Multi-institutional, prospective, observational study comparing the Gastrografin challenge versus standard treatment in adhesive small bowel obstruction

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INTRODUCTION: Existing trials studying the use of Gastrografin for management of adhesive small bowel obstruction (SBO) are limited by methodological flaws and small sample sizes. We compared institutional protocols with and without Gastrografin (GG), hypothesizing that a SBO management protocol utilizing GG is associated with lesser rates of exploration, shorter length of stay, and fewer complications.

METHODS: A multi-institutional, prospective, observational study was performed on patients appropriate for GG with adhesive SBO. Exclusion criteria were internal/external hernia, signs of strangulation, history of abdominal/pelvic malignancy, or exploration within the past 6 weeks. Patients receiving GG were compared to patients receiving standard care without GG.

RESULTS: Overall, 316 patients were included (58 ± 18 years; 53% male). There were 173 (55%) patients in the GG group (of whom 118 [75%] successfully passed) and 143 patients in the non-GG group. There were no differences in duration of obstipation (1.6 vs. 1.9 days, $p = 0.77$) or small bowel feces sign (32.9% vs. 25.0%, $p = 0.14$). Fewer patients in the GG protocol cohort had mesenteric edema on CT (16.3% vs. 29.9%; $p = 0.009$). There was a lower rate of bowel resection (6.9% vs. 21.0%, $p < 0.001$) and exploration rate in the GG group (20.8% vs. 44.1%, $p < 0.0001$). GG patients had a shorter duration of hospital stay (4 IQR 2–7 vs. 5 days IQR 2–12; $p = 0.036$) and a similar rate of complications (12.5% vs. 17.9%; $p = 0.20$). Multivariable analysis revealed that GG was independently associated with successful nonoperative management.

CONCLUSION: Patients receiving Gastrografin for adhesive SBO had lower rates of exploration and shorter hospital length of stay compared to patients who did not receive GG. Adequately powered and well-designed randomized trials are required to confirm these findings and establish causality. (*J Trauma Acute Care Surg.* 2017;83: 47–54. Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.)

LEVEL OF EVIDENCE: Therapeutic, level III.

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The motto, "the sun should never rise and set on a complete small bowel obstruction (SBO)" has been the traditional management for patients presenting acutely with SBO.[1] The notion of a "complete" SBO is antiquated, however.[2] Originally described as the dilated small bowel on abdominal radiograph concurrent with air-fluid levels and the absence of colonic gas, the definition has evolved to imply the need for urgent operative exploration.[3] The accuracy of surgeons' preoperative prediction for complete SBO, and therefore need for urgent exploration, is low.[4] The recommendation for urgent exploration should no longer be limited to a simple partial versus complete designation.[5] Rather, the focus should be on reliable methods that eliminate nonoperative management of strangulation obstructions, ensure timely exploration for patients who will not successfully pass nonoperative management, and avoid unnecessary explorations.

Gastrografin (GG—diatrizoate meglumine and diatrizoate sodium; Bracco Diagnostics, Inc., Monroe Township, NJ), a hyperosmotic oral contrast agent, has been advocated as a diagnostic and therapeutic tool for the management of adhesive SBO.[6] The use of GG serves dual purposes. First, GG can be visualized on x-ray. If the contrast agent can be noted in the colon, then surgeons can be assured that the point of obstruction has been passed and there will be a lower need for operative exploration. Second, the hyperosmotic property of GG theoretically draws edema present in the obstructed bowel wall into the bowel lumen thereby helping to reverse the obstruction.[3] The existing literature on these potential benefits, however, suffers from disparate methodologies and results. Despite the presence of multiple randomized controlled trials (RCTs), there is no consensus on the therapeutic effects of hyperosmolar contrast agents because of significant methodological flaws inherent within these RCTs.[6–11] Although meta-analyses of these and other trials report that the GG challenge provided both a therapeutic and diagnostic effect,[12,13] there were significant limitations to this meta-analysis because of the fundamental flaws underlying these studies, including (1) heterogeneous nature of the RCTs, (2) inclusion of non-controlled studies, (3) lack of blinding, (4) lack of standardized treatment protocols, (5) differing hyper- and iso-osmolar contrast agents, (6) differing timing of oral contrast administration, and (7) heterogeneous timing of the follow-up abdominal radiograph. Because of these limitations, we performed a prospective, observational, multi-institutional clinical study comparing standardized SBO treatment protocols with and without the GG challenge. We hypothesized that a standardized

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adhesive SBO protocol enhanced with the GG challenge will have a greater accuracy for predicting the need for operative exploration and will decrease rates of operative exploration, length of stay, and complications.

METHODS

We performed a prospective, observational, multi-institutional clinical study comparing standardized adhesive SBO treatment protocols with and without the GG challenge (Figs. 1 and 2). Approval for the study was provided by each institutional IRB. There were a total of 14 institutions; all institutions except three had previously implemented the GG challenge as an option for SBO management in their current practice. The choice of the respective SBO management protocol (GG protocol vs. non-GG protocol) was based on surgeon discretion. At the three participating sites without GG availability, these institutions

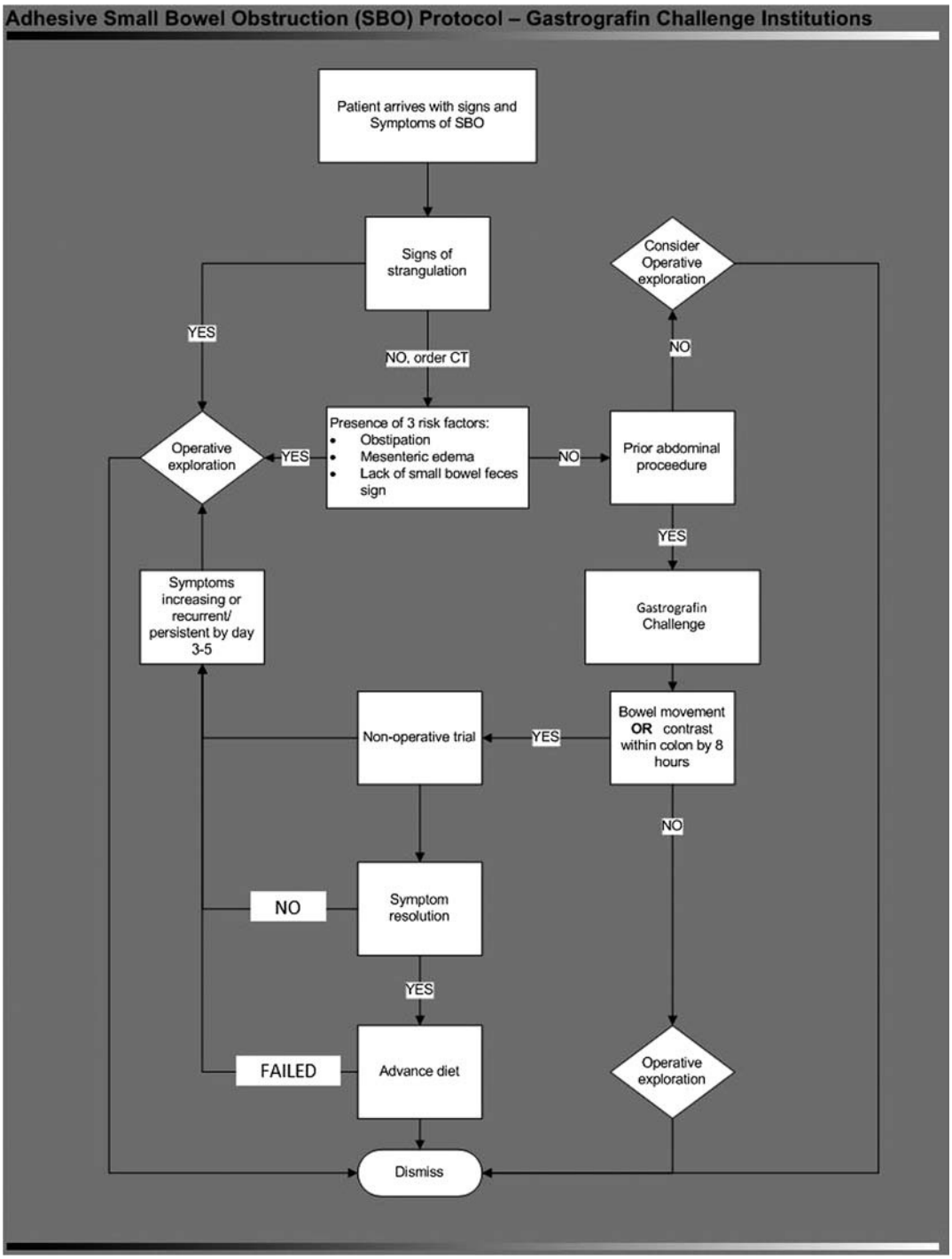

Figure 1. Management protocol for patients not undergoing the GG challenge.

defaulted to the non-GG protocol. The diagnosis of adhesive SBO was based on radiographic imaging demonstrating dilated loops of small bowel with a transition point, in the clinical setting of nausea, vomiting, abdominal pain, and distension. To ensure only adhesive SBO patients were included, we excluded potential subjects for the presence of an internal or external hernia, a history of abdominal/pelvic malignancy, or an abdominal exploration within the preceding 6 weeks. Patients were also excluded for signs of strangulation such as peritonitis, hypotension, closed-loop obstruction, pneumatosis intestinalis, or portal venous gas. Patients less than 18 years of age were also excluded as were prisoners and pregnant patients.

Radiographic findings were then noted. Mesenteric edema was defined as hazy fluid attenuation in the mesentery of the involved intestinal segment, the "small bowel feces sign" was defined as gas bubbles and debris within the obstructed small-bowel lumen, and obstipation was defined as the lack of flatus or bowel movement for 24 or more hours. The GG challenge protocol has been previously described.[14] Briefly, patients without signs of strangulation obstruction undergo nasogastric decompression for 2 hours after which 100 mL of GG mixed in 50 mL of water is instilled. An abdominal x-ray is obtained 8 hours after GG administration. Patients were considered to have passed the GG challenge if they had a bowel movement

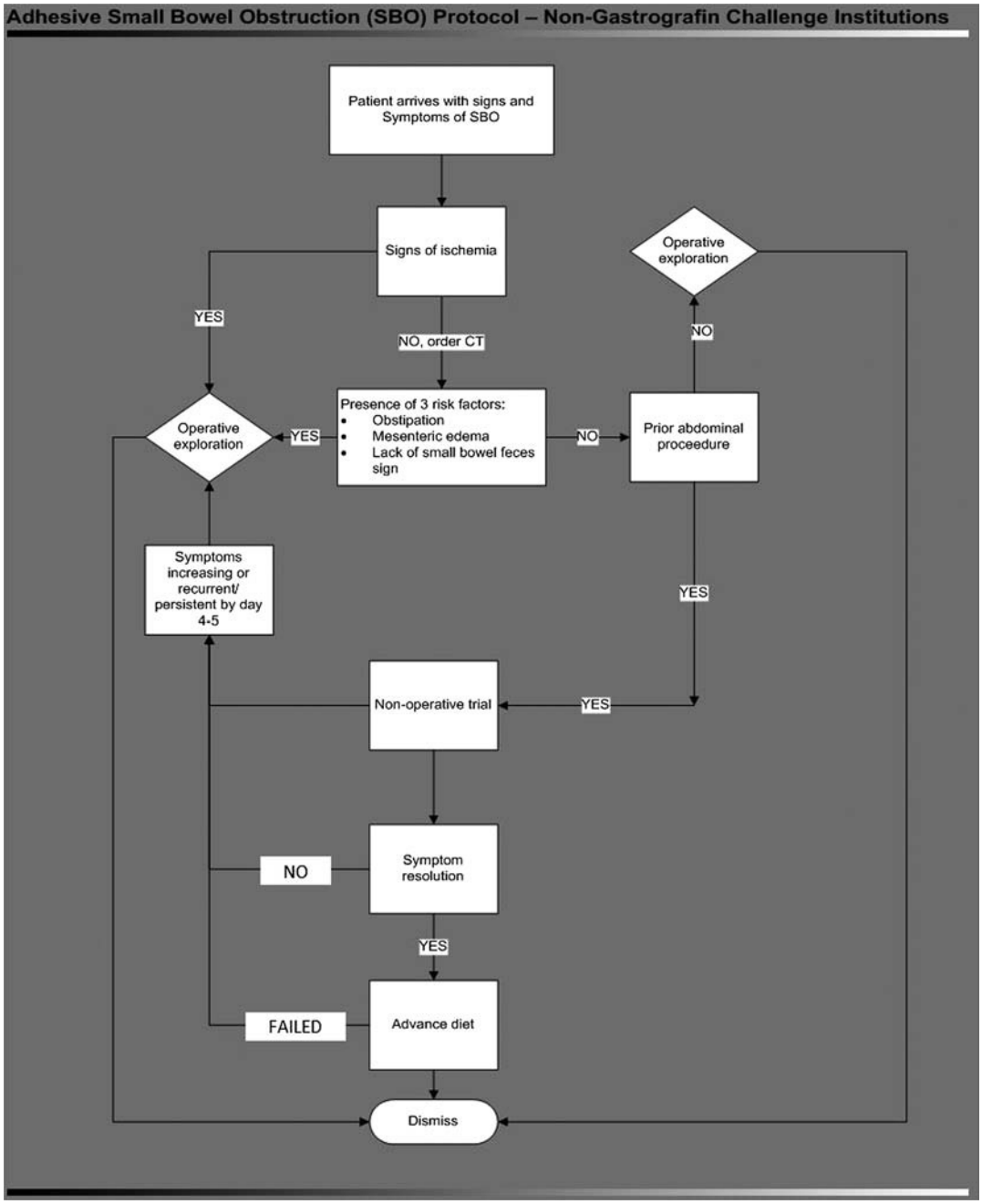

Figure 2. Management protocol for patients undergoing the GG challenge.

TABLE 1. Baseline Characteristics Comparing Patients Undergoing the Gastrografin Challenge and Those Not Undergoing the Gastrografin Challenge

Feature	GG Challenge (n = 173)	Non-GG Challenge (n = 143)	*p*
Age, y	58.5 ± 18.2	57.5 ± 18.5	0.63
Male sex, %	52.0%	55.2%	0.57
BMI	28.0 ± 7.6	27.9 ± 8.4	0.71
Obstipation	71.3%	64.8%	0.25
Comorbidities, %			
Dementia	1.7%	1.4%	0.81
MI	10.4%	6.3%	0.19
CHF	10.4%	7.7%	0.41
DM	13.3%	18.9%	0.18
COPD	11.0%	7.0%	0.22
PUD	4.0%	4.2%	0.95
CVD	5.2%	6.0%	0.50
Past surgical Hx			
SBO	35.3%	34.3%	0.85
Gastric bypass	4.0%	4.7%	0.79
Ventral hernia	19.7%	20.0%	0.96
CT data, %			
Small bowel feces sign	32.9%	24.8%	0.14
Mesenteric edema	16.3%	29.6%	0.01
Transition point	77.6%	70.2%	0.14
Free intraperitoneal fluid	29.0%	35.5%	0.23

MI, myocardial infarction; GG, Gastrografin; BMI, body mass index; CHF, congestive heart failure; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disorder; PUD, peptic ulcer disease; CVD, cerebrovascular disease; SBO, small bowel obstruction; CT, computed tomography.

after GG administration or if they had contrast noted in the colon on the abdominal x-ray 8 hours after GG administration. For patients without colons, any ileostomy production after GG administration was also considered a pass. A failed GG challenge was considered if none of these outcomes were achieved. The definition of a missed strangulation obstruction was any patient who passed the GG challenge that had strangulated bowel at eventual exploration in the patients who passed their GG challenge whereas it was defined as any patient treated initially nonoperatively in the non-GG cohort who had strangulated bowel at eventual exploration. The overall complication rate was calculated using the combination of specific complications of acute kidney injury, pneumonia, organ space infection, surgical site infections, and anastomotic leak. Acute kidney injury was defined as a threefold increase in the serum creatinine, or GFR decrease by 75%, or urine output of <0.3 mL/kg per hour for 24 hours, or anuria for 12 hours.[15]

Continuous variables were presented as means with standard deviation and compared using the unpaired two-sample test whereas non-normally distributed data were presented as median (interquartile range; IQR) and compared using the Mann-Whitney *U* test. Categorical variables were presented as percentages and analyzed with Fisher's exact test. Statistical significance was defined as p value ≤0.05. The predictive ability of the GG challenge was analyzed with the area under the receiver operating characteristic curve (AUROC). Assuming an alpha of 0.05 and a power of 0.80 as well as an exploration rate of 25% in the GG institutions versus 42% in non-GG institutions, 132 subjects were estimated to be required in each arm to demonstrate significance.[14] Logistic multivariable regression was performed to determine features that were independently associated with lesser rates of operative exploration using features which were statistically and clinically significant. To determine the relative predictive ability of the GG challenge protocol, the AUROC was calculated.

TABLE 3. Diagnostic Ability for the Need for Operative Exploration of the GG Protocol

Sensitivity	87.2%
Specificity	71.9%
Positive predictive value	92.4%
Negative predictive value	59.0%
Accuracy	84.1%
C-statistic	0.76

GG, Gastrografin; OR, odds ratio; CI, confidence interval.

RESULTS

Overall, 316 patients were included in the final cohort with a mean age of 58 ± 18 years; of these, 169 (53%) were male. There were 173 (55%) patients in the GG group and 143 in the non-GG group. The overall rate of exploration was 31.3%. Baseline characteristics were similar among the groups (Table 1). There were no differences in number of previous SBO admissions (35.3% vs. 34.3%, p = 0.904), duration of obstipation (1.6 vs. 1.9 days, p = 0.77), or small bowel feces sign (32.9% vs. 24.8%, p = 0.14) although there was a lower rate of mesenteric edema on CT in the GG cohort (16.3% vs.

TABLE 2. Comparison of Presenting Laboratory and Vital Signs Among GG and Non-GG Cohorts

Feature	GG Protocol (n = 173)	Non-GG Protocol (n = 143)	*p*
Temperature, °C	36.8 ± 0.4	36.8 ± 0.5	0.914
Heart rate	82 ± 16	88 ± 18	<0.001
SBP, mm Hg	134 ± 22	137 ± 25	0.402
WBC $\times 10^9$/L	10.3 ± 0.37	108 ± 0.40	0.375
Creatinine	1.1 ± 0.07	1.1 ± 0.07	0.820
Lactate, mmol/L	1.4 ± 0.78	1.7 ± 1.2	0.093

SBP, systolic blood pressure; WBC, white blood cell count.

TABLE 4. Comparison of Complication Rates Between GG and Non-GG Cohorts

Complication	GG Protocol (n = 173)	Non-GG Protocol (n = 143)	*p*
AKI	5.8%	9.0%	0.828
Pneumonia	3.9%	5.0%	0.772
Organ space infection	1.2%	4.0%	0.405
SSI	3.5%	4.8%	0.742
Anastomotic leak	2.3%	2.4%	1.00

AKI, acute kidney injury; SSI, superficial surgical site infection.

TABLE 5. Multivariable Model for Features Associated With Successful Nonoperative Management

Feature	OR (95% CI)
Age (per year)	1.0 (0.98–1.02)
Male sex	1.6 (0.90–3.1)
Heart rate, beats per minute	0.99 (0.97–1.01)
Obstipation	0.88 (0.46–1.7)
Mesenteric edema	1.01 (0.50–2.1)
SB feces sign	1.11 (0.58–2.2)
GG challenge protocol	0.23 (0.12–0.43)

GG, Gastrografin; OR, odds ratio; CI, confidence interval.

29.6%, $p = 0.01$). All patients except for 12 underwent CT imaging. There was a similar rate of GG administration for CT purposes between groups (9% vs. 18%, $p = 0.14$). There was no difference in presenting laboratory values or vital signs, save for a clinically insignificant greater heart rate (Table 2).

GG Challenge Protocol Diagnostic Ability

The sensitivity, specificity, positive predictive value, and accuracy for the need for operative exploration based on the GG challenge results are reported in Table 3. There was a positive predictive value of 92.4% and corresponding negative predictive value of 59.0%. The AUROC for the use of the GG challenge protocol associated with rates of surgical exploration was 0.76. Adhesions were the cause of all patient's SBO except for four patients with unrecognized malignant SBOs; one in the GG cohort and three in the non-GG cohort.

GG Challenge Protocol Therapeutic Ability

Out of the patients undergoing the GG protocol, 118 (68%) successfully passed the GG challenge. There was a 20.8% rate of surgical exploration for the patients in the GG protocol arm, which was less than half the rate of exploration than in the patients in the non-GG protocol arm (20.8% vs. 44.1%, $p < 0.0001$). Overall, the GG patients had a correspondingly lesser rate of bowel resection regardless if they underwent operative exploration or not (6.9% vs. 21.0%, $p < 0.001$) although the rate of bowel resection was equal in both groups in those patients who underwent exploration (34.2% vs. 49.0%, $p = 0.162$). There were three non-therapeutic laparotomies in each group (1.7% vs. 2.0%, $p = 0.803$). In addition, GG patients had a longer median duration of time from admission to operative exploration (3 vs. 2 days, $p = 0.005$) if they underwent operative exploration but had a shorter hospital length of stay (4 IQR 2–7 vs. 5 days IQR 2–12, $p = 0.036$) regardless if they underwent exploration or were successfully treated nonoperatively. Both groups of patients has similar rates of overall (12.5% vs. 17.9%, $p = 0.22$) and specific complications (Table 4). The rate of operative exploration in patients who passed the GG challenge was 7.6% whereas the rate was 59% in patients failing the GG challenge. Of those who passed the GG challenge but underwent exploration, there was one non-therapeutic laparotomy and one missed strangulation obstruction requiring small bowel resection. Of those who failed the GG challenge, there was one non-therapeutic laparotomy and strangulation obstruction. There was a significantly lesser rate of missed strangulation obstructions in the GG cohort compared to the non-GG cohort (0.6% vs. 7.7%, $p < 0.001$). There were no cases of GG pneumonitis, but there was a single case of GG aspiration in a 96-year-old woman with baseline dementia and a previous aspiration history. She did not develop hypoxia nor respiratory complications but failed her GG challenge and underwent a therapeutic laparoscopic lysis of adhesions. Multivariable analysis revealed that GG challenge protocol was the only feature independently associated with successful nonoperative management (Table 5).

DISCUSSION

In the largest study of oral contrast agents for SBO management to date, we demonstrated that patients treated with an adhesive SBO protocol that includes Gastrografin had significantly lower rates of operative exploration, shorter durations of stay, and similar complication rates. Additionally, the diagnostic capabilities for undergoing operative exploration seemed to be adequate using the GG challenge protocol.

The management of SBO remains challenging as surgeons must predict, at patient admission, which patients have, or will develop, strangulation. Several predictive models have been developed to help guide SBO management.[16–19] These models, however, use limited portions of the entire clinical scenario with varying degrees of accuracy. Most importantly, these models have not been validated and refined prospectively. A single model has been prospectively validated and enhanced with the use of the GG challenge.[14] The use of the GG challenge, in conjunction with a standardized SBO management protocol, was shown to substantially reduce the rates of operative exploration as well as identify those patients who were at great risk for failure of nonoperative management.[20] This protocol was the same one used in the current study; the only difference between cohorts was in the use of the GG challenge.

GG is a hyperosmotic oral contrast agent and is used routinely, in diluted form, in diagnostic imaging studies such as CT scans and fluoroscopic gastrointestinal series. As a result of these properties, GG holds the potential for diagnostic and therapeutic effects. Several studies have evaluated the diagnostic capabilities of GG in SBO management. If the GG can pass through the obstructed segment of small intestine, then there should be a greater chance for resolution and therefore nonoperative management can be safely pursued. In a meta-analysis pooling the results of seven studies, Branco et al. demonstrated excellent distinguishing characteristics with a 96% sensitivity and 98% specificity in patients who passed the GG challenge.[14] There was no further discerning capability when the abdominal x-ray results were beyond 8 hours. These results correlate well with the most recent meta-analysis of 13 studies representing 947 patients with adhesive SBO; Cerosoli et al. demonstrated 92% sensitivity and 93% specificity.[13] Our study also supports these results using 8 hours for abdominal x-ray timing. GG has hyperosmolar properties at approximately six times the osmolarity of extracellular fluid. Because of this property, GG has the potential to decrease bowel wall edema by between the bowel lumen and the edematous, obstructed segment of small intestine by drawing fluid from the bowel wall into the bowel lumen.[6,21] The current study provides additional evidence supporting a therapeutic effect. Both Branco et al. and Cerosoli et al.

demonstrated reductions in operative explorations (OR 0.62; 95% CI 0.44–0.88 and OR 0.55, 95% CI 0.32–0.37, respectively) as a result of GG administration.

Despite the presence of several RCTs and meta-analyses, controversy remains as there were multiple issues with the RCTs on which the meta-analyses were based. Cerosoli et al. acknowledge that many of the included studies were of "poor quality."[13] For this reason, the current study was undertaken to eliminate many of these inherent quality issues. Our study eliminates multiple biases that were present in previous studies. First, we outlined specific SBO management protocols (Figs. 1 and 2). Although the protocol of choice was based on surgeon discretion, the protocols offered homogenous practice guidelines dictating which patients should undergo operative exploration and which patients can be safely monitored with nonoperative approaches. In addition, the contrast agent and volume used was universal as was the timing of the abdominal radiographs. Unlike previous studies, CT scanning to confirm the diagnosis (and exclude internal hernia or malignant etiology) was near universal. Using this approach, we showed a substantial decrease in operative rates when the GG challenge protocol was utilized.

Despite the multiple strengths, significant limitations remain. First, because of the lack of randomization and blinding, there is a possibility for bias confounding our results. Treating surgeons may have elected to forgo the GG challenge and proceed directly to the operating room because of a perceived risk of strangulation. By eliminating all of the patients presenting with signs of strangulation, this effect should have been minimized. It should be acknowledged, however, that the non-GG group had higher rates of mesenteric edema seen on CT, and this may have resulted in confounding by indication. Also of note, there was a significantly lower rate of mesenteric edema in the patients who underwent the GG challenge protocol. As a result, there may a bias toward a greater rate of exploration in the patients who underwent the non-GG challenge protocol. Additionally, there were variable levels of experience and comfort in using the GG challenge among treating surgeons and institutions, potentially confounding our results. We were unable to control for these factors. Nevertheless, there was an associated benefit from both a diagnostic and therapeutic standpoint using the GG challenge protocol. Despite these limitations, we feel our results are important and contribute meaningfully to the literature.

CONCLUSIONS

Inclusion of Gastrografin in the standardized management of adhesive SBO was associated with a decreased rate of operative exploration and shorter hospital length of stay without increase in complications. In the absence of criteria mandating immediate operation, administration of Gastrografin seems to be beneficial. An adequately powered and well-designed randomized controlled trial comparing adhesive SBO management protocols with and without the GG challenge will be the only definitive method of determining the therapeutic and diagnostic effects of GG.

AUTHORSHIP

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DISCLOSURES

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EDITORIAL CRITIQUE

I would like to congratulate Dr. Zielinski, his colleagues, and the Eastern Association for the Surgery of Trauma on this large, prospective, multicenter study. This study provides a very comprehensive look at the role of gastrografin in the management of small bowel obstruction due to adhesive disease. The authors have shown that a well-developed protocol for the use of a gastrografin challenge is associated with decreased rates of operative exploration, decreased rates of bowel resection, and shortened hospital stays. They have also demonstrated no increase in either medical or surgical complications for patients undergoing gastrografin challenge. Perhaps most importantly, this study demonstrated the safety of this protocol, showing an extremely low rate of missed strangulation in the gastrografin arm (0.6%), and an alarmingly high rate of missed strangulation in their control arm (7.7%). This data is very important to every general surgeon, as the decision not to operate on a small bowel obstruction can be much more difficult than the decision to operate.

While this study continues to add to the body of literature for the use of gastrografin, it does have several limitations. The authors discuss the lack of randomization, and the selection bias introduced by allowing surgeons to decide which treatment arm the patients would enter. Additionally, there were significantly more patients with mesenteric edema in the non-gastrografin arm. These confounders do raise concerns about the studies validity. What the authors have done, though, is to provide a framework for the randomized control trial needed to finally answer the question, "does a gastrografin challenge accurately predict which patients require an operation for adhesive small bowel obstruction?" The treatment algorithms for each arm, and standardized gastrografin challenge, should be used in future research. This work should be seen as a proof of concept, and should encourage investigators to finally perform the definitive trial on this common surgical dilemma.

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