Original Research

Dose Optimization of Mannitol Solution for Small Bowel Distension in MRI

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Purpose: To optimize the dose of a hydro solution containing 2.5% mannitol and 0.2% locust bean gum (LBG) for small bowel MRI in terms of bowel distension and patient acceptance.

Materials and Methods: A total of 10 healthy volunteers ingested a hydro solution containing 2.5% mannitol and 0.2% LBG. Four different volumes (1500, 1200, 1000, and 800 ml) were assessed on four different examination days. Small bowel distension was quantified on coronal two-dimensional TrueFISP images by measuring the diameter of eight bowel loops throughout the jejunum and the ileum. In addition, volunteer acceptance was evaluated for every single examination by using a questionnaire.

Results: Optimal distension was obtained with either, 1000, 1200, or 1500 ml, with no statistically significant differences in distension between these groups. Administration of 800 ml led to significantly less distension of the small bowel. Significantly less side effects were noted using either 800 or 1000 ml compared to using larger volumes.

Conclusion: We recommend a dose of 1000 ml mannitol/LBG solution as an oral contrast agent for optimal bowel distension and minimal side effects.

Key Words: mannitol; dose; small bowel distension; small bowel MRI; locust bean gum; True FISP imaging
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INFLAMMATORY BOWEL DISEASE (IBD), which includes Crohn's disease (CD), represents one of the main pathologies of the small bowel. Malignant processes of the small bowel are less common (1). MRI of the small bowel has been shown to have potential utility for diagnostic evaluation of IBD (2).

Small bowel distension is mandatory for the assessment of the bowel wall. It can be based on the oral ingestion of a hyperosmolar solution, thereby reducing water resorption. Thus, a noninvasive method for the distension of the small bowel in abdominal MRI has been established for the diagnosis of IBD (3–5). Recently, the use of a hydro solution containing an osmotic substance (2.5% mannitol) and a nonosmotic component locust bean gum (LBG) (0.2%) has been propagated (6). A 1500-ml dose of this combination is given orally over 45 minutes before the MR small bowel examination (6). However, side effects of mannitol are well known, including flatulence and alteration of bowel flora, which can lead to bowel spasms and diarrhea (7–10). These side effects may reduce patient acceptance (6).

The purpose of our study was to optimize both dosage and timing of the mannitol/LBG solution as an oral contrast agent for MR-based small bowel imaging in a healthy volunteer cohort. Furthermore, volunteers' acceptance and side effects were documented and compared.

MATERIALS AND METHODS

A total of 10 healthy volunteers (four male and six female; age range 24–46 years) without a history of previous abdominal surgery, gastrointestinal disease, or gastrointestinal symptoms such as postprandial belching, nausea, or early satiety were included in this study. Written informed consent was obtained from all subjects, in accordance with the approving local institutional review board.

Bowel Distending Agent

A 0.2% LBG solution (Roeper, Hamburg, Germany) was used as a baseline substance. The baseline LBG solution was mixed with mannitol 2.5% (Merck, Darmstadt, Germany). The following doses were tested in a randomized order: 1500, 1200, 1000, and 800 ml. A minimal interval of 48 hours was ensured between two single examinations of the same volunteer.

Examination Protocol

To assure homogenization of bowel activity, all MR exams were performed following a six-hour fasting period.

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Prior to each examination, the respective contrast solution was orally ingested continuously over 45 minutes at an evenly distributed rate. To enhance gastric emptying, 100 mg of erythromycin (Abbott Pharmaceutics, Wiesbaden, Germany) was administered intravenously directly following the ingestion of the first 100–150 ml of the contrast solution. Erythromycin in low doses can be used to enhance gastric emptying (11,12); earlier attempts without erythromycin had shown a delayed gastric emptying with associated nausea and vomiting (Susanne C. Goehde, personal observation).

MR examinations were performed on a 1.5-T system (Magnetom Sonata; Siemens Medical Systems, Erlangen, Germany) equipped with high-performance gradient systems, characterized by a maximum gradient amplitude of 40 mT/meter and a slew rate of 200 mT/meter/msec. For signal reception, a set of two large flex surface coils was used. Neither spasmolytic agents nor paramagnetic contrast compounds were applied intravenously. Patients were placed in the prone position in the MR scanner. Coronal two-dimensional images were collected using a fast T2-weighted steady state precession sequence (fast imaging by steady precession [FISP] with gradients balanced in all directions [TrueFISP]; TR/TE/flip = 3.9 msec/1.9 msec/70°) every 5 minutes until 30 minutes after contrast ingestion (i.e., 0, 5, 10, 15, 20, 25, and 30 minutes). Imaging parameters included: 35-cm field of view, 7-mm slice thickness with an intersection gap of 1 mm (25 slices), a matrix size of 144 × 256, and an acquisition time of 22 seconds. Imaging was performed under breath-hold conditions.

Data Analysis

Images were analyzed independently by two radiologists who were blinded to the dose of oral contrast employed. Datasets were read and evaluated on a postprocessing workstation (Virtuoso; Siemens Medical Systems, Erlangen, Germany). In a first step, a quantitative assessment was performed. For each dataset, the coronal image depicting the highest degree of small bowel distension was identified in consensus by both interpreters. Subsequently, each reader measured the diameters of eight small bowel loops throughout the jejunum and the ileum. For the measurements, bowel loops with maximal diameter were chosen. Thus, 16 bowel diameter measurements were obtained for each MR data set. Eventually, a mean value for bowel distension was calculated on the basis of these 16 measurements.

For a qualitative assessment, MR images of all four examinations obtained from each volunteer were presented as hardcopies in a randomized and blinded fashion to two radiologists. These two readers had not been involved in the quantitative analysis. They were asked to rate the images regarding bowel distension in an ascending order for each volunteer. The distension was classified as follows: 0 = very poor; 1 = poor; 2 = fair; 3 = good; and 4 = excellent.

Side Effects

At 24 hours after each MR exam, volunteers were questioned regarding side effects such as diarrhea, flatulence, vomiting, or abdominal spasms. For this purpose, a standardized questionnaire was used, which was based on a four-point scale (1 = no side-effects; 2 = mild side-effects; 3 = moderate side-effects; and 4= severe side-effects).

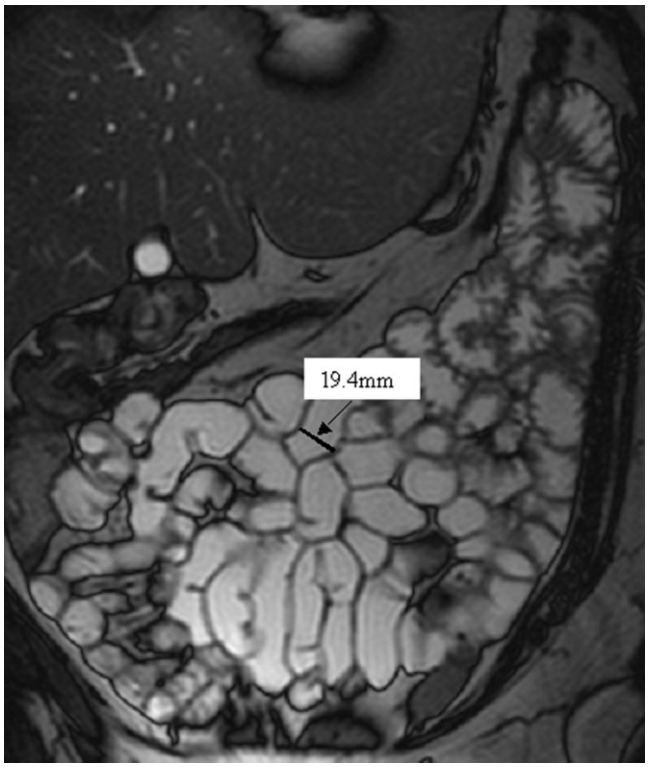

Figure 1. Two-dimensional True-FISP image after small bowel distension with 1000 ml of a contrast agent solution containing a nonosmotic substance (LBG 0.2%) and an osmotic sugar alcohol (mannitol 2.5%). The bowel wall can be depicted by a hypointense signal, whereas the bowel lumen (arrow) exhibits a hyperintense signal.

Statistical Analysis

Mean small bowel distension values obtained for each exam were compared with respect to the given dose using a paired *t*-test. Qualitative results concerning the grade of distension as well as the grades of discomfort were compared using the Wilcoxon rank test for each pair separately. For the adaptation to multiple samples, a Bonferroni-correction was employed. For all statistical analyses, a P value <0.05 was considered to indicate a statistically significant difference.

RESULTS

Each contrast solution was ingested within the target time of 45 minutes by all volunteers. The high contrast between the bright, liquid-containing small bowel lumen and the dark surrounding tissues on the TrueFISP images permitted a distinct delineation between bowel wall and bowel lumen (Fig. 1). Quantitative comparison of the four doses of contrast solution revealed high small bowel distension for the 1500-, 1200-, and 1000-ml doses; however, they were not statistically sig-

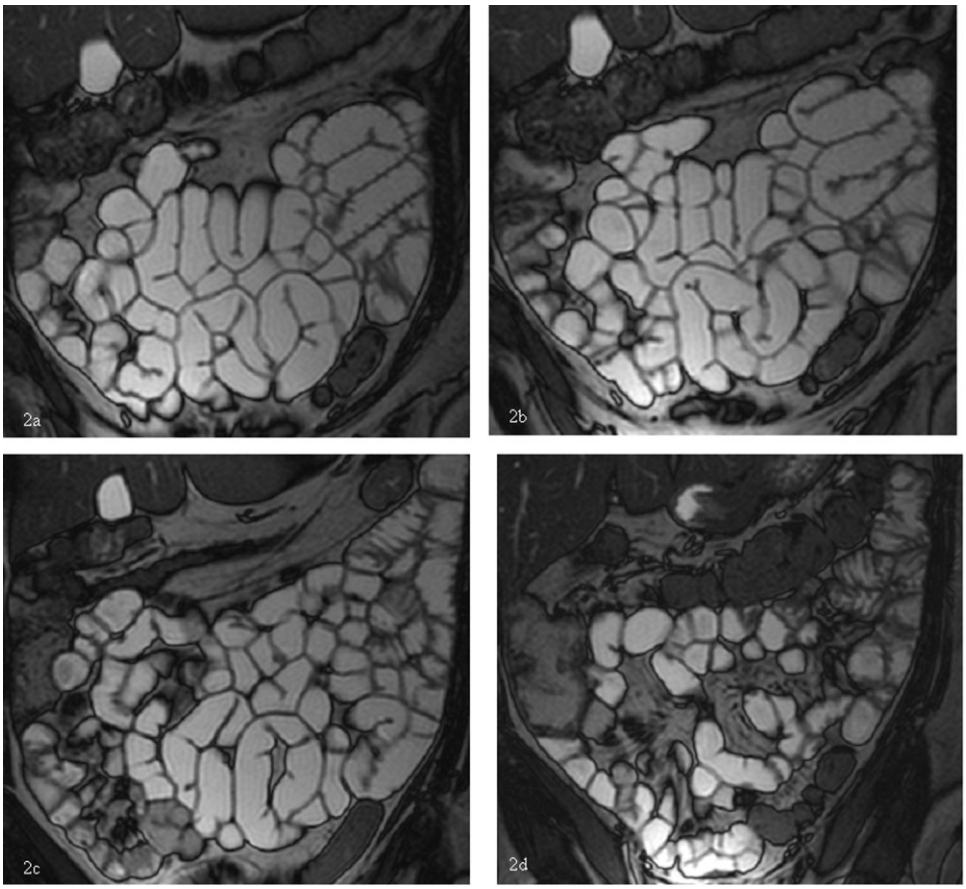

Figure 2. a–d: Distended small bowel of the same volunteer immediately after ingestion of four different doses of the 2.5% mannitol solution: 1500 ml (a); 1200 ml (b); 1000 ml (c); and 800 ml (d). All doses between 1000 and 1500 ml provided a high bowel distension. The lowest grade of small bowel distension was achieved after ingestion of 800 ml of the solution.

nificantly different. The smallest degree of small bowel distension was observed after ingestion of the 800-ml dose (Fig. 2a–d). The 1500-ml dose resulted in a mean small bowel diameter of 22.4 mm immediately following the completion of intake of the oral contrast agent. The mean small bowel diameter diminished to 21.0 mm 30 minutes later. Administration of 1200 ml of oral contrast resulted in a mean small bowel diameter of 22.2 mm immediately and 21.0 mm 30 minutes later. Ingesting 1000 ml of the solution led to continuous distension over the 30-minute interval, resulting in a mean small bowel diameter of 20.6 mm (Fig. 3a–d). Administration of 800 ml of the solution led to a homogenous distension during the 30-minute examination time as well; however, it resulted in the lowest mean small bowel diameter (14.8 mm) (Fig. 4), which turned out to be statistically significantly different in comparison to the other three examination groups.

The qualitative assessment of small bowel distension underscored the results of the quantitative evaluation. The average bowel distension grades were 3.4 (1500-ml dose), 3.2 (1200-ml dose), and 3.1 (1000-ml dose). The ingestion of the 800-ml dose led to a mean value of 2.0. Similar to the quantitative assessment, the difference between the 800-ml dose and the other three doses proved to be statistically significant.

As for the evaluation of side-effects, the highest degree of diarrhea was observed following the ingestion of the 1500- and 1200-ml doses of oral contrast solution (mean values 3.3 and 3.1). The ingestion of the 1000- and 800-ml doses led to a lower degree of diarrhea (mean values 1.6 and 1.3), which was statistically significant different compared to the rating of the 1500- and 1200-ml doses. Concerning flatulence, statistically the ingestion of 1500 and 1200 ml of the solution (mean values 3.1 and 2.7) was rated significantly higher than the ingestion of 1000 and 800 ml (mean values 1.9 and 1.7). Regarding vomiting and spasms, statistically significant differences were observed between the 800- or 1000-ml doses, on the one hand, and the 1200- or 1500-ml doses, on the other (Fig. 5).

DISCUSSION

The data presented indicate that there are no statistically significant differences regarding small bowel distension after an oral ingestion of 1500, 1200, or 1000 ml of 2.5% mannitol solution combined with 0.2% LBG. The lowest degree of small bowel distension was achieved after ingestion of 800 ml of solution. However, 800 and 1000 ml of solution led to the lowest rate of side effects, including diarrhea, flatulence, vomiting, and abdominal spasms. In addition, the ingestion of 1000 and 800 ml of solution led to an uniform distension of the small bowel over the 30 minutes examination time.

Sufficient small bowel distension is essential for the detection of small bowel pathologies because collapsed bowel loops can hide even large lesions or may falsely suggest the presence of pathology such as wall thickening (13–15). For conventional enteroclysis (CE), the

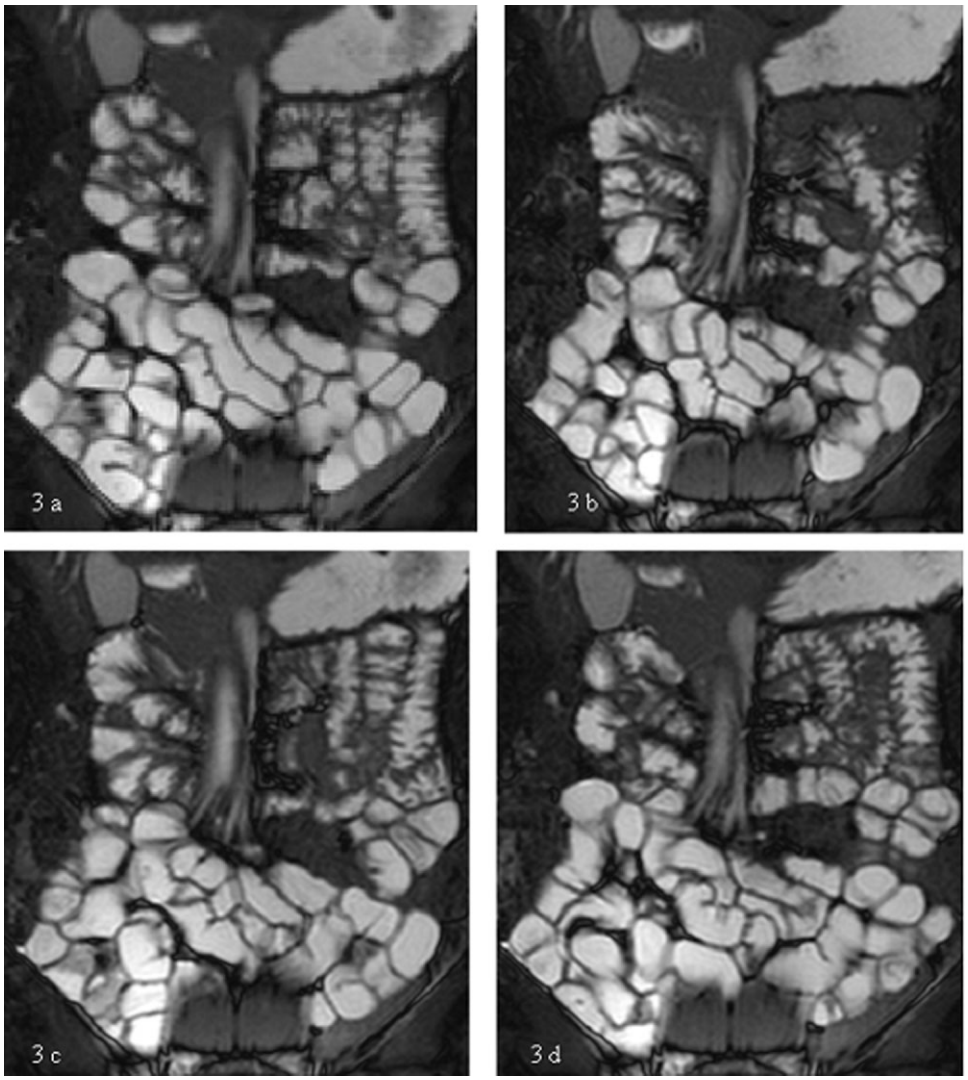

Figure 3. a–d: Distended small bowel, immediately (a), 10 minutes (b), 20 minutes (c), and 30 minutes (d) after ingestion of 1000 ml of the 2.5% mannitol solution (same volunteer in all four images). Uniform distension of the small bowel could be achieved over the 30 minutes examination time.

contrast medium is delivered via a nasoduodenal tube directly into the small bowel. It is a precise, rapid method for small bowel assessment and has been effective in the detection or exclusion of small bowel disease. The main advantage of CE relates to the fact that both jejunum and ileum can be readily distended. However, CE is invasive and may be painful, and it exposes the patient to a relatively high dose of ionizing radiation. Furthermore, it provides only indirect information about the state of the bowel wall (13–19).

Advances in MRI have led to an increasing use of MRI for the evaluation of the intestine, including the assessment of IBD (20,21). To date, most of the published strategies of small bowel MRI rely on the administration of bowel contrast via a jejunal tube for adequate distension (13,16,19,21,22). Thus, detailed morphological images can be obtained resembling those of CE. The clinical impact of this technique has been limited due to logistical difficulties associated with the required coordination of fluoroscopic tube placement and subsequent MRI examination. Besides, distending contrast liquids should be administered orally without duodenal intubation to further improve patients' acceptance, because many patients perceive jejunal intubation as traumatizing and unpleasant.

For a long time, respiratory motion artifacts in conjunction with susceptibility effects prohibited the MR-based analysis of the small bowel. Reflecting recent hardware and software developments, MRI of the abdomen and consequently of the small bowel has become possible by allowing the acquisition of multislice or three-dimensional datasets within a single breath-hold. Furthermore, real time imaging techniques even allow the assessment of intestinal function. TrueFISP can cover the entire abdomen within the confines of a single breath-hold lasting less than 25 seconds (22,23). Similarly, the abdomen can be depicted on fat-saturated three-dimensional gradient echo sequences in conjunction with the intravenous administration of T1-shortening contrast agents (24). Both sequence types rely on the presence of intestinal contrast for delineation and distension of individual bowel loops (3). The underlying contrast characteristics require a distending agent characterized by bright signal on T2-weighted images and dark signal on T1-weighted datasets. To avoid the need for the intravenous administration of paramagnetic contrast, the current study was based upon analysis of a two-dimensional TrueFISP sequence. The sequence permits excellent delineation of the small bowel

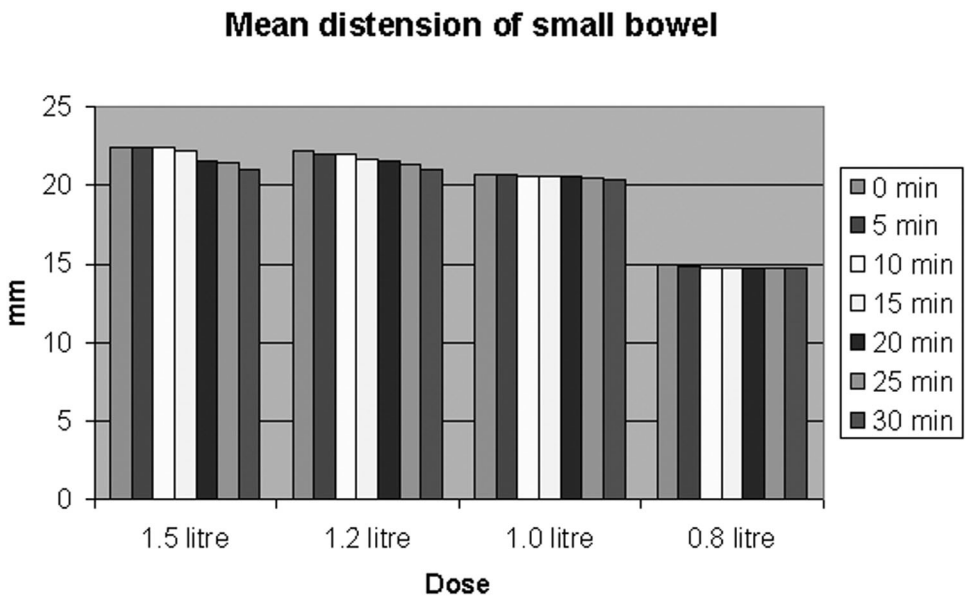

Figure 4. Qualitative assessment of bowel distension. No statistically significant differences were found between the three doses (1500, 1200, and 1000 ml) of the 2.5% mannitol solution. However, ingestion of 800 ml led to a significantly lower distension.

wall from surrounding fat as well as the bright, oral contrast-filled bowel lumen (25,26).

The oral administration of bowel distending contrast agents provides many advantages. Concerning the desired contrast properties, water appears to be ideal as an MR contrast agent for the delineation of the small bowel (20,27). To assure adequate small bowel distension, the rapid physiological absorption of water needs to be reduced (6,27). Thus, suitable additives preventing, or at least delaying, the absorption of water are desirable. Different groups of potential additives are known. LBG is extracted from the seeds of *Ceratonia siliqua*, the European carob tree. It is known for its thickening properties and is used in ice creams, dairy gels, and canned products (28). LBG binds water by means of a gelling mechanism, whereas the action of substances such as mannitol, meglumine gadoterate, as well as polyethylene glycol, is based upon their hyperosmolarity (4,5). While all of these agents have been shown to be feasible for small bowel distension, optimized results have been reported with a solution containing both LBG as well as the hyperosmolar mannitol (6).

Mannitol is obtained by reducing mannose, a hexose sugar. Due to their hyperosmolarity, mannitol solutions have been used for a long time for bowel cleansing prior to conventional colonoscopy, bowel surgery, and operative endoscopy (29,30). The recommended maximum oral daily dose of mannitol amounts to 25 g/day. A small part of mannitol is absorbed in the small bowel and is metabolized in the liver. The predominant portion reaches the colon, where it is metabolized by the bowel flora. Explosive gases (hydrogen and methane) can be by-products of mannitol (9,31). Thus, conventional colonoscopy with electrosurgical polypectomy or colonic surgical therapy with thermoablation can lead

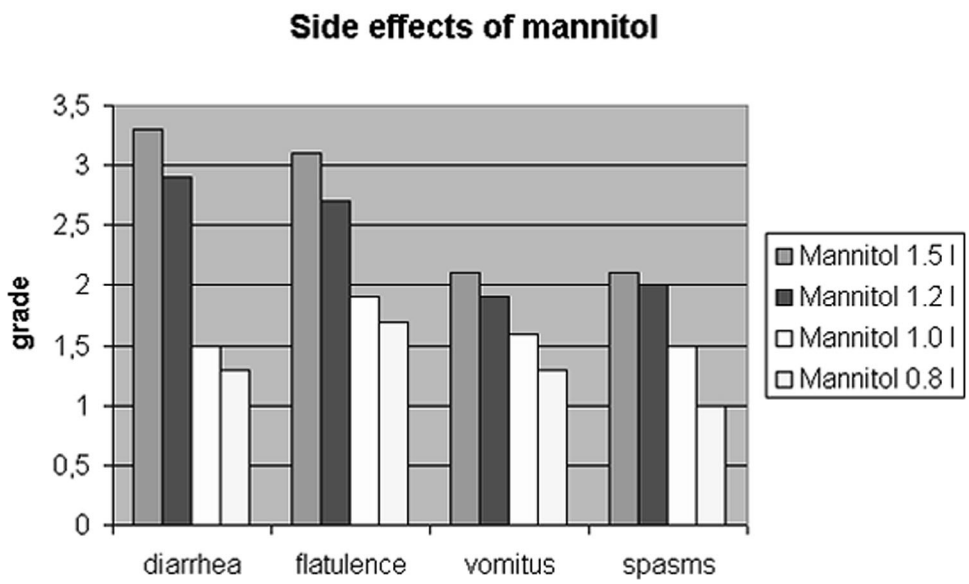

Figure 5. Side effects of the four doses of mannitol solutions. Primary side effects like diarrhea, flatulence, vomiting, and abdominal spasms are reduced if the total oral ingested dose of mannitol does not exceed the maximum daily dose.

to harmful explosions with potentially lethal consequences, if these procedures immediately follow mannitol ingestion (29–31).

Exceeding the maximum daily dose leads to diarrhea, flatulence, abdominal spasms, and hypovolemic collapse. The potential side-effects of high doses of mannitol are reflected by the results of this study: the total dose of 1500 and 1200 ml of 2.5% mannitol solution amounted to 37.5 and 30.0 g, and resulted in a relatively high grade of side effects. However, 1000 and 800 ml of the 2.5% mannitol solution contain 25.0 and 20.0 g mannitol, respectively, and showed the lowest grade of side effect.

Clearly, there are limitations of the present study. First and foremost, it needs to be proven if data and results from a healthy volunteer group can be transferred to the clinical routine, through which patients with abdominal pathologies are examined. Thus, further studies including patients with small bowel diseases have to be performed. Another drawback could be related to the qualitative assessment of the side-effects. Terms such as "mild," "moderate," and "severe" side-effects may have been perceived differently by volunteers. However, it was possible to assess intraindividual differences, which is more important than to determine interindividual differences.

In conclusion, this study shows that ingesting 1000 ml of a 2.5% mannitol/0.2% LBG solution appears to be optimal for small bowel MRI in terms of high bowel distension and low grade of side effects.

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