid to outcomes related to patient perception. The patient's point of view is becoming ever more important in the context of personalized medicine. In this context, the possibility of measuring the degree of patient satisfaction with appropriate and validated instruments assumes considerable relevance in randomized controlled trials. Based on these results, mannitol is perceived as a particularly satisfactory and well-tolerated product with limited impact on preparation-induced symptoms and limitations.

This analysis of the SATISFACTION study had some limitations. The study lacks a double-blind design because volumes and schedules differed between treatment arms: oral mannitol was used in a single dose on the day of colonoscopy, while 2L PEG-ASC was administered following a conventional split-dose regimen. On the other hand, the methodology was robust thanks to the implementation of 1:1 randomization, control group, endoscopic blindness, and large sample size.

Conclusions

Based on the above considerations, this analysis of the SATISFACTION study shows that intestinal preparation with mannitol is significantly preferable to patients than PEG-ASC-based preparation. These results thus allow mannitol to be considered an ideal preparation in that it provides an excellent patient satisfaction and tolerability profile.

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Statement of Ethics

The Ethics Committee of the principal center approved the study on 12 February 2020 (Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; EC MI-AREA 3 No.: 62-12022020).

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

G.T. analyzed the results and edited the manuscript. G.C. wrote the manuscript. M.V. designed the study and discussed the outcomes. C.S., F.R., and P.A.T. critically discussed and edited the manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due to privacy reasons but are available from the corresponding author upon reasonable request.

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