SAFETY OF MANNITOL USE IN BOWEL PREPARATION: a prospective assessment of intestinal methane (CH₄) levels during colonoscopy after mannitol and sodium phosphate (NaP) bowel cleansing

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ABSTRACT – Background – Adequate bowel preparation is critical for the quality of colonoscopy. Despite reported occurrence of colonic explosion due to methane and hydrogen production by bacterial fermentation during colonoscopy, gas exchange during the procedure is believed to be effective in lowering existing methane concentration, allowing for safe utilization of mannitol for bowel preparation. Thus, mannitol is widely used for bowel cleansing prior to colonoscopy, considering its low cost and effectiveness for bowel preparation. Objective – The aim of this study was to assess the safety of mannitol for bowel preparation, when compared to sodium phosphate (NaP). Methods – We conducted a prospective observational study in which 250 patients undergoing colonoscopy at Universidade Federal de São Paulo and Hospital Albert Einstein (São Paulo, Brazil) were approached for inclusion in the study. Patients received either mannitol (n=50) or NaP (n=200) for bowel preparation, based on physician indication. Study was conducted from August 2009 to December 2009. The main outcome of interest was presence of detectable levels of methane (CH₄) during colonoscopy and reduction in such levels after gas exchange during the procedure. Methane concentrations were measured in three intestinal segments during scope introduction and withdrawal. Safety was assessed as the absence of high levels of methane, defined as 5%. Measurements were made using a multi-gas monitor (X-am 7000, Dräger Safety AG & Co. KGaA, Lübeck, Germany) connected to a plastic catheter introduced into the working channel of the colonoscope. Additional outcomes of interest included levels of O₂. Methane and O₂ levels are reported as ppm. Mean, difference and standard deviation of levels of gas measured in both moments were calculated and compared in both groups. Proportions of patients with detectable or high levels of methane in both groups were compared. Continuous variables were analyzed using t test and categorical variables using qui-square tests. The Ethics Committee in both study sites approved the study protocol. Results – Patients in both groups were similar regarding demographics, colonoscopy indication, ASA status and quality of bowel preparation. Seven (3.5%) patients in the NaP group had methane detected during introduction of the endoscope. Methane levels became undetectable during withdrawal of the scope. None of the patients in the mannitol group had detectable levels of methane. O₂ levels did not differ in the groups. Conclusion – This is the largest study to assess the safety of mannitol for bowel preparation, considering methane measurements. Our results indicate that mannitol use is as safe as NaP, and gas exchange was efficient in reducing methane concentrations.


INTRODUCTION

Colonoscopy is currently the standard method for mucosa imaging of the entire colon and is widely used for the diagnosis and treatment of colonic disorders¹²,₂². The effectiveness of colonoscopy, including its ability to diagnose precancerous lesions and prevent colorectal cancer, is highly dependent on adequacy of bowel cleansing⁷. In addition to lower effectiveness of the procedure, inadequate bowel preparation in colonoscopy can result in higher costs and complication rates⁷,₂³,₂₈.

Ideally, bowel preparation for colonoscopy should reliably empty the colon of all fecal material in a rapid fashion with no gross or histologic alteration of the colonic mucosa. The preparation should not cause patient discomfort or shifts in fluids or electrolytes. In order to achieve that, oral medications that are safe, convenient, tolerable, and inexpensive are to be used. Unfortunately, none of the currently commercially available formulation fit all of the above criteria⁷.

Colonoscopía durante colonoscopia se ha atribuido a la presencia de inefables gases - hidrógeno (H₂) y metano (CH₄), en combinación
with oxygen (O₂), and application of a heat source (electro
cautery or argon plasma coagulation)\(^{(13,14,18,25)}\).

Accumulation of colonic gas to potentially explosive
concentrations results mainly from inadequate bowel
preparation\(^{(14)}\). It has also been hypothesized that methane
and hydrogen production by bacterial fermentation during
colonoscopy may be increased as a result of non-absorbable
carbohydrate preparations for bowel preparation, such as
mannitol, sorbitol, and lactulose. For this reason, routine use
of non-absorbable carbohydrate preparations is not favored
in Europe and in North America\(^{(14,21)}\). Nonetheless, manni-
tol is widely used globally, due to its effectiveness in bowel
cleansing, good tolerability, low complication rates, and low
cost\(^{(9)}\). Gas exchange during the procedure is believed to be
effective in lowering existing methane concentration prior
to colonoscopy, allowing for safe utilization of mannitol for
bowel preparation\(^{(4)}\).

Mannitol is the most used laxative in Brazil\(^{(24,27)}\). Consid-
ering the above, we propose to evaluate the safety of mannitol
for bowel preparation, when compared to sodium phosphate,
which has been reported as among the most frequently used
product for bowel preparation\(^{(5)}\).

In order to assess the safety of mannitol, we aimed at
evaluating the presence of detectable levels of methane
(CH₃) levels during colonoscopy, and whether reduction
in detected levels occurred after gas exchange during the
procedure, in patients receiving either mannitol or sodium
phosphate.

**METHODS**

**Study design**

We conducted a prospective observational study of
patients undergoing colonoscopy who received either man-
nitol or sodium phosphate for bowel preparation prior to
the procedure.

**Study location**

Study subjects were enrolled in two sites, both located
in São Paulo, Brazil. Hospital A, Hospital Albert Ein-
stein, is a tertiary level private hospital, with 670 beds and
performing around 1000 colonoscopies/month. Hospital
B, Hospital São Paulo, is a public tertiary level univer-
sity hospital with 712 bed hospital, performing about 100
colonoscopies/month and providing healthcare services
free of charge to users of the Brazilian public healthcare
system (SUS).

**Selection of patients**

From August 2009 to December 2009, adult outpatients
with a colonoscopy procedure scheduled at any of the two
study sites were invited to participate in the study. Systematic
enrollment of patients was performed, once a week in Hos-
pital São Paulo, and twice a week in Albert Einstein. Exclu-
sion criteria were ASA scores III and IV prior to procedure,
being hospitalized at the moment of the procedure, and not
agreeing to sign an informed consent.

**Ethical issues**

This study protocol was approved by the Ethics Com-
mittees of both institutions involved and was conducted in
accordance with the World Medical Association Declara-
tion of Helsinki – Ethical Principles for Medical Research
Involving Human Subjects. Written informed consent was
obtained from all patients.

**Colonoscopic procedure**

After accepting to participate in this study, patients were
assigned to one of the two study groups, based on physician
preference and recommendation.

All patients were asked to adhere to a liquid diet the day
before the examination. According to patient’s preference,
colon cleansing could be performed on a home or Hospital
basis. In both regimens drugs dosages were the same. In
home cleansing the patient received the drug and was ori-
ented in how to ingest it at home, and arrived at the hospital
ready for the procedure. In Hospital cleansing, the patient
received the drug into the Hospital, and was observed in the
Endoscopy Unit until preparation was considered adequate
by the nursing team.

In the mannitol group, patients received 150 g of mannitol
diluted in 500 mL of water the night before the procedure
(examinations scheduled for the morning or home prepara-
tion) or 6 hours prior to the procedure (afternoon or Hospital
based examinations). In the NaP group, patients received 20
mg of the salt diluted in 500 mL of water the night before the
procedure (examinations scheduled for the morning or home
preparation) or 6 hours prior to the procedure (afternoon or
Hospital based examinations). In both groups, patients
were encouraged to drink water (up to 2 liters) until 3 hours
before beginning of the sedation.

Before the procedure, an intravenous cannula was placed
in the forearm for the injection of propofol and other
medications. According to the ASA Task Force on Sedation
and Analgesia by Non-anesthesiologists recommendation,
supplemental oxygen (2 L/min) was given to all patients
unless specifically contraindicated\(^{(9)}\). Monitoring included
continuous electrocardiogram, noninvasive blood pressure
measurement and pulse oximetry.

In both groups, we attempted to pass the colonoscope
to the cecum with minimum air insufflation or suction.
Intermittent infusions of small quantities of water were
used as necessary. Not more than 400 mL of water was
infused in any one occasion\(^{(9)}\). Based on the need to in-
sufflate air/water the difficulty level of each colonoscopy
procedure was subjectively classified in easy, intermediate
or difficult.

**Gas measurements**

The following gases were measured during colonos-
copy procedures: oxygen (O₂) and methane (CH₃) Gas
concentrations were measured in the rectum and transverse
colon during introduction and withdrawal of the scope. A
physician blinded to the cleansing solution performed gas
measurements. Another single measurement was performed
Study outcomes
The main study outcome was detectable levels during colonoscopy, and decreasing methane concentrations after gas exchange. Additional outcomes of interest included levels of methane and O2 in both groups. Concentration of any gas higher than 0 was defined as presence of the gas. Methane levels were converted to % LEL (lower explosive limit) by dividing the measured value (in ppm) by 10,000.

Data collection
The following variables were recorded: (1) indication of the procedure; (2) time interval between laxative administration and beginning of the procedure; (3) quality of bowel preparation; (4) time to reach the cecum; (5) total examination time; (6) technical difficulty of the procedure; (7) CH4 and O2 in the rectum and transverse colon and when reaching the cecum; (8) presence of complications.

Statistical analysis
Descriptive analysis of patient and procedures characterization was conducted. For continuous parameters, results were expressed as mean (SD). Categorical data were expressed using absolute frequencies and percentages.

Mean, difference and standard deviation of gas levels were calculated. Stratified analysis by colonic segment (rectum, cecum, and transverse), and moment of measurement (calibration, introduction or withdrawal) was also performed. Mean level of gas concentrations during scope introduction and withdrawal were compared.

Patient’s characterization, outcomes, and average gas levels were compared in the two groups – receiving mannitol and sodium phosphate. Patients who presented detectable methane concentrations were compared to those without methane detected. Continuous variables were analyzed with two sample Student’s unpaired t test. Categorical data were examined with qui-square and Fisher’s Exact Test when appropriate. Statistical significance level was P<0.05. All statistical analyses were performed with statistical software SPSS for Windows (SPSS version 23.0, SPSS Inc.) or EpiInfo 6 (CDC and WHO).

RESULTS
Of the 250 patients included in this study, 136 (54.4%) were male. Average age was 56.2 years (range 19-88 years, SD 12.2). Average time between laxative administration and beginning of examination was 5.84 hours (range 3-14 hours, SD 2.47). Major indications for colonoscopy were screening in asymptomatic patients (n=109, 43.6%), abdominal pain (n=41, 16.4%), diarrhea (n=30, 12%) and constipation (n=29, 11.6%). Most colonoscopy procedures were performed at Study Site B (n=212, 84.8%). Fifty (20%) patients received mannitol for bowel preparation whereas 200 (80%) patients received sodium phosphate. Of these, 123 (61.5%) performed preparation in the hospital, and 77 (38.5%) prepared at home. Bowel preparation was judged adequate in all except one (0.4%) patient. Time to reach the cecum ranged between 6 and 21 minutes (mean 10.4 min, SD 2.5). Total examination time varied between 14 and 50 minutes (mean 24.2, SD 5.5). Subjects in the study groups did not differ significantly in terms of demographics and clinical characterization (Table 1).

Colonoscopy procedure was considered easy in 194 (77.6%) subjects, intermediate in 47 (18.8%) and difficult in 9 (3.6%). Most study subjects (n= 154, 61.6%) presented some finding in the procedure. Of these, the most significant finding was polyps and/or diverticula (n=133, 86.4%). Ninety-six patients (38.4%) had a normal colonoscopy.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients receiving mannitol (n=50)</th>
<th>Patients receiving Sodium Sulphate (n=200)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Categorical variables, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male Gender</td>
<td>23 (46)</td>
<td>113 (56)</td>
<td>0.206</td>
</tr>
<tr>
<td>Reason for colonoscopy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screening / asymptomatic</td>
<td>17 (34)</td>
<td>92 (46)</td>
<td>0.126</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9 (18)</td>
<td>21 (10.5)</td>
<td>0.144</td>
</tr>
<tr>
<td>Obstipation</td>
<td>5 (10)</td>
<td>24 (12)</td>
<td>0.693</td>
</tr>
<tr>
<td>Melena</td>
<td>0 (0)</td>
<td>12 (5.5)</td>
<td>0.089</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>11(22)</td>
<td>30 (15)</td>
<td>0.232</td>
</tr>
<tr>
<td>Others</td>
<td>6 (12)</td>
<td>12 (6)</td>
<td>0.142</td>
</tr>
<tr>
<td>Anemia</td>
<td>2 (4)</td>
<td>10 (5)</td>
<td>0.767</td>
</tr>
<tr>
<td>Study site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital A</td>
<td>12 (24)</td>
<td>200 (100)</td>
<td></td>
</tr>
<tr>
<td>Hospital B</td>
<td>58 (76)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Difficulty level of colonoscopy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Easy</td>
<td>35 (70)</td>
<td>159 (79.5)</td>
<td>0.150</td>
</tr>
<tr>
<td>Intermediate</td>
<td>13 (26)</td>
<td>34 (17)</td>
<td>0.736</td>
</tr>
<tr>
<td>Difficult</td>
<td>2 (4)</td>
<td>7 (3.5)</td>
<td>0.865</td>
</tr>
<tr>
<td>Continuous variables, mean (standard deviation)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>52.16 (14.23)</td>
<td>57.16 (11.40)</td>
<td>0.963</td>
</tr>
<tr>
<td>Duration of colonoscopy (minutes)</td>
<td>23.64 (6.49)</td>
<td>24.31 (5.19)</td>
<td>0.931</td>
</tr>
</tbody>
</table>
Methane concentrations were identified in seven patients receiving sodium phosphate during colonoscopy procedure, all of which had preparation performed at home. CH₄ levels were measured in the rectum in five cases, in the transverse in five and in the cecum in five patients. In all seven patients, bowel preparation was considered adequate. No patients receiving mannitol had detectable amounts of methane. During withdrawal of the scope, no patient presented CH₄ concentrations. Detailed characterization of such patients is presented in Table 2.

No patient had methane gas concentration during scope withdrawal as shown in Table 3. When considering the reduction in gas levels from scope introduction to withdrawal (Δ = level at introduction - level at withdrawal) for rectum and transverse segments, whereas a significant reduction of CH₄ was demonstrated for both rectum and transverse segments (P<0.001), O₂ levels maintained at similar levels.

Subjects presenting with detectable CH₄ levels did not differ from those with undetectable CH₄ (Table 4). However, numbers were small to identify factors associated to this outcome.

**DISCUSSION**

We hypothesized that detectable and high levels of CH₄ would be present during scope introduction, when gas exchange – air insufflation and aspiration is minimal, particularly in patients receiving mannitol. Although our main goal was to assess whether gas exchange could reduce CH₄ concentration after colonoscopy in patients receiving mannitol solution for cleansing, surprisingly we did not observe high levels of CH₄ concentrations. To our knowledge this is the first report to show such results.

Secondly, as anticipated, CH₄ levels were reduced at the moment of scope withdrawal, when compared to levels at scope introduction, possibly as a result of gas exchange during the colonoscopy procedure. This was true in both study groups.

### Table 2. Characteristics of 7 patients with detectable methane (CH₄) levels. Cohort study to assess safety of mannitol for bowel preparation, Brazil, 2009

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Reason for colonoscopy</th>
<th>Bowel preparation</th>
<th>Quality of bowel preparation</th>
<th>Colonoscopy Findings</th>
<th>Level of CH₄ (ppm) Rectum</th>
<th>Level of CH₄ (ppm) Transverse</th>
<th>Level of CH₄ (ppm) Cecum</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>42</td>
<td>Screening</td>
<td>Sodium phosphate/ Home</td>
<td>Adequate</td>
<td>Normal</td>
<td>0 – 0 – 3,000</td>
<td>20.900</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>82</td>
<td>Screening</td>
<td>Sodium phosphate/ Home</td>
<td>Adequate</td>
<td>Normal</td>
<td>2,800 – 48,000 – 3,000</td>
<td>20.900</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>62</td>
<td>Screening</td>
<td>Sodium phosphate/ Home</td>
<td>Adequate</td>
<td>Diverticula</td>
<td>3,800 – 0 – 0</td>
<td>20.900</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>62</td>
<td>Screening</td>
<td>Sodium phosphate/ Home</td>
<td>Adequate</td>
<td>Polyps</td>
<td>15,400 – 21,000 – 32,000</td>
<td>20.900</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>46</td>
<td>Screening</td>
<td>Sodium phosphate/ Home</td>
<td>Adequate</td>
<td>Normal</td>
<td>28,000 – 32,000 – 5,600</td>
<td>20.900</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>53</td>
<td>Screening</td>
<td>Sodium phosphate/ Home</td>
<td>Adequate</td>
<td>Normal</td>
<td>12,000 – 23,000 – 8,000</td>
<td>20.900</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>57</td>
<td>Diarrhea</td>
<td>Sodium phosphate/ Home</td>
<td>Adequate</td>
<td>Diverticula + polyps</td>
<td>0 – 4,000 – 0</td>
<td>20.900</td>
<td></td>
</tr>
</tbody>
</table>
Further, despite recent evidence reporting high rates (10%–30%) of inadequate preparation, particularly when performed at home(7,10,12,15,23), our study found that almost all patients had adequate preparation, regardless of having had home or hospital preparation. The fact that our study population was composed only by ASA I and II patients could explain such a good preparation quality.

Hyperosmotic purges with non-absorbable carbohydrates, such as mannitol, sorbitol, and lactulose, exert an osmotic effect, drawing water into the intestine, leading to bowel distention and stimulation of evacuation. The routine use of non-absorbable carbohydrate preparations is not favored in Europe and in North America due to the risk of explosion(21).

Colonic explosion during colonoscopy has been attributed to the presence of inflammable gases, chiefly hydrogen (H₂) and methane (CH₄) in the colon, which are produced in the colonic lumen from fermentation of non absorbable (e.g. lactulose, mannitol) or incompletely absorbed (lactose, fructose, sorbitol) carbohydrates by the colonic flora(14).

The potentially explosive range of H₂ is 4.1% to 72% and of CH₄ is 5% to 15%. Oxygen concentration must be above 5% in the total gas mixture for these gases to be combustible(14).

It has been reported that almost half of the patients (42.8%) with unprepared colon have potentially explosive concentrations of hydrogen and methane(20). Although formation of H₂ is dependent upon the delivery of ingested fermentable material to the colonic bacteria, CH₄ production does not have a clear-cut relation to diet(40). Gas exchange during colonoscopy (air insufflation and aspiration) has long been reported as efficient in lowering methane concentrations to safe levels(43).

In a systematic review of the medical literature from 1952 to 2006, a total of 20 cases of colonic gas explosion were identified. Eleven cases occurred during surgery and nine cases during colonoscopy procedures. Bowel preparation by ingestion of a mannitol solution was used in 14 cases, a cleansing solution containing sorbitol in one, and enemas with no fermentable agents in the remaining five cases(14).

Selected studies have pointed towards a risk of explosion after mannitol preparation during colonoscopic polypectomy lower than anticipated, with high levels of CH₄ also reported in patients receiving castor oil(4).

Strocchi et al.(25) described absence of explosive levels of methane and hydrogen in patients prepared to colonoscopy with polyethylene glycol solution (Colyte ®). Similar results were obtained by Monahan et al.(18) in patients prepared with polyethylene glycol solutions and phosphosoda enemas for sigmoidoscopy. None of these studies used mannitol as colonic cleansing.

Mannitol is still the most used drug for colon cleansing before colonoscopy in Brazil. Such preference, although not stated, is probably secondary to its low cost, and low ingestion volume. In addition, only recently commercially specific colon cleansing products for colonoscopy have become available in Brazil. Several studies have reported on the use of mannitol in Brazil, demonstrating effectiveness in colon preparation, good tolerability and very low complication rates(3,11,16,17,19,24,27).

Methane production in the bowel is poorly understood. Methane is produced by a group of anaerobes called methanogens, in the intestine(26). Interestingly, individuals can be categorized as methane producers and non-producers, respectively about 35% and 65% of healthy Western population(46). Recently, methane production has been linked to intestinal transit time. An association between methane production and slow transit time has been shown(28). If the association between elevated methane production and slow intestinal transit time is related to altered colonic flora is still to be proved(2). Accelerated transit time after mannitol (or any other cleansing colon substance) ingestion could explain such a low methane production. That could also explain why methane concentrations could be present during colonoscopy in patients with less than optimal colonic cleansing, improving the chance of colonic explosion during electrocauthery use.
Our results indicate that mannitol use is as safe as sodium sulphate, and gas exchange was efficient in reducing methane concentrations. Further studies evaluating cost-effectiveness of mannitol for bowel preparation in developing settings are warranted and will provide useful results for guidance regarding its use and safety. Such studies should take into consideration recent evidence on factors related to CH₄ production, reported rates of detectable CH₄ levels when using different types of laxatives for bowel preparation, and practices associated to reduction of gas levels during colonoscopy.

Authors’ contributions
REFERENCES


