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2-Litre polyethylene glycol-citrate-simethicone plus bisacodyl versus 4-litre polyethylene glycol as preparation for colonoscopy in chronic constipation

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ABSTRACT

Background: Chronic constipation is a risk factor of inadequate bowel preparation for colonoscopy; however, no large clinical trials have been performed in this subgroup of patients.
Aims: To compare bowel cleansing efficacy, tolerability and acceptability of 2-L polyethylene-glycol-citrate-simethicone (PEG-CS) plus 2-day bisacodyl (reinforced regimen) vs. 4-L PEG in patients with chronic constipation undergoing colonoscopy.
Methods: Randomized, observer-blind, parallel group study. Adult outpatients undergoing colonoscopy were randomly allocated to 2-L PEG-CS/bisacodyl or 4-L PEG, taken as split regimens before colonoscopy. Quality of bowel preparation was assessed by the Ottawa Bowel Cleansing Scale (OBCS). The amount of foam/bubble interfering with colonic visualization was also measured.
Results: 400 patients were enrolled. There was no significant difference in successful cleansing (OBCS score $\leq$6): 80.2% in the 2-L PEG-CS/bisacodyl vs. 81.4% in the 4-L PEG group. Significantly more patients taking 2L PEG-CS/bisacodyl showed no or minimal foam/bubbles in all colonic segments (80% vs. 63%; $p < 0.001$). 2-L PEG-CS/bisacodyl was significantly more acceptable for ease of administration ($p < 0.001$), willingness to repeat ($p < 0.001$) and showed better compliance ($p = 0.002$).
Conclusion: Split 2-L PEG-CS plus bisacodyl was not superior to split 4-L PEG for colonoscopy bowel cleansing in patients with chronic constipation; however, it performed better than the standard regimen in terms of colonic mucosa visualization, patient acceptance and compliance.

1. Introduction

Currently, colonoscopy constitutes the most effective screening tool for colorectal cancer and the only procedure allowing for the simultaneous detection and removal of colonic polyps [1]. Several recent studies have documented the benefit of screening colonoscopy with polypectomy in reducing colorectal cancer mortality both by early-stage detection of cancers and by removal of precancerous lesions (i.e. adenomatous polyps) [2–4].

The effectiveness of colonoscopy in colorectal cancer screening is based upon adequate rates of adenoma detection and is mainly dependent on both the endoscopist's skill and the quality of the bowel preparation [5,6].

In particular, the quality of bowel preparation before colonoscopy has a direct impact on the quality of colonoscopy. Inadequate bowel preparation, which may occur in as many as one-third of colonoscopies in clinical practice, is associated with a high rate of missed adenoma, greater discomfort for the patient and shortened surveillance intervals, according to recommendations provided by competent professional organizations [7–10]. Despite the high

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frequency of chronic constipation in the general population and the fact that it is considered an important medical predictor of inadequate bowel preparation [11], to date, and to our knowledge, no large randomized trial has specifically evaluated the efficacy of different bowel regimens in these patients. There is insufficient evidence to support the use of a specific bowel preparation or a specific regimen in patients with chronic constipation unless the generic statement that the adjunct of another laxative (such as magnesium citrate, bisacodyl or senna), seems to be beneficial in improving the efficacy of PEG-based regimens for patients at risk of inadequate bowel preparation [12].

The recent introduction in Italy of a new iso-osmotic, sulphate-free, 2-L formulation of PEG-Citrate-Simethicone (PEG-CS) associated with oral bisacodyl (a well-established stimulant laxative) prompted us to propose a reinforced cleansing regimen by extending the duration of bisacodyl 15 mg over two days prior to colonoscopy in this subgroup of hard to prepare patients.

We therefore designed a multicentre randomized observer-blind study to assess the efficacy, tolerability and acceptance of split 2-L PEG-CS combined with bisacodyl compared with the split-dose 4-L PEG for bowel cleansing in patients with chronic constipation undergoing colonoscopy.

2. Materials and methods

This was a multicentre, randomized, observer-blind study in outpatients undergoing colonoscopy, conducted in five centres in northern Italy. The study was designed in compliance with internationally recognized guidelines for clinical studies (EUDRACT NUMBER: 2011-002188-58). The study protocol was approved by the Ethics Committee of all participant Institutions, and written informed consent was obtained from all patients.

2.1. Study population

Consecutive adult outpatients with chronic constipation, aged >18 years and <85 years and undergoing elective routine colonoscopy for diagnostic or follow-up reasons were enrolled in the study from March 2012 to February 2013. Although accurate information on indication for colonoscopy was not specifically looked for, most outpatients enrolled were undergoing colonoscopy for colorectal cancer screening, endoscopic follow-up after polypectomy or diagnostic evaluation for abdominal symptoms. Chronic constipation was defined according to a modified version of the Rome III criteria, in which a reduction of spontaneous bowel movements (less than three per week) for ≥6 months was the necessary condition for inclusion and one or more of the following symptoms: straining, hard stools, feeling of incomplete evacuation [13].

Exclusion criteria for enrolment were the following: pregnancy or lactation, known or suspected hypersensitivity to the active principle or any product ingredients, known or suspected intestinal obstruction or perforation, toxic megacolon, major colonic resection, heart failure (class III or IV), serious cardiovascular disease, severe liver failure or end-stage renal insufficiency. To avoid a large variability in the interval between bowel preparation and colonoscopy, all colonoscopies were scheduled for the late morning or early afternoon (between 11.00 a.m. and 2.00 p.m.). A complete medical history, physical examination with vital signs, and information regarding previous and concomitant medications were taken at the time of enrolment by a physician who was not involved in the subsequent colonoscopy.

2.2. Bowel preparations

The study preparation is a combination of PEG-CS and bisacodyl. PEG-CS is a new sulphate-free iso-osmotic formulation of PEG-4000 with citrates and simethicone (Lovol-esse; Alfa-Wassermann, Italy) available as a powder to be dissolved in 2 L of water. Subjects allocated to the study preparation were instructed to take 3 bisacodyl 5-mg tablets (Lovoldyl) daily (at bedtime two days before and at 4:00 p.m. the day before the procedure, followed by 2 L of PEG-CS solution (the 1st litre taken at least 3 h after the tablets on the day before and the 2nd litre the following morning 5 h before the scheduled colonoscopy). The patients were instructed to drink 250 mL in 15–20 min (all of the solution in about 1–1½ h). As an active control, 4-L PEG (SELG 1000, Alfa-Wassermann, Italy) given as split doses, 2 L at 6.00 pm the day before and 2 L in the early morning 5 h before colonoscopy. The preparations were dispensed by an endoscopy nurse who carefully explained how the products should be taken, stressing the importance of the complete intake of the solution to ensure a safe and effective procedure. Moreover, each patient was provided with a detailed dietary instruction card with a low residue diet for 3 days before colonoscopy. After intake of the PEG preparation, solid food was not allowed. Clear liquid could be taken until 2 h before the procedure.

2.3. Randomization and blinding

A computer-generated randomization list was prepared centrally by a qualified statistician with a block of four and separate lists for each centre. Subjects satisfying all the inclusion/exclusion criteria were consecutively assigned to the next available number. The study was observer-blind: the endoscopists were not allowed to perform any activities associated with study preparation and had to avoid any discussion with the patients and the staff that might disclose the type of bowel preparation taken.

2.4. Evaluation of bowel preparations

Bowel cleansing efficacy. Preparation efficacy was evaluated by the blinded endoscopists according to the validated Ottawa Bowel Cleansing Scale (OBCS) giving a score (0–4) to the main colonic segment (right, transverse and left colon). The overall colonic fluid was rated according to a 3-point scale. The total score (bowel cleansing total score; primary end-point) may range from 0 (best) to 14 (worst). A total OBPS score ≤6 was considered successful bowel preparation [14].

In addition, we also measured the amount of foam and bubbles in terms of the overall impact on mucosal visualization, as excellent (clear imaging, no or minimal amount of bubbles or foam that can be easily removed), fair (modest amount of bubbles and foam that can be cleared, with some waste of time) and insufficient (a large amount of foam and bubbles that reduces significantly the clear visualization of the mucosa) in each bowel segment.

Prior to study initiation, designated observers performed a calibration exercise on 50 colonoscopies using the scoring systems adopted in this study to reach a satisfactory level of concordance among the study endoscopists.

Safety. Vital signs and complete physical examination were performed at the time of patient enrolment and on the day of colonoscopy. Adverse events were assessed on the day of colonoscopy by direct questioning. New symptoms and exacerbations of pre-existing symptoms occurring after the treatment (except those expected and included in the evaluation of gastrointestinal tolerability) were assumed to be related to the bowel preparation regimen.

Tolerability. On the day of colonoscopy, immediately before the procedure, an endoscopy nurse questioned each patient about