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ARTICLE

Factors influencing the presence of potentially explosive gases during colonoscopy: Results of the SATISFACTION study

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Abbreviations: ANOVA, analysis of variance; BBPS, Boston Bowel Preparation Scale; CH_4, methane; GCP, good clinical practice; H_2, hydrogen; ICH, International Conference of Harmonization; O_2, oxygen; PEG, polyethylene glycol.

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Abstract

This study tested the hypothesis that bowel preparation with mannitol should not affect the colonic concentration of H_2 and CH_4. Therefore, the SATISFACTION study, an international, multicenter, randomized, parallel-group phase II–III study investigated this issue. The phase II dose-finding part of the study evaluated H_2, CH_4, and O_2 concentrations in 179 patients randomized to treatment with 50 g, 100 g, or 150 g mannitol. Phase III of the study compared the presence of intestinal gases in 680 patients randomized (1:1) to receive mannitol 100 g in single dose or a standard split-dose 2 L polyethylene glycol (PEG)-Asc preparation (2 L PEG-Asc). Phase II results showed that mannitol did not influence the concentration of intestinal gases. During phase III, no patient in either group had H_2 or CH_4 concentrations above the critical thresholds. In patients with H_2 and/or CH_4 levels above detectable concentrations, the mean values were below the risk thresholds by at least one order of magnitude. The results also highlighted the effectiveness of standard washing and insufflation maneuvers in removing residual intestinal gases. In conclusion, bowel cleansing with mannitol was safe as the concentrations of H_2 and CH_4 were the same as those found in patients prepared with 2 L PEG-Asc. In both groups, the concentrations of gases were influenced more by the degree of cleansing achieved and the insufflation and washing maneuvers performed than by the preparation used for bowel cleansing. The trial protocol was registered with ClinicalTrials.gov (https://clinicaltrials.gov/ct2/show/NCT04759885) and with EudraCT (eudract_number: 2019-002856-18).

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Bowel explosion during colonoscopy is a rare, but dramatic, event. Some cases have been attributed to the use of oral mannitol causing increased intestinal CH_4 and H_2 content.

WHAT QUESTION DID THIS STUDY ADDRESS?

Safety of colonic gas concentrations during colonoscopy.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The SATISFACTION study investigated gas production after mannitol or polyethylene glycol (PEG) preparation. The effect of mannitol on CH_4 and H_2 concentrations during colonoscopy was lower than that of PEG.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

This study provided evidence that mannitol for bowel preparation was safe as it did not affect gas concentrations. Daily practice could be changed in light of these findings.

INTRODUCTION

Explosions during gastrointestinal surgery or therapeutic colonoscopy are extremely rare.[1] The simultaneous presence of several critical factors is necessary to trigger an explosion of the combustible intestinal gases hydrogen (H_2) and/or methane (CH_4). These include critical colonic concentrations of H_2 (>4% vol) and CH_4 (>5% vol), enough oxygen (O_2) to act as a combustion gas (O_2 >5% vol), and the application of a sparking source (electrocautery or argon plasma coagulation).[2–4] In some cases of intestinal explosion reported in the 1970s and 1980s, bowel preparation was carried out using poorly absorbable sugars, mainly mannitol, which was the most frequently used

agent for bowel cleansing at that time. This observation led to the hypothesis that the use of mannitol for bowel preparation could increase the colonic concentration of H_2 and CH_4 by altered microbiota. However, other extremely rare cases of intestinal explosion were also reported in patients prepared for colonoscopy using the standard enema polyethylene glycol (PEG) and sorbitol.[1,5] Namely, osmotic laxatives cause important qualitative/quantitative alterations in the intestinal microbiota, which transiently reduces its usual fermentation and metabolic activity and, consequently, gas production.[6,7] In addition, converging lines of evidence have shown that potentially explosive concentrations of H_2 and CH_4 can be found in up to half of subjects whose bowels have not been prepared.[8–10]

Interestingly, such events have not been described in recent years, even in countries where mannitol is widely used.[11] The explanation lies in the fact that the way a colonoscopy is prepared and performed has changed over time. First, an effective bowel preparation reduces the concentrations of H_2 and CH_4 through a thorough colon cleansing. The routine maneuvers of insufflation and washing to optimize bowel cleansing contribute to effective gas exchange with ambient air and equalize the distribution of combustible gases, overcoming the compartmentalization of the colon.[12,13] In addition, modern electrosurgical units and disposable electrosurgical devices provide safer and stable cutting and coagulation of tissue.

Therefore, these considerations, together with the absence of clinical evidence from adequately sized controlled clinical trials, led us to hypothesize that the amount of residual intestinal gas detectable during colonoscopy reflects the degree of bowel cleansing rather than the use of a specific type of laxative. The "Efficacy and Safety of mAnniTol in bowel preparation: assessment of adequacy and presence of Intestinal levelS of hydrogen and methane during elective colonoscopy aFter mAnnitol or standard split 2-liter PEG solution plus asCorbaTe – a phase II/III, International, multicentre, randomized, parallel-group, endoscOpist-bliNded, dose-finding/non-inferiority study – SATISFACTION" study initially investigated the pharmacokinetics and the ideal mannitol dose for bowel preparation.[14,15] Moreover, this study concurrently tested the hypothesis that bowel preparation with mannitol should not affect the colonic concentration of H_2 and CH_4. Therefore, the aim of this paper is to report in detail the results relating to concentrations of intestinal gases.

MATERIALS AND METHODS

Study design

The SATISFACTION study was a phase II/III international, multicenter, randomized, parallel-group, endoscopist-blinded trial, that has been run in 32 centers located in Italy, Germany, France, and Russia. The design of the study is summarized in Figure 1.

The phase II study had to determine which of 50 g, 100 g, or 150 g mannitol was the most effective and safe dose for bowel cleansing to be used in the subsequent comparative noninferiority phase III.

The inclusion criteria were: ability of the patient to consent and provide signed written informed consent, age greater than or equal to 18 years, male and female patients scheduled for elective (screening, surveillance, or diagnostic) colonoscopy to be prepared and performed according to European guidelines, and patients willing and able to complete the entire study and to comply with instructions. The main exclusion criteria were: pregnancy or breast feeding, severe renal failure (estimated glomerular filtration rate [eGFR] <30 ml/min/1.73 m^2), severe heart failure (New York Heart Association [NYHA] Class III–IV), severe anemia (Hb <8 g/dL), severe acute and chronically active inflammatory bowel disease, chronic liver disease (Child–Pugh class B or C), electrolyte imbalance, recent (<6 months) symptomatic acute ischemic heart disease, a history of significant gastrointestinal surgery, and use of laxatives or colon motility-altering drugs.

The purpose of phase II was to assess (i) if mannitol had a specific pharmacological effect resulting in smaller volumes of dangerous intestinal gases being removed with bowel cleansing, and (ii) the possible presence of a dose/effect relationship between the administered doses (50, 100, and 150 g) and the gas concentrations detected in the different colonic segments.

The purpose of phase III was to demonstrate that the single mannitol dose selected (100 g) was not inferior to the split-dose regimen of the standard split-dose 2 L PEG-Asc laxative (2 L PEG-Asc) in terms of bowel cleansing efficacy, and that it was superior as regard to patient acceptance.

In addition, the relative risk between the two preparations of patients having possibly critical H_2 and/or CH_4 levels was evaluated together with the role of other factors potentially relevant to the presence of residual concentrations of H_2 and CH_4, such as the degree of intestinal cleansing achieved and the insufflation and washing maneuvers performed during the colonoscopy. O_2 concentrations were also measured in all colonic segments in order to evaluate the effectiveness of insufflation: O_2 concentrations in the lumen of the colon very similar to that of ambient air (>20% vol) would indicate gaseous equilibrium (complete gas exchange) had been achieved.

In phases II and III, intestinal gases (H_2, CH_4, and O_2) were measured during the colonoscopy. The population in phase III did not include participants from phase II.

Endoscopists were blinded to treatment assignment. Separate, unblinded staff were responsible for assigning

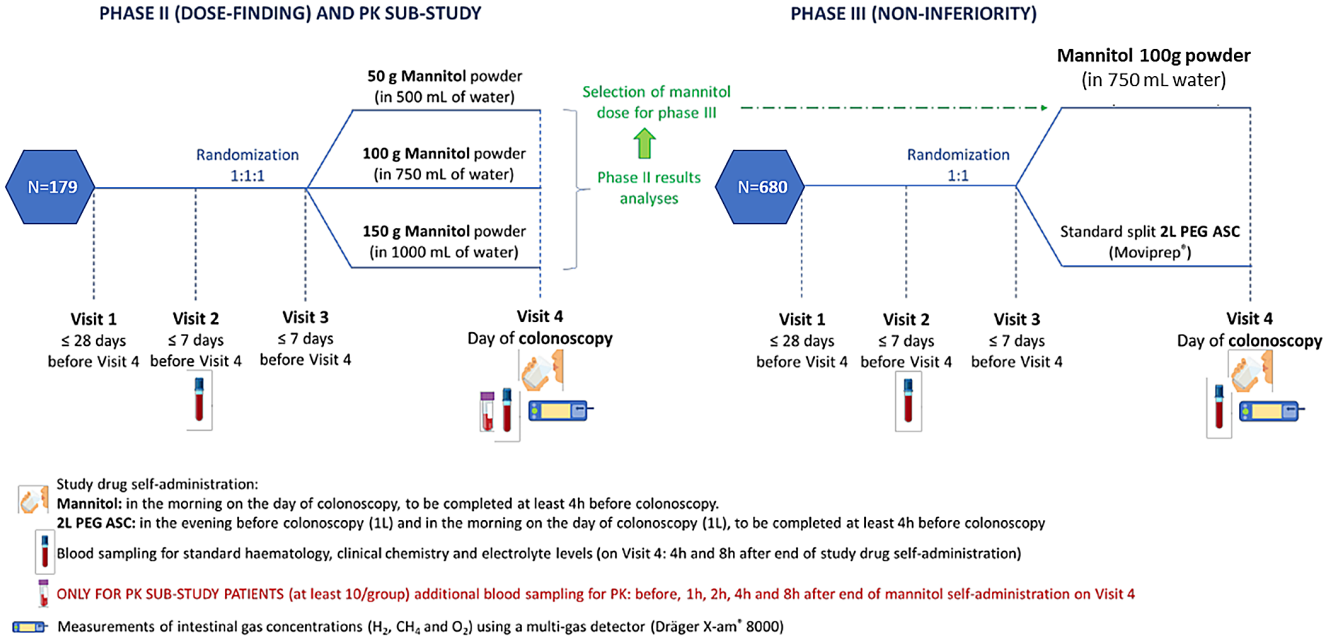

FIGURE 1 Study design. PEG, polyethylene glycol; PK, pharmacokinetic.

and dispensing/returning study treatments. Experienced endoscopists underwent training to decrease interobserver variability in the evaluation of bowel cleansing and measurement of intestinal gases.

Gas measurement

In phases II and III, intestinal gas concentrations (H_2, CH_4, and O_2) in each colon segment (right, transverse, and sigmoid-rectal junction) were measured during colonoscope retraction after standard washing and air insufflation maneuvers. The use of CO_2, which would decrease the risk of explosion by reducing the presence of O_2, was ruled out as the intention was to verify the safety of bowel preparation with mannitol under conditions of maximum potential risk. In phase III, intestinal gases were also measured at the sigmoid-rectal junction during colonoscope insertion, prior to any insufflation and washing maneuvers.

Intestinal gas concentrations were measured using a multi-gas detector (Dräger X-am 8000, Drägerwerk AG & KGaA) previously used in a controlled clinical study[14] (Figure S1). The detector contains three different sensors, one for each gas measured (H_2, CH_4, and O_2). The sensors use different physical principles for the determination of the individual gases (absorption of infrared radiation for CH_4 and H_2, and partial pressure measurement for O_2), and operate independently of each other. Therefore, the measurement made by one sensor for a specific gas does not affect the measurements made simultaneously by the other sensors for the other gases, even in the event of a malfunction. The device allows the measurement of gas levels easily, continuously, and in real-time, and the results are easy for operators to interpret. The detector is equipped with an automatic suction system, which conveys the gases to a sensor that measures their concentrations. The pump is unidirectional, so gases can flow only from the sampling site to the detector. The detector measures gas levels every 2 s, and shows the results on an integrated display. If the gas concentration exceeds the safety threshold, a visual alarm is shown on the display. The Dräger detector and filter were connected to a standard endoscopic cannula certified as a medical device class I. The second port of the cannula was closed with a plug to avoid any gas dispersion into the environment. A three-way faucet valve between the filter and the cannula directs the intake flow from either the patient or the environment to the detector, thus avoiding the need to continuously suction air from the patient. Only the cannula came into direct contact with the patient (Figure 2). The endoscopist drew the volume of gas necessary for analysis from the cannula by moving the lever of the three-way faucet valve. Once the gases were drawn into the detector, they could not return to the patient and were available for measurement. Gas concentrations inside the colon were thus shown in real time on the detector display. At no time was the detector in contact with the patient during the procedure.

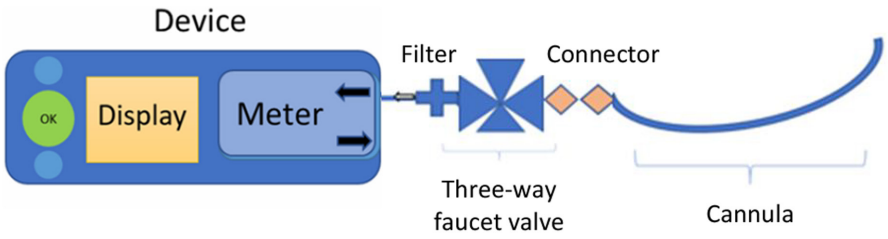

FIGURE 2 Scheme of gas detector system.

Sample size determination

The sample sizes for phases II and III were calculated based on the principal end point of the study, that is, the proportion of patients in each treatment group with adequate bowel cleansing (Boston Bowel Preparation Scale [BBPS] total score ≥6, with BBPS ≥2 for each segment).

Randomization

The randomization list was generated by an independent statistician (i.e., a statistician not involved in the study) according to the requirements of the study protocol in balanced blocks using a 1:1 allocation ratio for the treatment groups.

Analysis populations

The following populations were used for the statistical analyses: a safety set (all randomized patients who took the study preparation, even if only partially), a modified safety set (all randomized patients who took the study preparation, even if only partially, and who did not have any significant protocol violations), a full analysis set (FAS; all randomized patients with a BBPS score available for at least one colon segment), and a per protocol set (PP; all patients who met the following criteria: treatment with the study drug completed, colonoscopy completed, BBPS and H_2 and CH_4 measurements available for all colon segments, and no significant protocol violations).

Statistical analysis

Descriptive statistics (mean, standard deviation, and median if appropriate) were used to summarize continuous data. Frequencies and percentages were used to summarize categorical data. Intestinal gases (H_2 and CH_4) in the right colon, transverse colon, and sigmoid-rectal junction were compared among the three mannitol doses by means of one-way analysis of variance (ANOVA; phase II). The two cleansing treatments (phase III) were compared in patients with gas values greater than zero by means of the Wilcoxon test, mainly for illustrative purposes. The efficacy of the insufflation and lavage maneuvers performed during colonoscopy to remove residual intestinal gases after bowel cleansing, in all patients with H_2 and/or CH_4 levels greater than zero, regardless of treatment group, was determined by calculating Pearson's correlation coefficient between the O_2 concentration and the H_2 and CH_4 concentrations in the right and transverse colon, the colon segments with higher levels of intestinal gas. Finally, to further evaluate the factors affecting residual concentrations of intestinal gases in all patients, regardless of treatment group and separately for H_2 and CH_4, a multivariable regression analysis was conducted using as independent variables the preparation used for bowel cleansing, the degree of cleanliness obtained (BBPS score), and the oxygen concentration measured (indicating the degree of insufflation and washing performed during colonoscopy). All inferential analyses were performed using SAS release 9.4 (SAS Institute).

Ethics statement

The protocol, protocol amendments, and patient consent documents were reviewed and approved by the independent Ethics Committees of all centers participating in the study. The study was conducted in compliance with the recommendations regarding biomedical research on human subjects of the Declaration of Helsinki, International Conference of Harmonization, and Good Clinical Practice Guidelines. Written consent and privacy authorizations were obtained from the patients before any study-specific procedure was undertaken.

RESULTS

Patient characteristics

Patient enrollment started on June 18, 2020, and concluded on July 16, 2021. A total of 859 patients were enrolled in the study. The demographic characteristics of the study population are shown in Table 1. Patients included in phase II of the study had a mean age of ~55 years, with

small differences among dose groups; there was a slight predominance of women (54%). In phase III, mean ages were 54.8 and 54.6 years in the mannitol 100 g and 2 L PEG-Asc groups, respectively. As in phase II, there was a slight predominance of women in phase III.

Phase II results

Table 2 shows the least squares means of H_2 and CH_4 from the type III effect calculated from the ANOVA model together with their 95% confidence interval (CI) and *p* values at the right and transverse colon and at the sigmoid-rectal junction. For each colon segment, the differences among the three doses were not statistically significant, even though the mean H_2 and CH_4 values tended to be higher in patients treated with the lower dose of mannitol (50 g).

No potentially critical levels of H_2 (>4% vol) or CH_4 (>5% vol) were reported in any colon segment in any patient in the PP population. Potentially critical levels of H_2 were reported in one patient in the 150 g dose group in the FAS, but only in the right colon.

Phase III results

Table 3 summarizes H_2 and CH_4 values measured in the mannitol and 2 L PEG-Asc groups. No value was above the risk thresholds for either H_2 or CH_4.

The concentrations of H_2 and CH_4 measured in the different colonic segments were non-normally distributed and were fully comparable between the two groups (Table 4). For both gases, concentrations greater than zero in the two groups, analyzed using a nonparametric approach (Wilcoxon test), were comparable, as shown Table 5.

Analysis of the correlation between O_2 concentrations, an indicator of the extent of flushing and insufflation maneuvers, and H_2 and CH_4 concentrations in the right and transverse colon shows a significant inverse correlation between O_2 concentrations and H_2 and CH_4 concentrations in the right colon (ρ −0.35, $p < 0.0001$ for H_2; and ρ −0.28, $p = 0.0007$ for CH_4) and in the transverse colon (ρ −0.32, $p < 0.0001$ for H_2; and ρ −0.21, $p = 0.016$ for CH_4).

In both groups, the gas concentrations measured at insertion of the colonoscope at the sigmoid-rectal junction were slightly higher than those measured at the same level during retraction of the instrument (i.e., at the end of the colonoscopy), as shown in Table 5.

The multivariable regression model shows that the factors most influencing residual levels of H_2 are the concentrations of O_2 ($p < 0.0001$) and the degree of cleanliness obtained ($p = 0.0009$).

DISCUSSION

The results of the dose-finding phase II part of the study, in which 179 patients were randomized to receive 50, 100, or 150 g of mannitol (which resulted in an adequate level of bowel cleansing in 75%, 94.4%, and 93.9% of patients, respectively),[15] showed in all treatment groups that mean concentrations of H_2 and CH_4 decreased from the right colon to the transverse and sigmoid-rectal junction, but were always below the critical thresholds by at least one order of magnitude. An ANOVA model with H_2 and CH_4 concentrations in each colon segment as the dependent variable and the mannitol dose as the independent variable, ruled out the existence of a mannitol dose–gas concentration relationship in all colon segments. The absence of a correlation among the different doses of 50, 100, and 150 g, and H_2 and CH_4 concentrations in all colon segments

TABLE 1 Demographic characteristics of enrolled patients (full analysis set).

	Phase II of the study			Phase III of the study	
	Mannitol 50 g (*N* = 65)	Mannitol 100 g (*N* = 57)	Mannitol 150 g (*N* = 57)	Mannitol 100 g (*N* = 333)	2 L PEG-Asc (*N* = 347)
Age, years					
Mean (SD)	57.4 (11.20)	54.4 (11.19)	54.1 (13.65)	54.8 (12.57)	54.6 (12.76)
Sex, *n* (%)					
Male	35 (53.85)	25 (43.86)	23 (40.35)	128 (38.44)	153 (44.09)
Female	30 (46.15)	32 (56.14)	34 (59.65)	205 (61.56)	194 (55.91)
Ethnicity, *n* (%)					
Hispanic or Latino	2 (3.08)	0 (0.00)	2 (3.51)	3 (0.9)	4 (1.15)
Not Hispanic or Latino	62 (95.38)	54 (94.74)	54 (94.74)	325 (97.60)	665 (97.79)
Unknown	1 (1.54)	3 (5.26)	1 (1.75)	5 (1.50)	3 (0.86)

TABLE 2 Intestinal H_2 and CH_4 concentrations in phase II of the study (ANOVA models and PP population).

	50 g mannitol ($N = 60$)	100 g mannitol ($N = 54$)	150 g mannitol ($N = 49$)
H_2 concentrations			
ANOVA model: right colon – H_2 (% vol)			
p value from type III effect*			0.2291
Least squares mean (95% CI)	0.254 (0.135, 0.373)	0.108 (−0.014, 0.230)	0.155 (0.026, 0.283)
Difference in least squares mean (95% CI), *p* value	Reference	−0.146 (−0.339, 0.047), 0.166	−0.099 (−0.297, 0.099), 0.434
ANOVA model: transverse colon – H_2 (% vol)			
p value from type III effect*			0.4236
Least squares mean (95% CI)	0.094 (0.045, 0.143)	0.061 (0.011, 0.111)	0.049 (−0.004, 0.101)
Difference in least squares mean (95% CI), *p* value	Reference	−0.033 (−0.112, 0.046), 0.547	−0.046 (−0.127, 0.036), 0.353
ANOVA model: sigmoid-rectal junction – H_2 (% vol)			
p value from type III effect*			0.3361
Least squares mean (95% CI)	0.019 (−0.003, 0.041)	0.038 (0.015, 0.061)	0.016 (−0.009, 0.040)
Difference in least squares mean (95% CI), *p* value	Reference	0.019 (−0.017, 0.055), 0.386	−0.003 (−0.041, 0.034), 0.969
CH_4 concentrations			
ANOVA model: right colon – CH_4 (% vol)			
p value from type III effect*			0.3108
Least squares mean (95% CI)	0.043 (0.016, 0.070)	0.025 (−0.003, 0.053)	0.012 (−0.017, 0.042)
Difference in least squares means (95% CI), *p* value	Reference	−0.018 (−0.062, 0.026), 0.566	−0.031 (−0.076, 0.014), 0.227
ANOVA model: transverse colon – CH_4 (% vol)			
p value from type III effect*			0.0942
Least squares mean (95% CI)	0.023 (0.011, 0.034)	0.010 (−0.001, 0.022)	0.005 (−0.007, 0.017)
Difference in least squares mean (95% CI), *p* value	Reference	−0.013 (−0.031, 0.006), 0.220	−0.0177 (−0.0365, 0.0011), 0.068
ANOVA model: sigmoid-rectal junction – CH_4 (% vol)			
p value from type III effect*			0.1329
Least squares mean (95% CI)	0.003 (−0.004, 0.011)	0.012 (0.005, 0.019)	0.002 (−0.006, 0.010)
Difference in least squares mean (95% CI), *p* value	Reference	0.009 (−0.003, 0.020), 0.176	−0.001 (−0.013, 0.011), 0.958

Note: An ANOVA model with gas concentration in each colon segment as the dependent variable and dose as the independent variable was applied to assess the dose–gas concentration relationship.

Abbreviations: ANOVA, analysis of variance; CI, confidence interval; PP, per protocol.

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

indicates that mannitol did not affect the concentrations of potentially critical intestinal gases. Conversely, the mean H_2 and CH_4 values tended to be higher in patients treated with the 50 g dose, which could be related to the reduced cleanliness obtained with the lower dose. In other words, the 50 g dose would have eliminated the gases present before preparation less efficiently. Potentially critical levels of H_2 (>4% vol) or CH_4 (>5% vol) were not seen in any colon segment in any patient in the PP population. However, a potentially dangerous level of H_2 was reported for one patient in the 150 g dose group in the FAS, but only in the right colon. This finding was associated with an O_2 level (13.5% vol) far below that of ambient air (>20% vol), whereas the H_2 values were much lower than the critical threshold or those found in the transverse colon (1.54% vol) and the sigmoid-rectal junction (0.44% vol) with O_2 concentrations similar to those of ambient air. So, the most likely interpretation is that this finding is due to insufficient gas exchange, and not to bowel cleansing with mannitol, and was caused by difficulties performing

TABLE 3 Intestinal H_2 and CH_4 concentrations in phase III of the study (safety set).

	Mannitol ($N = 343$)	2 L PEG-Asc ($N = 347$)
Right colon		
H_2 (% vol)		
n	325	341
Mean (SD)	0.155 (0.363)	0.081 (0.175)
CH_4 (% vol)		
n	325	341
Mean (SD)	0.031 (0.097)	0.045 (0.196)
Transverse colon		
H_2 (% vol)		
n	327	340
Mean (SD)	0.072 (0.201)	0.047 (0.130)
CH_4 (% vol)		
n	327	340
Mean (SD)	0.022 (0.069)	0.021 (0.057)
Sigmoid-rectal junction		
H_2 (% vol)		
n	327	338
Mean (SD)	0.023 (0.071)	0.012 (0.060)
CH_4 (% vol)		
n	327	338
Mean (SD)	0.015 (0.039)	0.017 (0.062)

Note: Some patients were excluded from the analysis because their gas concentrations were measured through a device with malfunction issues.
Abbreviation: SD, standard deviation.

correct insufflation of the cecum during the colonoscopy. Air insufflation and suction used in routine colonoscopy should adequately dilute colonic gases to below dangerous levels, and electrocautery may be dangerous only within a pocket of undiluted intraluminal gas, as already reported in the literature.[6,12,13] This situation can occur irrespective of the drug used for bowel cleansing.

In phase III, 680 patients were randomized to receive a single dose of mannitol (100 g) or the standard split-dose 2 L PEG-Asc preparation (2 L PEG-Asc). Single-dose of mannitol was noninferior to split-dose 2 L PEG-Asc in the proportion of patients with adequate bowel cleansing (91.1% and 95.5%, respectively; *p* value for the noninferiority = 0.0095). H_2 or CH_4 concentrations were below the critical threshold in all colon segments in all patients in both groups. In approximately half of the patients in both groups, no H_2 or CH_4 was detected in any colon segment, indicating that bowel cleansing with either preparation, combined with standard washing and insufflation, resulted in complete elimination of gases present before bowel preparation. In patients with H_2 and/or CH_4

TABLE 4 Summary of H_2 and CH_4 concentrations in each colon segment for levels greater than zero after standard washing and air insufflation for luminal distension (safety set).

	Mannitol ($N = 343$)	2 L PEG-Asc® ($N = 347$)
H_2 concentrations (% vol)		
Right colon – H_2 (% vol)		
n	205	174
Mean (SD)	0.245 (0.432)	0.158 (0.218)
Median	0.100	0.080
Comparison of cecum – H_2 (% vol)		
p value (Wilcoxon rank test)	0.0732	
Transverse colon – H_2 (% vol)		
n	157	140
Mean (SD)	0.150 (0.270)	0.113 (0.184)
Median	0.060	0.040
Comparison of transverse colon – H_2 (% vol)		
p value (Wilcoxon rank test)	0.0523	
Sigmoid-rectal junction – H_2 (% vol)		
n	98	64
Mean (SD)	0.076 (0.112)	0.063 (0.126)
Median	0.040	0.040
Comparison of sigmoid-rectal junction – H_2 (% vol)		
p value (Wilcoxon rank test)	0.6506	
CH_4 concentrations (% vol)		
Right colon – CH_4 (% vol)		
n	72	69
Mean (SD)	0.140 (0.1661)	0.220 (0.3898)
Median	0.1000	0.1000
Comparison of cecum – CH_4 (% vol)		
p value (Wilcoxon rank test)	0.4150	
Transverse colon – CH_4 (% vol)		
n	63	63
Mean (SD)	0.114 (0.1189)	0.113 (0.0856)
Median	0.100	0.100
Comparison of transverse colon – CH_4 (% vol)		
p value (Wilcoxon rank test)	0.8497	
Sigmoid-rectal junction – CH_4 (% vol)		
n	53	58
Mean (SD)	0.093 (0.0481)	0.101 (0.1186)
Median	0.100	0.050
Comparison of sigmoid-rectal junction – CH_4 (% vol)		
p value (Wilcoxon rank test)	0.3869	

Abbreviation: SD, standard deviation.

TABLE 5 Summary of intestinal gas concentrations in the sigmoid-rectal junction before and after standard washing and air insufflation for luminal distension (safety set).

	Before standard washing and air insufflation		After standard washing and air insufflation	
	Mannitol ($N = 343$)	2 L PEG-Asc ($N = 347$)	Mannitol ($N = 343$)	2 L PEG-Asc ($N = 347$)
Sigmoid-rectal junction				
H_2 (% vol)				
n	331	342	327	338
Mean (SD)	0.051 (0.222)	0.026 (0.079)	0.023 (0.071)	0.012 (0.060)
CH_4 (% vol)				
n	331	342	327	338
Mean (SD)	0.027 (0.102)	0.041 (0.2129)	0.015 (0.039)	0.017 (0.062)

Note: Some patients were excluded from the analysis because their gas concentrations were measured through a device with malfunction issues.
Abbreviation: SD, standard deviation.

levels above detectable concentrations, the mean values decreased from the right colon to the transverse and descending colon and were still below the risk thresholds by at least one order of magnitude. In both groups, values above zero were non-normally distributed and similar in all segments, including the sigmoid-rectal junction where gas was also measured per protocol before washing and suction maneuvers. The two preparations were highly effective in removing potentially dangerous gases. These results for mannitol used for bowel cleansing are consistent with real-world data. In Latin America, particularly Brazil, mannitol continues to be the most widely used preparation for bowel cleansing due to its efficacy, ease of use and high acceptance rates by patients, with no case of explosion reported.[16,17]

The results of phase III also allow evaluation, for the first time ever, of the role of other factors possibly affecting residual concentrations of H_2 and CH_4, such as the insufflation and washing maneuvers performed during colonoscopy. The O_2 levels indicate the efficacy of insufflation: an O_2 concentration similar to that in ambient air (>20% vol) denotes gaseous equilibrium between the lumen of the colon and the outside air, that is, complete gas exchange. A wider interpatient variability was observed for O_2 concentrations compared to H_2 and CH_4 concentrations; this wider variability is attributable to the fact that the extent of air insufflation was at the discretion of the endoscopist, who performing it, as per usual clinical practice, according to the need found in each individual patient for a correct progression of the endoscope within the intestinal lumen.

To confirm the importance of insufflation and washing in patients with H_2 and/or CH_4 levels greater than zero, regardless of treatment group, a statistical evaluation was carried out of the correlation between O_2 concentrations and H_2 and CH_4 concentrations in the right and transverse colon, the segments where intestinal gas concentrations were higher. This analysis showed a significant inverse correlation between O_2 concentrations and H_2 and CH_4 concentrations in both the right and the transverse colon: the higher the O_2 concentration (i.e., after more efficient insufflation and washing), the lower the H_2 and CH_4 concentrations. This correlation is valid regardless of the drug used for bowel cleansing. The effectiveness of the washing and insufflation maneuvers in removing intestinal gases present before colonoscopy is also demonstrated by the fact that, in both groups, the gas concentrations measured at insertion of the colonoscope at the sigmoid-rectal junction were higher than those measured at the same location during retraction of the instrument at the end of the colonoscopy.

Finally, to further evaluate the factors affecting residual concentrations of intestinal gases in all patients, regardless of treatment group, multivariate analysis was conducted considering the drug used for bowel cleansing, the degree of cleanliness obtained (BBPS score), and oxygen concentration (indicating degree of insufflation and washing) as covariates. This analysis showed that the factors most influencing residual levels of H_2 were O_2 concentrations (i.e., the degree of air insufflation and the degree of cleanliness), whereas the type of drug used for bowel cleansing was less relevant. This further indicates that insufficient washing and insufflation were responsible for H_2 or CH_4 concentrations above the center of distribution (median and/or mean) in the few patients affected, regardless of the drug used for bowel cleansing. Consequently, the likelihood of H_2 or CH_4 concentrations above the critical threshold is very low and most likely depends not on the preparation used, but on the colonoscopy method. To further minimize residual risk, it is important (i) to perform electrocautery or argon plasma coagulation maneuvers only after the colonoscope has been retracted,

after standard insufflation and lavage maneuvers have been performed, (ii) to pay particular attention to the right and transverse colon where intestinal gas concentrations are potentially higher, and (iii) not to perform therapeutic procedures in the presence of nonoptimal bowel cleansing.

This study had some limitations, including the single blind design, the air insufflation before gas measurement, and the lack of microbiota assessment.

The double-blinding could not be performed because of the different preparations and intake (single dose and double dose) characteristics of the individual treatments under investigation. In addition, it has to be underlined that the gas measurement occurred after air insufflation. This procedure may affect the initial gas concentrations; however, it reflects what occurs during clinical practice. Moreover, air insufflation and washing are a part of the endoscopic procedure as recommended by international guidelines to aid endoscope progression, elimination of residual gas pockets, and optimizing the visualization of the colonic mucosa. Finally, the study design did not include an investigation concerning the microbiota change after bowel preparation. It could be interesting to explore the possible relationship between microbiota change and gas concentrations. Further studies should investigate this issue.

In conclusion, the results of our large, international, multicenter, randomized, and endoscopist-blinded study clearly showed that the use of mannitol for intestinal preparation was safe regarding the risk of explosion, as the preparation did not exert a dose-dependent pharmacological effect causing an increase of H_2 and CH_4 concentrations in the different sections of the colon. In patients prepared with mannitol, the concentration of potentially explosive gases was similar to that found in patients prepared with the standard comparative laxative agent (2 L PEG-Asc). In both groups of patients, the concentrations of H_2 and CH_4 were more influenced by the degree of cleansing achieved and the insufflation and washing maneuvers performed during colonoscopy than by the preparation used for bowel cleansing.

AUTHOR CONTRIBUTIONS

M.C. wrote the manuscript. M.C., M.V., G.E.T., M.C., A.P., B.M.C., A.P.F., and A.O. designed the research. C.S., P.U., P.B., R.C., F.C., P.C., G.C., D.D.P., C.H., S.K., A.M., E.M., T.P., F.R., S.S., P.S., P.A.T., G.E.T., M.V., and G.F. performed the research.

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CONFLICT OF INTEREST STATEMENT

A.O. is an employee of NTC. M.C. and B.M.C. are paid consultants with NTC. All other authors declared no competing interests for this work.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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