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Waleed Ajaj
Susanne C. Goehde
Hubert Schneemann
Stefan G. Ruehm
Jörg F. Debatin
Thomas C. Lauenstein

Oral contrast agents for small bowel MRI: comparison of different additives to optimize bowel distension

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W. Ajaj (✉) · S. C. Goehde · S. G. Ruehm
J. F. Debatin · T. C. Lauenstein
Department of Diagnostic
and Interventional Radiology,
University Hospital Essen,
Hufelandstrasse 55, 45122 Essen, Germany
e-mail: Waleed.ajaj@uni-essen.de
Tel.: +49-201-7231517
Fax: +49-201-7231548

H. Schneemann
Institute of Pharmacy
and Pharmaceutical Sciences,
University Hospital Essen,
Essen, Germany

Abstract The purpose of this study was to compare two osmotic carbohydrate sugar alcohols (mannitol 2.5% and sorbitol 2.5%, 2.0%, and 1.5% watery solutions) in combination with 0.2% locust bean gum (LBG) for small bowel distension for MR imaging. Small bowel distension was quantified on coronal 2D True-FISP images by measuring the diameters of 16 small bowel loops in each of 12 healthy subjects (age range 31–55 years). Additionally, the grade of small bowel distension was rated qualitatively. Patient acceptance concerning nausea, vomiting, flatulence, and diarrhea was noted for each solution, and all results were compared by a Wilcoxon test or *t* test, respectively. The ingestion of water combined with LBG and either 2.5% mannitol or 2.0% sorbitol showed the best distension of the small bowel. The lowest side effect rate was observed following ingestion of sorbitol in a concentration of 2.0 and 1.5%. Based on these data, we recommend a combination of LBG and 2% sorbitol use for optimal bowel distension and minimal side effects resulting in enhanced patient acceptance.

Keywords MR colonography · Bowel distension · Mannitol · Sorbitol · Patient acceptance

Introduction

The clinical diagnosis of small bowel disease is complicated by non-specific symptoms and a low index of suspicion. Homogeneous distension of the small bowel represents an absolute requirement for the morphologic assessment of the small bowel with imaging techniques [1, 2, 3, 4, 5]. This can be accomplished by infusing a contrast medium directly into the small bowel via a nasoduodenal tube. Observed under fluoroscopy, conventional enteroclysis has been shown to be reliable in the evaluation of the small bowel by providing excellent image quality and based upon sufficient bowel distension [6, 7]. The most obvious advantage of conventional enteroclysis relates to the unsurpassed high spatial resolution: small mucosal pathologies can presently be depicted to great advantage only by this technique. Conventional enteroclysis has thus been effective in the detection or exclusion of small bowel disease [8, 9].

Conventional enteroclysis is, however, invasive and painful. Furthermore, it exposes the patient to a relatively high dose of ionizing radiation of around 8 mSv [10], which is similar to the radiation dose achieved by CT colonography [11], and provides only indirect information on the state of the bowel wall. A technique combining enteroclysis with cross-sectional imaging would be expected to take the diagnosis of small bowel disease a step further, by permitting assessment of the bowel wall itself.

Magnetic resonance imaging has recently been applied for the evaluation of the small bowel. Initial attempts were based on distending the bowel in a manner identical to that employed in conventional enterocolysis: a methylcellulose–water solution is administrated via a fluoroscopically placed nasoduodenal tube [7, 12]. Placement of the nasoduodenal tube under conventional fluoroscopy prior to the MR exam, however, proved to be invasive, unpleasant, and logistically difficult.

For small bowel MRI to gain wider clinical acceptance, the features of non-invasiveness will need to be retained; thus, distending contrast liquids will need to be administered orally without duodenal intubation. For this purpose an oral contrast agent consisting of a non-osmotic locust bean gum (LBG) solution combined with the osmotic substance mannitol was developed [13]. Reflecting the combination of osmotic action and reduced intestinal water absorption, oral ingestion of this contrast agent led to homogeneous bowel distension.

Mannitol is a carbohydrate classified as sugar alcohol. Side effects of mannitol and its by-products result from the development of potentially explosive intestinal gas. In addition, the negative influence of mannitol on the bowel flora can lead to bowel spasm and diarrhea [14, 15]. These side effects reduce patient acceptance for the MR-based exam. Sorbitol, a different carbohydrate classified as osmotic sugar alcohol, provides different metabolism characteristics compared with mannitol and is hence not associated with the undesired effects characteristic of mannitol [16].

The purpose of our study was to assess the optimal concentration of sorbitol vs mannitol for small bowel distension. Furthermore, the rate and type of sides effects was documented and compared.

Materials and methods

Twelve healthy volunteers (8 women and 4 men; age range 31–55 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. In accordance with the approving local institutional review board written informed consent was obtained from all subjects prior to being examined on four occasions. The volunteers were blinded with respect to the oral contrast composition. The interval between all examinations amounted to a minimum of 48 h.

Bowel distending agent

A 0.2% locust bean gum solution (Roeper, Hamburg, Germany) was used as a baseline substance. Locust bean gum is extracted from the seeds of *Ceratonia siliqua*, the European carob tree. It is known for its thickening properties and used in ice creams, dairy gels, and canned products [17].

The baseline LBG solution was mixed with the following four additives: mannitol 2.5% (Merck, Darmstadt, Germany); or sorbitol 2.5, 2.0, or 1.5% (Merck, Darmstadt, Germany). The choice of LBG and mannitol concentrations was based on previous studies [13, 18].

Examination protocol

To assure homogenization of bowel activity across subjects and examinations, all MR exams were performed following a 6-h fasting period. Prior to each examination, 1500 ml of the respective contrast solution was orally ingested continuously over 45 min at an evenly distributed rate. To ensure a consistent ingestion, volunteers were asked to drink 150 ml every 4 min. To enhance gastric emptying, 100 mg erythromycin (Abbott Pharmaceutics, Wiesbaden, Germany) was administered intravenously directly following the ingestion of the first 150 ml of the contrast solution [19]. Erythromycin in low doses can be used for faster emptying of the stomach [20]. Previous attempts without erythromycin had shown a delayed gastric emptying with associated nausea and vomiting (own observation).

Magnetic resonance 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/m and a slew rate of 200 mT/m ms^{-1}. For signal reception a set of two large "flex surface coils" was used. Neither spasmolytic agents nor paramagnetic contrast compounds were applied intravenously. Coronal 2D images were collected using a fast T2-weighted steady-state precession sequence (TrueFISP; TR/TE/flip angle: 3.9/1.9/70°). Patients were examined in the prone position as this reduces bowel and respiratory movement leading to higher image quality. 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 s. Imaging was performed under breath-hold conditions.

Data analysis

Images were quantitatively analyzed independently by two radiologists, who were blinded to the type of oral contrast employed. The data sets were viewed and evaluated on a post-processing workstation (Virtuoso, Siemens, Erlangen, Germany). In a first step, the single coronal image depicting most small bowel loops was identified in consensus by both interpreters. Subsequently, each reader measured the diameters of eight small bowel loops spaced 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 examination. Subsequently, a mean value for bowel distension was calculated for each individual on the basis of the 16 measurements.

For a qualitative assessment, MR images of all four examinations obtained from each volunteer were presented as hard copies 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

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

Statistical analysis

Mean small bowel distension values obtained for each exam were compared with respect to the given contrast agent using a paired *t* test. Qualitative results concerning the grade of distension as well as the grades of discomforts were compared using the Wilcoxon rank test for each pair separately. For the adaptation to multiple samples, a Bonferoni correction was employed. For all statistical analyses, $p<0.05$ was considered statistically significant.

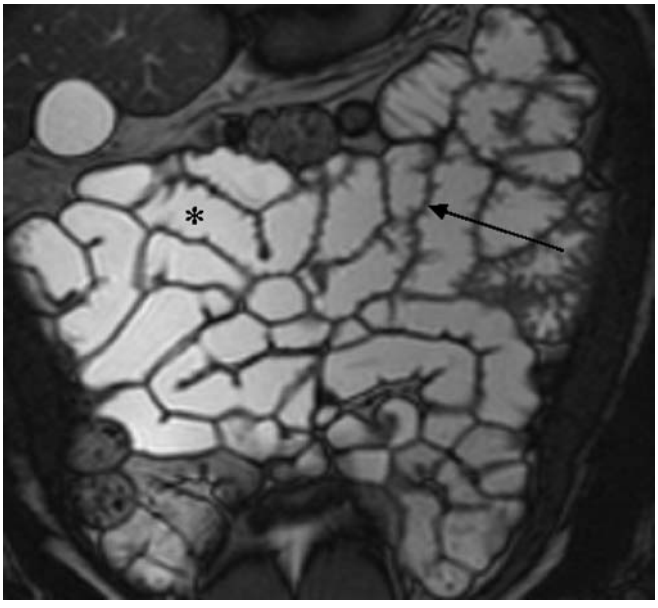

Fig. 1 Two-dimensional TrueFISP image after small bowel distension with an oral watery contrast agent containing a non-osmotic substance (locust bean gum; LBG 0.2%) and an osmotic sugar alcohol (sorbitol 2.0%). The bowel wall (*arrow*) is characterized by a hypointense signal, whereas the bowel lumen, distended by the watery solution, exhibits a very hyperintense signal (*asterisk*)

Results

Fifteen hundred millileters of each contrast solution were ingested within the target time of 40 min by all volunteers at all occasions. The high contrast between the bright, liquid-containing small bowel lumen and the dark surrounding tissues on the TrueFISP images (Fig. 1) permitted a distinct delineation between bowel wall and bowel lumen. Quantitative comparison of the four solutions revealed the highest small bowel distension for the 2.5% mannitol solution and the 2.0% sorbitol solution. The 2.5% mannitol solution resulted in a mean small bowel diameter of 19.79 mm compared with 18.8 mm with 2.0% sorbitol, 18.21 mm with 2.5% sorbitol, and 17.88 mm with 1.5% sorbitol (Fig. 2).

The differences for quantitative small bowel distension was statistically significant for mannitol compared with sorbitol 2.5% and sorbitol 1.5% (Fig. 3). The sorbitol 2.0% solution showed no statistically significant difference to mannitol. No statistically significant difference in loop diameter was found between ileum and jejunum for all four contrast solutions (Fig. 4). The qualitative assessment of small bowel distension underscored the results of the quantitative evaluation. The average grade in qualitative bowel distension rating (average

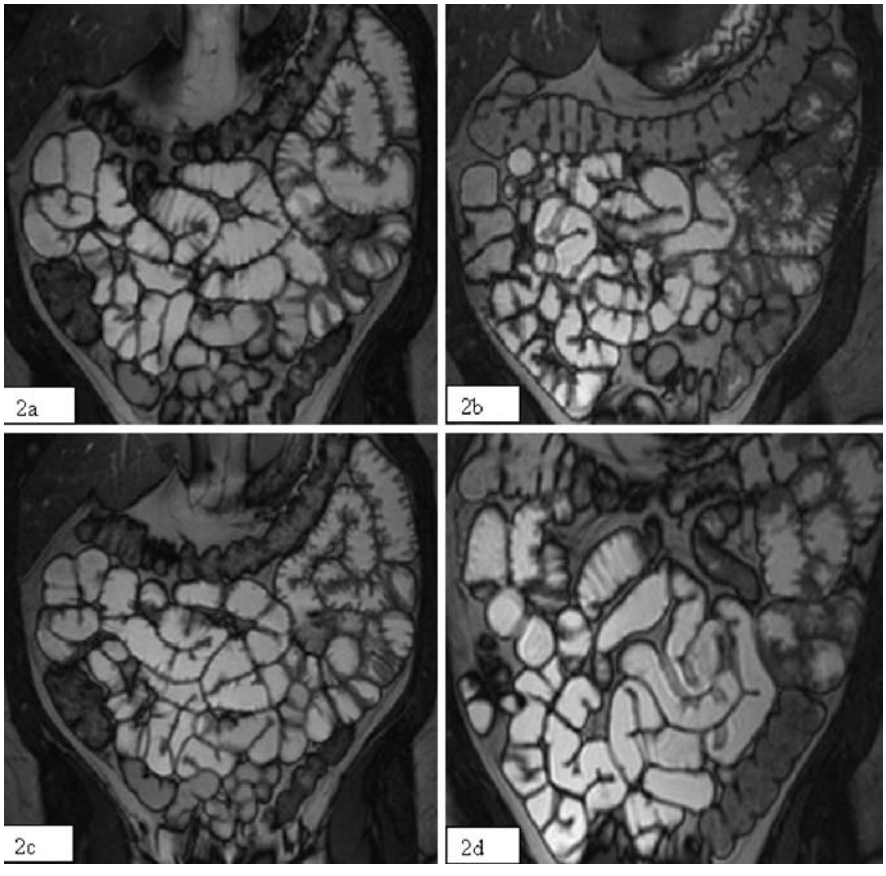

Fig. 2a–d Distended small bowel after ingestion of four oral contrast agents (same patient in all four images). **a** The small bowel was distended by a 2.5% mannitol solution which leads to the best distension. **b** Obtained after ingestion of 2.5% sorbitol solution. **c** The second best distension of the small bowel is obtained after ingestion of 2.0% sorbitol solution. **d** The smallest small bowel distension was achieved after ingestion of a 1.5% sorbitol solution. The difference of small bowel distension between **a** 2.5% mannitol and **c** 2.0% sorbitol solution was not statistically significant

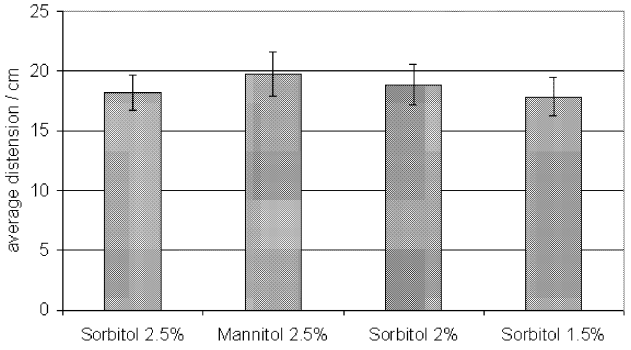

Fig. 3 Quantitative assessment of bowel distension. The standard deviation relates to the average distensions in the 12 subjects

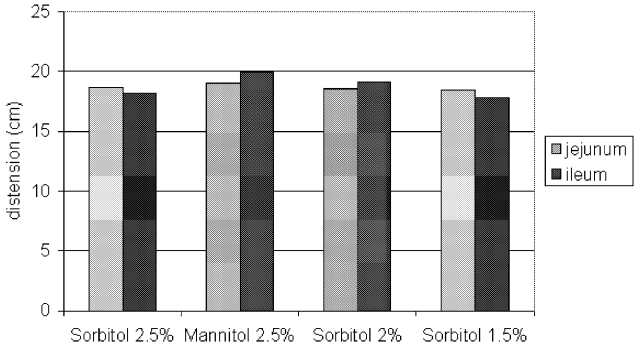

Fig. 4 Average distensions of jejunum and ileum of all 12 subjects. No statistically significant difference is found for the distension of ileum and jejunum

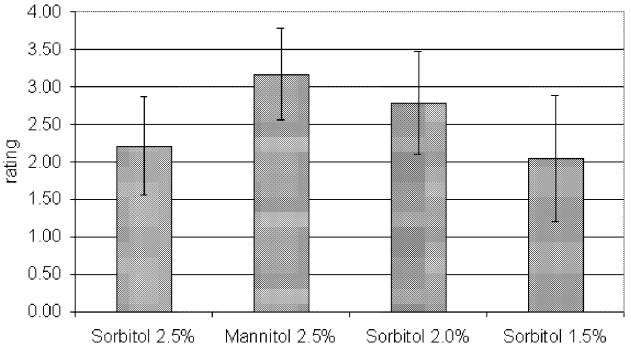

Fig. 5 Qualitative assessment of bowel distension. The standard deviation relates to the 12 data sets of the 12 subjects containing the mean rating of the two reviewers for each subject. No statistically significant difference was found between mannitol 2.5% and sorbitol 2.0%

value across all subjects and the two readers) was highest for 2.5% mannitol (3.2) and 2.0% sorbitol (2.8). The 2.5% sorbitol reached a value of 2.2 (Fig. 5). Only the difference between 2.5% mannitol and 2.5%/1.5% sorbitol proved to be statistically significant.

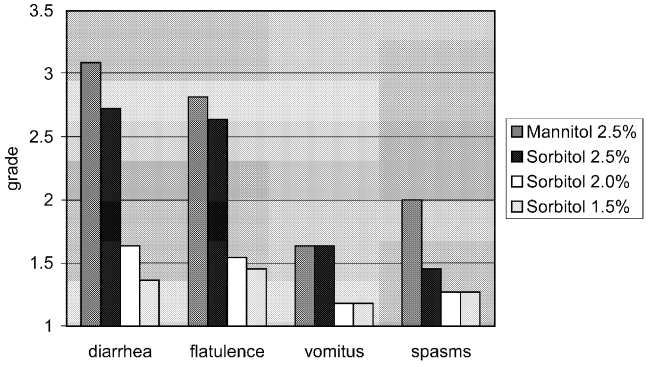

Fig. 6 Side effects of mannitol and sorbitol solutions. Primarily diarrhea and flatulence are reduced if sugar alcohol concentrations below 2.5% are ingested

The highest degree of diarrhea was observed following the ingestion of the solution containing 2.5% mannitol (mean value 3.0). The ingestion of the 1.5 and 2% sorbitol solution led to the lowest degree of diarrhea (mean value 1.3 and 1.6, statistically significant difference against 2.5% mannitol and 2.5% sorbitol). Concerning flatulence, the ingestion of 2.0 and 1.5% sorbitol was rated statistically significantly better than the 2.5% mannitol solution (Fig. 6). Although not statistically significant, 2.0% sorbitol exhibited better ratings concerning vomiting and spasms than 2.5% sorbitol and mannitol.

Discussion

Respiratory motion artifacts in conjunction with susceptibility effects had for a long time prohibited the MR-based analysis of the small bowel. Reflecting recent hard- and software developments, MR imaging of the abdomen and consequently of the small bowel has become possible by allowing the acquisition of multislice or 3D data sets within a single breathhold. Fast imaging with steady-state presession sequences (TrueFISP) cover the entire abdomen within the confines of a comfortable breathhold lasting less than 25 s [21]. Similarly, the abdomen can be depicted on fat-saturated 3D gradient-echo sequences in conjunction with the intravenous administration of T1-shortening contrast agents [22]. To be suited for small bowel MRI both sequence types rely on the presence of intestinal contrast for delineation and distension of individual bowel loops [23]. The underlying contrast characteristics call for a distending agent characterized by bright signal on T2-weighted images and dark signal on T1-weighted data sets. To avoid the need for the intravenous administration of paramagnetic contrast, the current study was based upon analysis of a 2D TrueFISP sequence. The sequence permits excellent delineation of the small bowel wall from surrounding fat as well as the bright, oral contrast-filled bright bowel lumen [24, 25].

Small bowel distension is essential for small bowel MR imaging because collapsed bowel loops can hide even large lesions or may falsely suggest the presence of pathology such as wall thickening [26]. To date, most of the published strategies of small bowel MRI rely on the administration of bowel contrast via a nasojejunal tube for adequate distension [7, 12, 27, 28]. The principal advantage of MR enteroclysis of the small bowel via a nasojejunal tube is that the jejunum and ileum can be optimally distended, so that detailed morphological can be obtained resembling those of conventional enteroclysis. Furthermore, real-time imaging techniques even open up the possibility of assessing intestinal function. The clinical impact of the technique has been limited due to logistical difficulties associated with the required coordination of fluoroscopic tube placement and subsequent MRI examination. Furthermore, many patients perceive jejunal intubation as traumatizing and unpleasant [7, 12].

Clearly the oral administration of bowel distending contrast agents carries many advantages. In view of the desired contrast properties, water appears to be ideal as an MR contrast agent for delineation of the small bowel [12, 23, 26, 28, 29]. To assure adequate small bowel distension, the rapid physiological absorption of water needs to be delayed [29]; thus, suitable additives preventing, or at least delaying the absorption of water are desirable. Potential additives can be differentiated based upon their action. Locust bean gum binds water by means of a "gelling" mechanism, whereas the action of mannitol [18], meglumine gadoterate [30], as well as polyethylene glycol is based upon their hyperosmolarity [31]. 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 the gelling LBG as well as the hyperosmolar mannitol [13].

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 [32, 33]. The maximum oral daily dose of mannitol amounts to 25 g/day [16]. Exceeding the maximum daily dose leads to diarrhea, abdominal spasms, and hypovolemic collapse. The potential effects of high doses of mannitol are reflected by the results of this study: the total dose of mannitol 2.5% amounted to 37.5 g and resulted in a relatively high grade of side effects.

A small portion 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 colonic by-products of mannitol [32, 34]; thus, conventional colonoscopy with electrosurgical polypectomy or colonic surgical therapy with thermoablation can lead to harmful explosions with potentially lethal consequences, if these procedures follow mannitol ingestion immediately [15, 32, 35].

Reflecting similarities in structure and action, sorbitol appears to be a suitable substitute for mannitol in small bowel distension. Sorbitol can be obtained by reduction of glucose and is used for the production of sublingual and lozenge pills. The maximum daily dose of sorbitol amounts to 30 g/day. In high doses sorbitol exhibits laxative properties. The maximum dose of sorbitol in our study contained a total sugar alcohol dose of 37.5 g. A fraction of sorbitol is absorbed by the small bowel and is metabolized to fructose, lactate, and pyruvate [36, 37]; however, the main part reaches the colon where it is metabolized by the bowel flora to lactulose and consecutively to acetic acid and lactate [16]; the latter explains the laxative effect of high doses of sorbitol. A rise of explosive colonic gases is not observed [37]. Lower concentrations of the sorbitol solution resulted in significantly less side effects in our study.

This study confirms the bowel distending action of sorbitol in a manner very similar to that associated with mannitol. The best small bowel distension was achieved with 2.5% mannitol and 2.0% sorbitol solutions. Although a 2.0% solution of sorbitol resulted in slightly inferior small bowel distension compared with a 2.5% solution of mannitol, this difference was not statistically significant. The poorer performance of the 1.5% sorbitol solutions is readily explained by the lower osmolarity. The lesser distending action of the highest sorbitol dose (2.5%) might be explained by the laxative effect of high doses of sorbitol

Among the most important potential side effects of erythromycin, potential central reactions are noteworthy if erythromycin is administered at high injection rate (tinnitus, anxiety). Also, adverse reactions can occur (tachycardia, nausea, vomiting). The onset of nausea and vomiting was clearly related in time to the oral solution ingestion, and the grade of these side effects was dependent on the solution composition, reflecting the very low dose of erythromycin.

The limitations of this study, beyond the limited size of the study population, certainly lies in the problem to identify the corresponding small bowel loops, as they are assessed across different oral contrast solution studies. We tried to overcome this limitation with an additional qualitative assessment of "general'" small bowel distension, which resulted in results which mirror the quantitative analysis.

Based on this study, a combination of LBG and a 2.0% solution of sorbitol resulted in an excellent distension of the small bowel that was statistically not significantly different from that achieved with a 2.5% solution of mannitol; however, the 2.0% solution of sorbitol resulted in significantly less objectionable side effects than seen with mannitol; therefore, a combination of LBG and a 2.0% solution of sorbitol is recommended for MR assessment of the small bowel, but larger series need to confirm these preliminary results.

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