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Evaluation of Clensia®, a new low-volume PEG bowel preparation in colonoscopy: Multicentre randomized controlled trial *versus* 4L PEG

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ABSTRACT

Background: Success of colonoscopy is linked to the adequacy of bowel cleansing. Polyethylene glycol 4 L (PEG 4 L) solutions are widely used for colonic cleansing but with limitations concerning tolerability and acceptability.
Aim: To demonstrate the equivalence of a new low-volume PEG containing citrates and simeticone (Clensia) *versus* a standard PEG 4 L.
Methods: In this, multicentre, randomised, observer-blind trial, patients received either Clensia 2 L or PEG 4 L solution. Primary endpoint was the proportion of patients with colon cleansing evaluated as excellent or good.
Results: 422 patients received Clensia (n = 213) or PEG 4 L (n = 209). Rate of excellent/good bowel cleansing was 73.6% and 72.3% in Clensia and PEG 4 L group respectively. Clensia was demonstrated to be equivalent to PEG 4 L. No SAEs were observed. Clensia showed better gastrointestinal tolerability (37.0% *vs* 25.4%). The acceptability was significantly better with Clensia in terms of proportion of subjects who felt no distress (Clensia 72.8% *vs* PEG 4 L 63%, $P = 0.0314$) and willingness-to-repeat (93.9% *vs* 82.2%, $P = 0.0002$). The rate of optimal compliance was similar with both formulations (91.1% for Clensia *vs* 90.9% for PEG 4 L, $P = 0.9388$).
Conclusions: The low-volume Clensia is equally effective and safe in bowel cleansing compared to the standard PEG 4 L, with better gastrointestinal tolerability and acceptability.

1. Introduction

Colonoscopy is considered the gold standard for colonic exploration: it represents the most effective screening tool and the only procedure allowing simultaneous detection and removal of polyps [1,2]. The success of colonoscopy is largely dependent on the level of bowel cleansing: a higher cleansing level being associated to a higher detection rate of clinically relevant neoplastic lesions. The substantial adverse consequences of inadequate or sub-optimal bowel preparation include: lower likelihood of detection of small or large adenomas, longer procedure times and, in general, more difficulties during the exam [3–6]. This has inevitably a negative impact on the efficiency of colonoscopy, waiting lists and costs of screening programmes [7].

Polyethylene glycol (PEG) solutions are widely used in clinical practice as they are effective and safe, due to the negligible net absorption of water and electrolytes and are recommended by both

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the European [8] and American Guidelines [9]. The conventional formulations of PEG-based bowel cleansing agents administered at high volume (4 L) are considered the gold standard for efficacy [10]. However, the large volume and unpleasant taste may limit the gastrointestinal tolerability and decrease the compliance to the recommended dose regimen, affecting indirectly the efficacy for high-quality level of bowel preparation in clinical practice.

A novel low-volume PEG bowel cleansing agent (Clensia) (Alfa Wassermann S.p.A., Bologna, Italy) was developed to overcome the above issues with a formulation aiming to improve patient compliance by reducing the volume of the solution to 2 L in order to minimize the volume-related gastrointestinal symptoms and discomfort. Clensia active ingredients include PEG 4000, sodium sulphate, citric acid, sodium citrate, sodium chloride, potassium chloride and simeticone. Citric acid and sodium citrate are not systemically absorbed and acting as osmotic agents and in synergy with PEG 4000 and sodium sulphate reduce the required solution volume and improve its taste. Simeticone was included in the formula due to its antifoaming properties, in order to improve the visualisation of the colonic mucosa [11,12].

Moreover, to further enhance patients' safety, Clensia has been formulated without ascorbates and aspartame. The aim of the study was to investigate whether Clensia and the standard PEG 4 L preparation are equivalent in terms of safety and efficacy for bowel cleansing. Tolerability, acceptability and compliance of both preparations were also evaluated.

2. Patients and methods

2.1. Study design

This was a multicentre, randomised, observer-blind, parallel group, phase-3 clinical trial designed to compare Clensia (Test) with a standard PEG 4 L solution (Reference). The study protocol was reviewed and approved by the Institutional Ethics Committees of the 6 participant sites and was registered in the European Union Clinical Trial Registry (EudraCT number: 2008-007144-33). All subjects provided written informed consent. Eligible subjects, who were aged between 18 and 85 years, were scheduled for routine colonoscopy. Patients were excluded if they had history of anaphylaxis to drugs or allergic reactions; known or suspected gastrointestinal obstruction or perforation, toxic megacolon, major colonic resection, heart failure (Class III or IV NYHA), serious cardiovascular disease, severe liver failure, end-stage renal disease, or relevant diseases that might interfere with the aim of the study; inability to comprehend the full nature and purpose of the study and unwillingness to co-operate with the Investigator.

At baseline all subjects underwent a physical examination and blood and urine sampling for clinically relevant laboratory tests were collected. Eligible subjects were allocated to receive either Clensia or PEG 4L according to a randomisation list generated using SAS PROC PLAN. Endoscopists were unaware of the assigned treatments and instructed to avoid any discussion with the patient that could disclose the type of bowel preparation.

2.2. Bowel cleansing agents

The Test preparation Clensia (Alfa Wassermann S.p.A., Bologna, Italy) is a new combination of macrogol (PEG) 4000 and electrolytes with new active ingredients that are sodium citrate, citric acid and simeticone, available as a powder for oral solution after reconstitution with 2 L of water. The schedule for bowel preparation differed according to the time of colonoscopy. When colonoscopy was scheduled before 12 a.m. patients were instructed to take 2 L of solution plus 1 L of clear fluids on the day before the colonoscopy; when colonoscopy was scheduled after 12 a.m., patients were instructed to split the dose: 1 L of solution plus 0.5 L of clear fluids on the day before and 1 L plus 0.5 L in the morning of the day of the colonoscopy.

Similarly, patients allocated in the Reference group (PEG 4L as SELG 1000®, Alfa Wassermann S.p.A., Bologna, Italy) were instructed to take 4 L of solution on the day before when colonoscopy was scheduled before 12 a.m. and to split the dose (2 L of solution on the day before and 2 L in the morning of the day of the procedure when colonoscopy was scheduled after 12 a.m.).

Low residue diet was prescribed for 3 days before colonoscopy. During and after bowel preparation solid food was not allowed. There were no restrictions about either previous or concomitant treatments.

2.3. Efficacy assessments

The primary efficacy endpoint was the proportion of patients with successful colon cleansing, defined as "excellent" or "good" according to the Ottawa bowel preparation scale [13]. This is a validated scale (score ranging from 0 to 14) that takes into account two aspects: the degree of segments cleaning and the amount of fluid in the entire colon. Each section of the colon (right, mid and recto-sigmoid colon) is rated according to a 5-point scale (0–4) as follows:

- Excellent: grade 0 = mucosal detail clearly visible. In case any fluid is present, it is clear. Almost no stool residue;
- Good: grade 1 = some turbid fluid or stool residue but mucosal detail still visible. Washing and suctioning not necessary;
- Fair: grade 2 = turbid fluid or stool residue obscuring mucosal detail. However, mucosal detail becomes visible with suctioning. Washing not necessary;
- Poor: grade 3 = presence of stool obscuring mucosal detail contour. However with suctioning and washing a reasonable view is obtained;
- Unprepared: grade 4 = solid stool obscuring mucosal detail and contour despite aggressive washing and suctioning.

The overall colonic fluid was rated according to a 3-point scale (0–2) as follows: small = grade 0; moderate = grade 1; large = grade 2. The degree of bowel cleansing was categorized according to the total score (sum of single assigned scores) as follows: excellent (0–3), good (4–6), fair (7–10) and inadequate cleansing (11–14).

Secondary efficacy endpoints included the overall mucosal visibility, (graded according to a 3-grade scale: grade 0 "optimal" = clear imaging, no or minimal amount of bubbles or foam, which could be easily removed; grade 1 "adequate" = modest amount of bubbles and foam, which could be removed requiring additional time; grade 2 "insufficient" = presence of foam and bubbles, which significantly decreased the clear visualization of the mucosa) and indicators of quality such as caecal intubation (full colonic examination), time to reach the caecum (intubation time) and withdrawal time from the descending-sigmoid junction to exit.

2.4. Safety and tolerability

The safety of the preparations was based on adverse events (AEs) occurrence and clinical laboratory test abnormalities. AEs were monitored throughout the study. The duration and intensity of each event were recorded by the Investigators, as well as the causative relationship with study drugs, outcome and seriousness. Standard laboratory blood and urine tests were performed at baseline and at the end of the study. Tolerability was assessed inquiring on the

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