Use of water-soluble contrast medium (gastrografin) does not decrease the need for operative intervention nor the duration of hospital stay in uncomplicated acute adhesive small bowel obstruction? A multicenter, randomized, clinical trial (Adhesive Small Bowel Obstruction Study) and systematic review

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Background. *This study evaluated the association between oral gastrografin administration and the need for operative intervention in patients with presumed adhesive small bowel obstruction.*
Methods. *Between October 2006 and August 2009, 242 patients with uncomplicated acute adhesive small bowel obstruction were included in a randomized, controlled trial (the Adhesive Small Bowel Obstruction Study, NCT00389116) and allocated to a gastrografin arm or a saline solution arm. The primary end point was the need for operative intervention within 48 hours of randomization. The secondary end points were the resection rate, the time interval between the initial computed tomography and operative intervention, the time interval between oral refeeding and discharge, risk factors for the failure of nonoperative management, in-hospital mortality, duration of stay, and recurrence or death after discharge. We performed a systematic review of the literature in order to evaluate the relationship between use of gastrografin as a diagnostic/therapeutic measure, the need for operative intervention, and the duration of stay.*
Results. *In the gastrografin and saline solution arms, the rate of operative intervention was 24% and 20%, respectively, the bowel resection rate was 8% and 4%, the time interval between the initial computed tomography and operative intervention, and the time interval between oral refeeding and discharge were similar in the 2 arms. Only age was identified as a potential risk factor for the failure of nonoperative management. The in-hospital mortality was 2.5%, the duration of stay was 3.8 days for patients in the gastrografin arm and 3.5 days for those in the saline solution arm (*P = .19*), and the recurrence rate of adhesive small bowel obstruction was 7%. These results and those of 10 published*

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studies suggest that gastrografin did not decrease either the rate of operative intervention (21% in the saline solution arm vs 26% in the gastrografin arm) or the number of days from the initial computed tomography to discharge (3.5 vs 3.5; P = *NS for both).*
Conclusion. *The results of the present study and those of our systematic review suggest that gastrografin administration is of no benefit in patients with adhesive small bowel obstruction. (Surgery 2016;■:■-■.)*

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Acute adhesive small bowel obstruction (ASBO) is a frequent gastrointestinal emergency, accounting for 1–3% of all such emergencies.[1,2] ASBO is associated with a mortality rate of between 2–8%, although this number may be as great as 25% if operative treatment is delayed.[3-6] According to the medical records of the Scottish National Health Service during a 10-year period, 5.5% (n = 1,169) of the 21,347 patients admitted for ASBO underwent operative interventions.[7]

In 2013, the working group on ASBO of the World Society of Emergency Surgery suggested 2 distinct approaches for the management of acute ASBO.[8] Nonoperative management can be initiated when there are "no signs of strangulation or peritonitis or history of persistent vomiting or combination of computed tomography signs (free fluid, mesenteric edema, lack of feces signs, devascularized bowel)," whereas operative management (with or without bowel resection) should be initiated before or during nonoperative management in the event of "free intraperitoneal fluid, mesenteric edema, presence of small bowel feces signs at CT scan, history of vomiting, severe abdominal pain (visual analog scale >4), abdominal guarding, raised white blood cells (WBC), and devascularized bowel at CT scan."[8]

Nonoperative management includes the use of a nasogastric tube (NGT), intravenous administration of fluids, and clinical and biochemical monitoring for 24–72 hours.[8] The efficiency of nonoperative management in this context, however, is subject to debate because such nonoperative management might delay the decision to operate and thereby increase the frequency of bowel resection (eg, in the presence of bowel necrosis) or, in contrast, prompt the performance of nontherapeutic laparotomies. Operative management consists of adhesiolysis and, if necessary, bowel resection. At present, there are no robust criteria for determining objectively the failure of nonoperative treatment or establishing the indications for operative intervention in acute ASBO. Soluble contrast media (such as gastrografin) have been suggested as a diagnostic test for resolution of the obstruction (ie, to establish whether the gastrografin reaches the cecum on the abdominal x-ray). The reputed therapeutic effect of gastrografin is thought to be due to a side effect based on the stimulation of bowel peristalsis possibly by the entry of water, due to the hyperosmolarity of gastrografin,[9] although the efficacy of water-soluble contrast medium in this respect is subject to debate.

The objective of the present study was to investigate the putative relationship between the administration of gastrografin on one hand and the need for operative intervention as well as the duration of hospital stay.

PATIENTS AND METHODS

Population. Between October 2006 and August 2009, 4 centers in northern France (Amiens, Beauvais, Lille, and Rouen) recruited patients with uncomplicated acute ASBO into a prospective, multicenter, parallel group, open-label, randomized trial (the Acute Bowel Obstruction Diagnostic [ABOD] Study; NCT00389116). The study was approved by the local investigational review board (Comité de Protection des Personnes Nord Ouest I) and the French national drug safety agency (Agence Nationale de Sécurité du Médicament et des Produits de Santé).

The main inclusion criteria for uncomplicated acute ASBO were as follows: a) presence of an obstruction thought to be secondary to adhesions (abdominal pain and distention, nausea and/or vomiting, and no gas and/or stool), b) uncomplicated presentation (no signs of strangulation or peritonitis), and c) a computed tomography (CT) of the abdomen consistent with an uncomplicated ASBO.

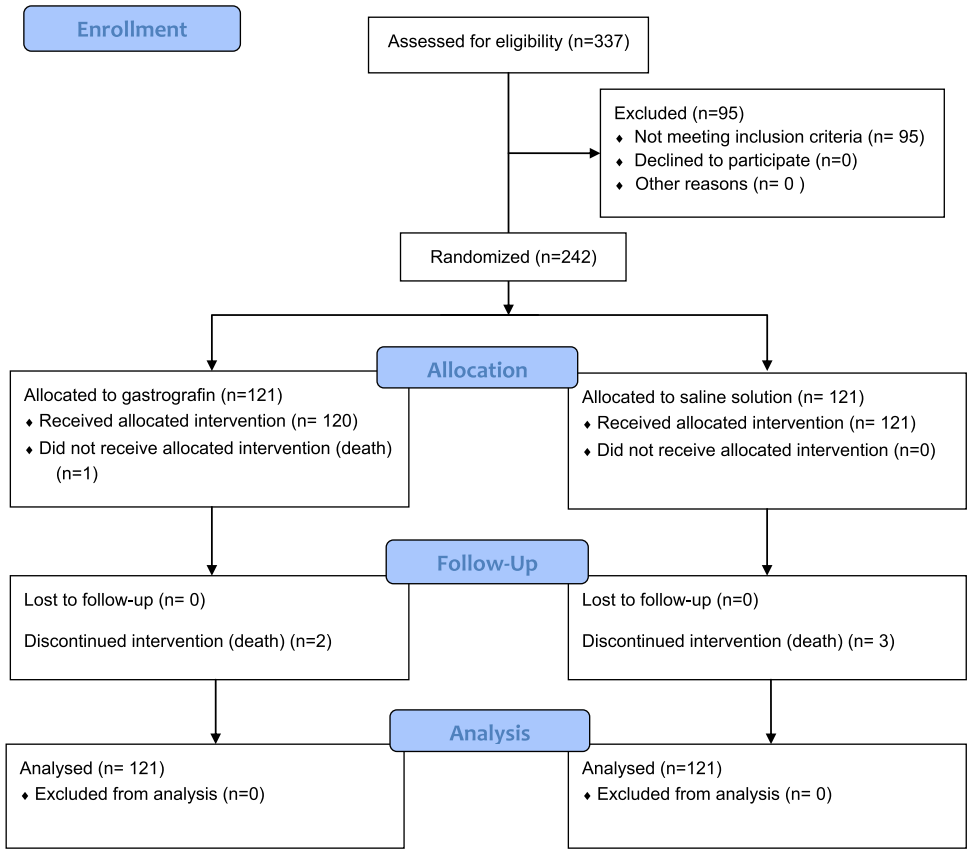


Fig 1. The CONSORT flowchart.

The exclusion criteria were as follows: an incarcerated and/or strangulated incisional hernia, colonic obstruction, clinical signs of peritonitis or strangulation (acute cramping pain, hyperthermia, and/or a WBC count >16,000/mL), radiologic signs of peritonitis or strangulation (bowel wall >3 mm or <1 mm, the "target sign," enhancement of the bowel wall, absence of intravenous contrast, pneumatosis intestinalis, air in the portal venous system, pneumoperitoneum), no previous abdominal operation, obstruction within 4 weeks after a recent operation, history of a gastrointestinal neoplasm, inflammatory bowel disease or abdominal radiotherapy, contraindication to intravenous contrast for the CT and any contraindications to participation in a clinical trial (age <18 years, pregnancy, breast feeding, or inability to provide informed consent). Each patient provided written, informed consent prior to inclusion in the study.

End points. The primary end point was the need for operative intervention within 48 hours of randomization. The indications for operative intervention were based on the following: suspected ischemia of the gut (acute cramping pain, signs of peritonitis, fever and/or a WBC >16,000/mL), absence of contrast in the cecum, and absence of flatus or stools 48 hours after randomization.

The secondary end points were the percentage of patients requiring bowel resection, the time interval between the CT and operative intervention, the time interval between oral refeeding and discharge from hospital, risk factors for the failure of nonoperative management, the in-hospital mortality rate, the duration of stay, and the proportion of patients with recurrence of ASBO or death within 10 weeks of discharge. Lastly, we complemented the ABOD study findings by performing a meta-analysis of recently published studies.

Study design. After confirmation of the diagnosis in a CT with IV (but not oral) contrast agent, and after patient consent to participate in the study, the surgeon opened a sequential, sealed, numbered, opaque randomization envelope which assigned the patient randomly to 1 of 2 equally sized treatment arms: use of oral gastrografin (the TG arm) or use of saline solution as the control arm (the TS arm). The randomization sequence

was generated according to a minimization technique by a methodologist (independently of the study investigators) and was stratified by center. The study flowchart (as specified by the CONSORT guidelines) is shown in Fig 1.

Patient management. Prior to randomization, an NGT with a negative pressure of 40 cm H_2O was inserted for aspiration of the stomach contents. The patient's electrolyte balance was restored or maintained intravenously during the aspiration. All patients were admitted to the digestive surgery department. After 2 hours of nasogastric aspiration, the patients in the TG arm received 100 mL of gastrografin (Bayer Healthcare, Loos, France) via the NGT, while those in the TS arm received 100 mL of a 0.9% NaCl solution. The NGT was then clamped for the next 2 hours. If the patient vomited, the NGT was reopened, but no additional gastrografin or saline solution was administered.

In both study arms, follow-up was based on the results of clinical examinations and laboratory tests. If flatus occurred, the NGT was removed, and oral refeeding (with water or with liquid food) was initiated. In order to increase the patients' chances of avoiding operative intervention, we chose a cut-off of 48 hours. If neither flatus nor accumulation of contrast in the cecum was observed after 48 hours, the decision to operate was taken. Operative intervention was performed at <48 hours if there were signs of peritonitis or strangulation (acute cramping pain, signs of peritonitis, fever and/or a WBC >16,000/mL). In the TS arm, the decision to operate was based purely on clinical signs; the surgeon waited 48 hours for the obstruction to resolve if there were no signs of strangulation or peritonitis.

In the TG arm, abdominal x-rays were performed 8, 12, 24, and 48 hours after administration of gastrografin. If the first x-ray (scheduled for 8 hours after administration of gastrografin) revealed the presence of gastrografin in the cecum, the NGT was removed, the patient was allowed to start eating, and no further abdominal x-rays were performed. If the gastrografin had not reached the cecum at 8 hours, another abdominal x-ray was scheduled at 12 hours. If gastrografin was observed in the cecum at 12 hours, the NGT was removed, and the patient was allowed to eat. If gastrografin had not reached the cecum at 12 hours, another abdominal x-ray was scheduled at 24 hours, and so on. If gastrografin did not reach the cecum at 48 hours, the decision to operate was taken. Hence, patients in the TG arm could undergo up to 4 abdominal x-rays (8, 12, 24, and 48 hours after administration of gastrografin infusion).

The presence of flatus was considered by the participating physicians to be more important than the presence of gastrografin in the cecum when considering starting oral feeding or the need for operative intervention.

Operative intervention. The operative procedure consisted of intestinal adhesiolysis and (in some cases, such as patients with strangulation) bowel resection with primary anastomosis. No patient required a diverting stoma. For each patient, the surgeon noted the presence or absence of intraoperative strangulation, necrosis, and/or adhesions and the details of the operative intervention on the case report form.

Systematic review. To the best of our knowledge, our study is the largest randomized clinical trial to date on the value of gastrografin in the treatment of ASBO. To put our results in context with regard to other studies on this topic, we searched PubMed, the Embase databases, and the Cochrane Library for articles on small bowel obstruction published between January 1990 and November 2015. The search terms were "small bowel obstruction," "gastrografin," "amidotrizoate," and "water-soluble contrast medium." The reference list of each selected article was checked for studies not listed in the PubMed and Embase databases or not found in the computerized search. Only prospective randomized controlled trials written in English were selected. All retrieved articles were screened for relevance. The methodologic quality of the diagnostic studies was evaluated independently by 2 reviewers, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria. The studies were graded according to items of relevance to the present review. Retrieved studies were divided into 3 groups as a function of the calculated PRISMA score: a score of 8 or 9 indicates good quality, a score of 6 or 7 indicates fair quality, and a score of 5 or less indicates poor quality.

Statistical analysis. *The ABOD study.* We expected 30% of the patients in the TS arm and 15% of the patients in the TG arm to undergo operative intervention.[10] For an α risk of 5% and a power of 80% in a χ^2 test, we calculated that 242 patients had to be randomized.

At the time of randomization, patient characteristics in both groups are presented as the median (interquartile range). In order to compare treatment arms at randomization, Fisher exact test (or the latter's Freeman-Halton extension) was used for categorical variables, and Wilcoxon test for independent samples was used for quantitative variables. The Kaplan-Meier method was used to study the overall duration of stay, while the time between oral refeeding and discharge, and the differences between groups with regard to these

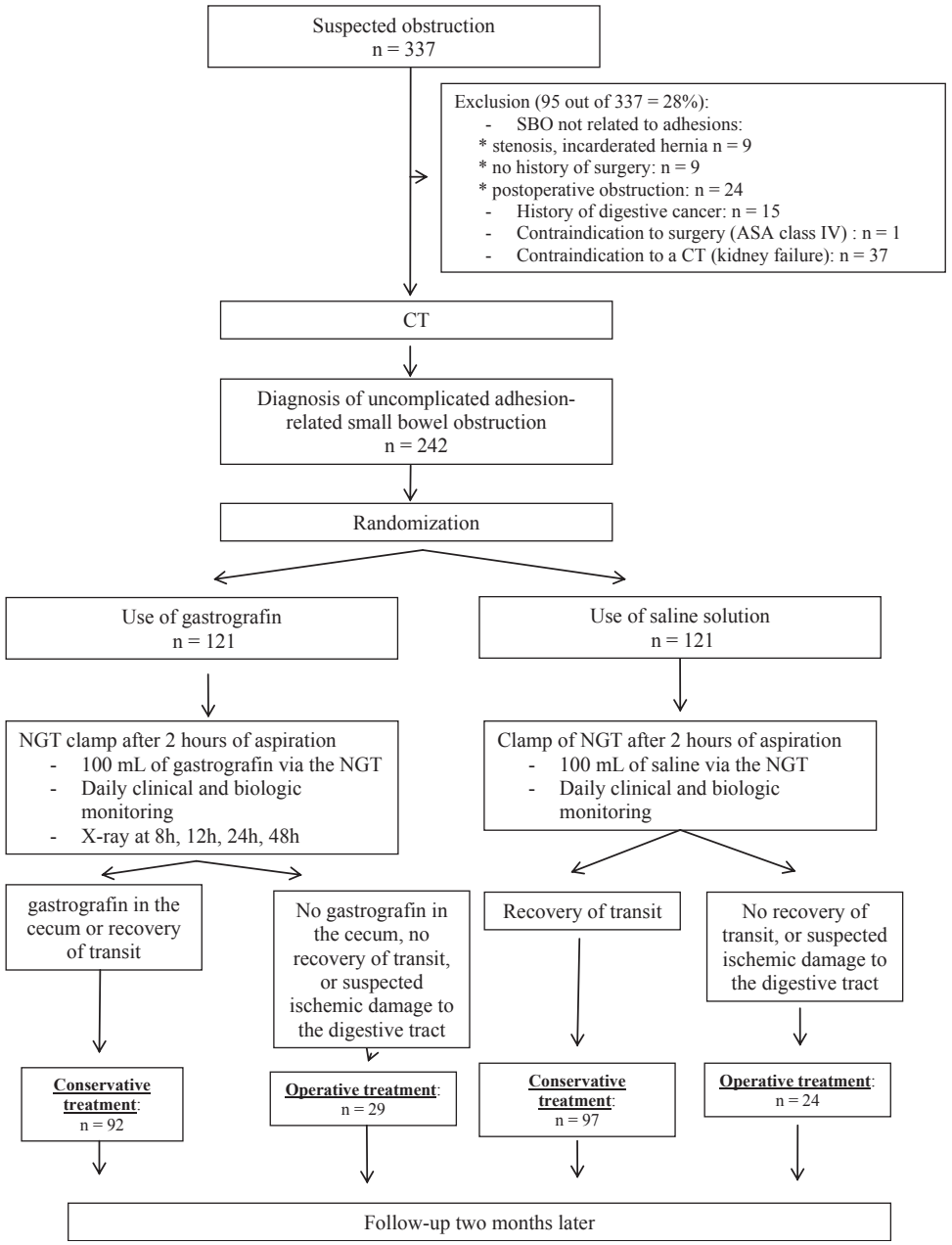


Fig 2. The study flowchart.

variables were assessed using the log-rank test. The frequencies of recurrence or death between discharge and the follow-up visit 2 months later were compared using a Poisson rate model.[11] Factors that were predictive of the need for operative intervention within 48 hours of the CT scan were evaluated by both uni- and multivariate analysis (with a P value $< .1$).

The systematic review. A fixed-effects model was used. The Cochran–Mantel test was used to assess heterogeneity, and an analysis of variance was used to assess the Z-value. All steps in the meta-analysis were performed with Review Manager (RevMan) software (version 5.3, 2014; The Nordic Cochrane Centre, The Cochrane Collaboration).

RESULTS

Demographic data. A total of 242 patients were included in the study (Figs 1 and 2). Demographic data are presented in Table I. The 2 arms were well matched in terms of demographic variables, operative history, and laboratory test

Table I. Demographic data of the study population

Variable	*TG arm* n = *121*	*TS arm* n = *121*	P *value*
Male, *n* (%)	53 (44)	61 (50)	.37
Age, y, median (IQR)	62 (51–77)	65 (51–79)	.51
Time interval between the first signs of ASBO and the CT, days, median (IQR)	1 (1–2)	1 (1–2)	.27
History of ASBO, *n* (%)	40 (33)	42 (35)	.89
History of supracolic operation, *n* (%)*	34 (28)	37 (31)	.67
History of infracolic operation, *n* (%)*	112 (93)	113 (94)	.80
WBC count, $10^3/mm^{3,}$ median (IQR)	11.2 (8.9–14.5)	11 (9.2–13.4)	.90
Serum creatinine, μmol, median (IQR)	77 (66–94)	82 (66–100)	.14
Serum C-reactive protein, mg/L, median (IQR)	12 (5–33)	10 (5–29)	.84
Serum lactate, mmol/L, median (IQR)	2 (1–2)	1 (1–2)	.53
Serum bicarbonate, mmol/L, median (IQR)	27 (25–28)	27 (25–29)	.25

*In the study, 55 patients (25 in the TG arm and 30 in the T arm) had a history of both infra- and supracolic operation.
IQR, Interquartile range.

results (Table I). The 2 arms differed in the number of abdominal x-rays, with a median (range) of 2 (1–4) in the TG arm and 0 in the TS arm.

Operative intervention within 48 hours of randomization. Operative intervention within 48 hours of randomization was required for 29 patients (24%) in the TG arm and 24 patients (20%) in the TS arm ($P = .534$).

Resection rate. Among patients who underwent operative intervention, 10 patients in the TG arm (8%) and 5 patients in the TS arm (4%) underwent bowel resection; resection was necessary due to ischemia resulting from strangulation in 12 cases and due to the presence of adhesions unable to be lysed to relieve the obstruction in 3 cases. The reasons for operative intervention were signs of strangulation in 20 patients (38%) and the failure of nonoperative treatment at 48 hours in 33 patients (62%).

The time interval between the CT and operative intervention. The probability of operative intervention as a function of the time from the CT was similar in the 2 arms ($P = .49$, Fig 3, *A*). The same was true for operative intervention (ie, resection or not; Fig 3, *B* and *C*). Although the cumulative probability of the need for bowel resection seemed to be consistently greater for patients allocated to the TG arm, the difference between the 2 arms was not significant ($P = .21$).

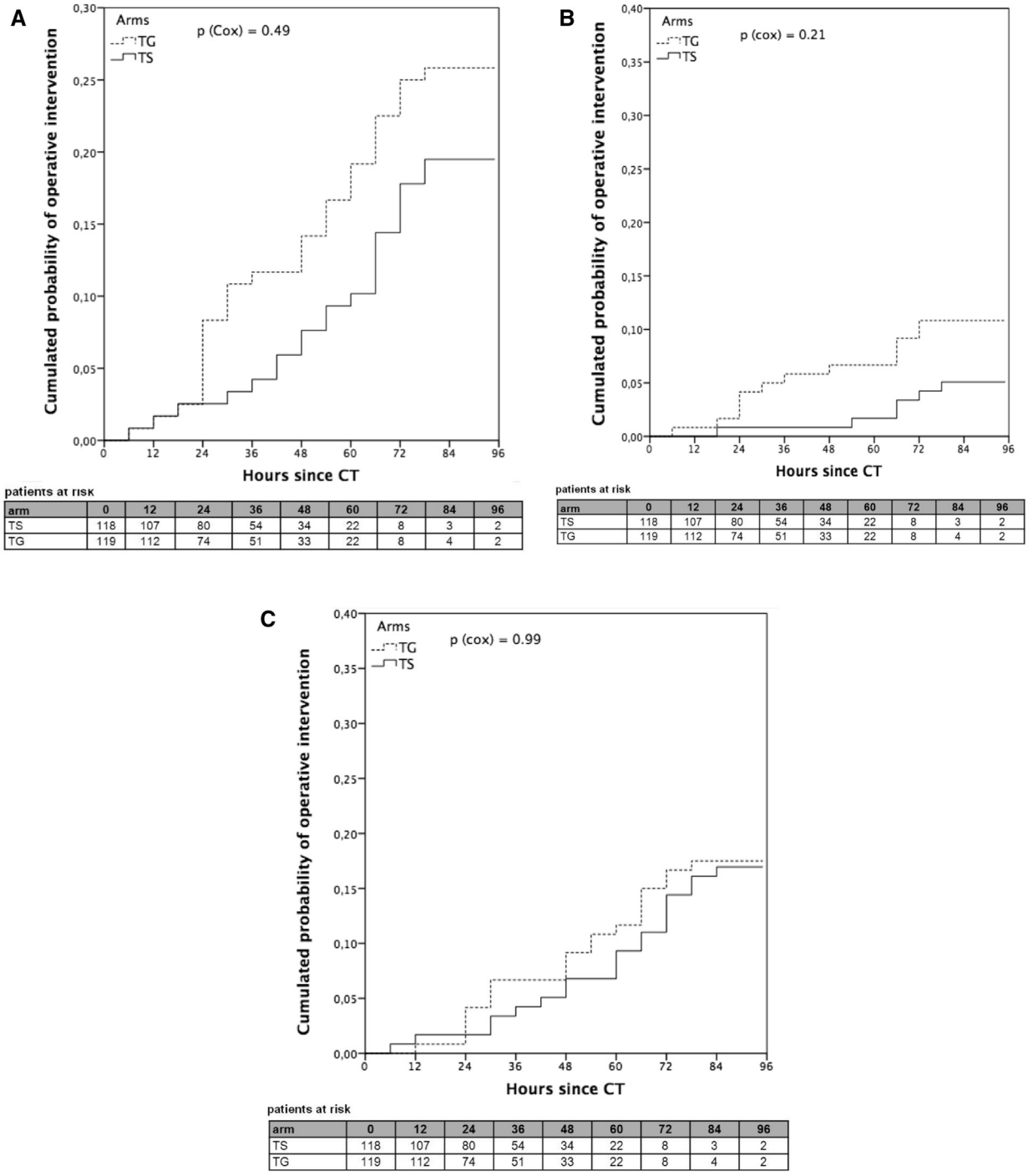
The time interval between oral refeeding and discharge. The time interval (95% confidence interval) between oral refeeding and discharge was 1.9 days (1.21–2.21 days) in the TG arm and 1.9 days (CI 1.67–2.04) in the TS arm.

Risk factors for the failure of nonoperative management. The risk factors for the failure of nonoperative management (in a univariate analysis) are presented in Table II. These included demographic variables (sex and a previous history of ASBO), morphologic signs observed on the initial CT scan (diagnostic items, suspected cause, and signs of ischemia), and biologic/clinical biochemistry parameters. Only age was identified as a potential risk factor for the failure of nonoperative management. Neither the treatment strategy (TG versus TS), the presence of signs of ischemia, nor biologic/clinical biochemistry parameters (the WBC and serum lactate level) were identified as risk factors.

In-hospital mortality. Six (2.5%) of the randomized patients (3 in each arm) died before they could be discharged (Fig 2). Four deaths were attributed to an aspiration pneumonia leading to cardiac arrest; 1 patient died with septic shock (although the primary cause of death of the septic patient was unknown), and 1 died after a cardiac arrest. During the study period, all adverse events were recorded. The only adverse event other than death was vomiting.

Duration of stay. The 2 arms did not differ significantly in terms of the median overall duration of stay in hospital after randomization (3.8 days for patients in the TG arm and 3.5 days for those in the TS arm ($P = .19$)).

Recurrence of ASBO or death within 10 weeks of discharge. The frequency of recurrence or death after discharge was 8 ± 1 (7%) in the TG arm and 9 ± 1 (7%) in the TS group ($P = .1$).



arm	0	12	24	36	48	60	72	84	96
TS	118	107	80	54	34	22	8	3	2
TG	119	112	74	51	33	22	8	4	2

Fig 3. Probability of operative intervention after the CT (in hours) for the study population as a whole (*A*), and for patients with (*B*) and without (*C*) small bowel resection.

Protocol deviations. Four protocol deviations were observed. The clinicians followed the protocol for all patients, except for 4 patients in the TG arm (considered as major protocol deviations). In these cases, gastrografin was not observed in the cecum on the x-ray at 48 hours, and, therefore, the patients should have undergone an operation. Nevertheless, all experienced flatus or tolerated oral refeeding at this time point; hence, on the basis of this clinical examination, operative intervention was not undertaken. The NGT was reopened in 1 case; however, this was not considered to

Table II. Univariate analysis of potential risk factors for the failure of nonoperative management

Variable	P *value*
• Epidemiologic data:	
○ Male	.08
○ Age at CT	.046
• ASBO-related signs:	
○ Days between symptom onset and CT scan	.2
○ History of ASBO	.056
○ Biologic/biochemical assays	
• Low WBC count	.7
• Serum creatinine	.1
• Serum C-reactive protein	.9
• Serum lactate	.7
• Serum bicarbonates	.7
○ Radiologic signs	
• Bowel diameter >25 mm and/or feces sign	1
• Beak sign and/or whirl sign and/or agglutinated bowel	.4
Treatment strategy (TG arm)	.5

be a case of early study termination, and the patient was included in the final analysis.

Systematic review. Our study data were pooled with data from 10 published studies (totaling 499 patients in the TG group and 491 patients in the control group). Eight of the 10 studies in the literature had a PRISMA score of between 6 and 8.[12-21] All 10 studies were randomized clinical trials published between 1994 and 2015. The data showed that gastrografin was of no benefit (Fig 4, *A* and *B*) in terms of decreasing the rate of operative intervention (21% vs 26% in the TG arm and TS arm, respectively; odds ratio [95% CI] = 0.69 [0.47–1.01], $P = .05$) or the duration of stay (Fig 4, *C* and *D*; 3.51 days vs 3.53 days in the TG arm and TS arm, respectively; difference in means [95% CI] = −0.02 [−0.18 to 0.13]; $P = .77$).

DISCUSSION

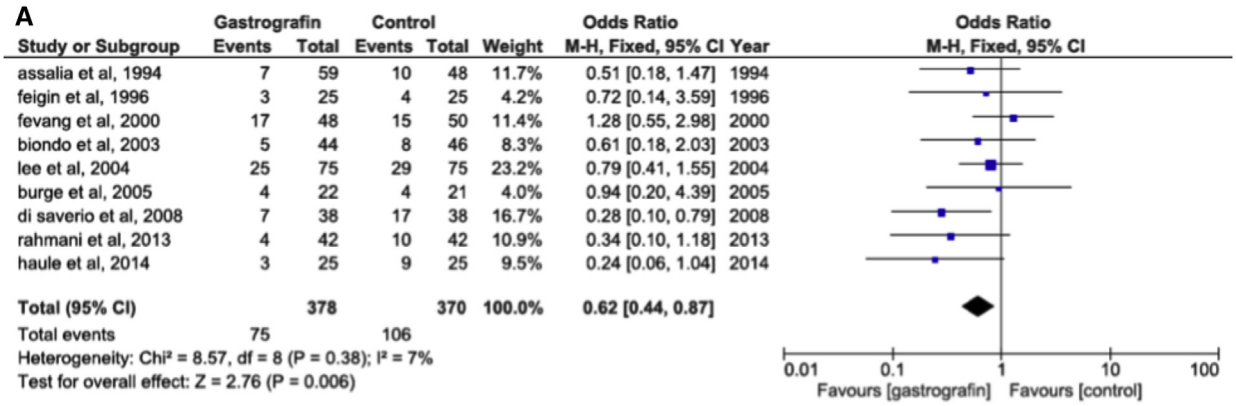
The results of this ABOD study failed to demonstrate that gastrografin administration was associated with a lesser rate of operative intervention after 48 hours (24% for TG arm versus 20% for TS arm) or a lesser mean duration of stay (3.8 for TG arm, versus 3.5 days for TS). A meta-analysis that pooled our data with the literature data confirmed that gastrografin did not have an impact on the rate of operative intervention or the duration of stay. Likewise, the differences for other end points (the time interval between CT and operative intervention, and the time between oral refeeding and discharge) were not statistically significant.

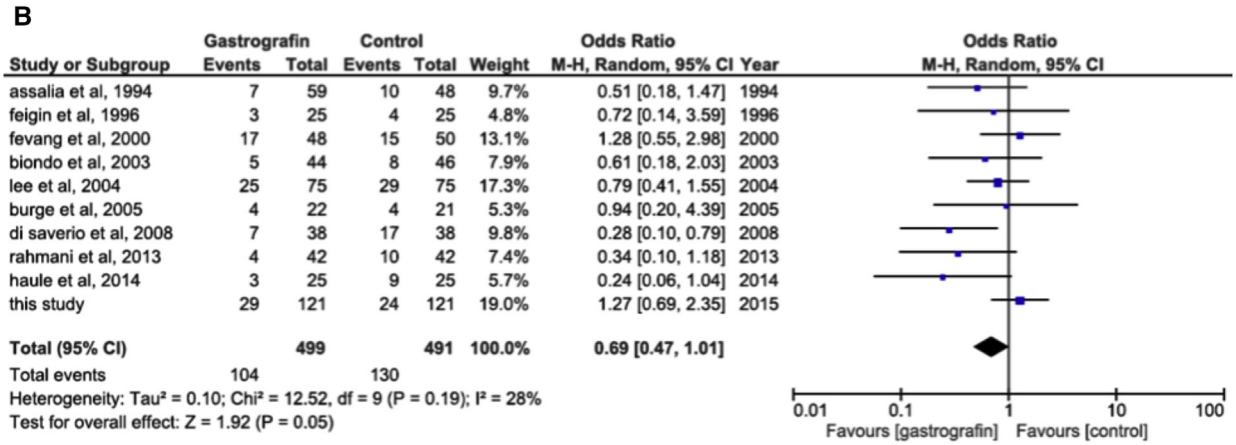
The present study is the largest (n = 242) to have evaluated the therapeutic value of gastrografin administration in CT-confirmed ASBO. The participants in our multicenter, randomized, controlled trial are representative of the target population, with the same characteristics and duration of stay as in previously published series.[12-18,22] Moreover, the definition of uncomplicated ASBO was consistent with those reported subsequently in the Bologna Guidelines.[8] The percentage of patients with a history of ASBO was similar to those reported by Di Saverio et al[8] and Farid et al[18] (40%). In the present study, the median time interval between symptom onset and operative treatment was 24 hours, which is somewhat less than the literature range (from 31.6–41.6 hours) because of the study design.[17,18]

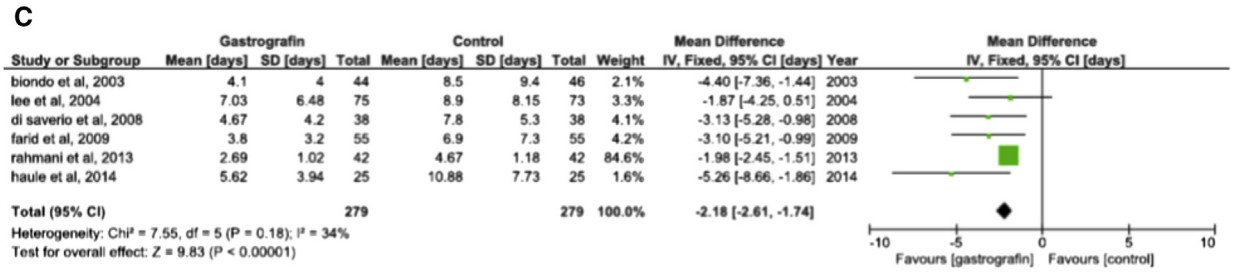
The overall rate of operative intervention in our series (22%) was less than that reported by Abbas et al[9] in 2007 (31%) but was similar to the value reported for the group receiving water-soluble contrast medium (22%). Furthermore, we waited for 48 hours before deciding whether to operate or not, whereas Abbas et al waited for 24 hours.[9]

The median duration of stay was 4 days, which is much shorter than in the literature.[10] This finding might have been due to the treatment algorithm of our ABOD study because patients with no flatus or gastrografin in the cecum could be operated on earlier than those in the above-mentioned studies. To evaluate the impact of our study data on the data from the literature, we decided to pool the 2 and thus decrease the disparity in the duration of stay. None of the end points of the study differed significantly when comparing the 2 arms, and the values were similar to or less than those in the literature.[10]

Given the present trend toward the development of early rehabilitation programs (even for severe medical conditions and contexts like cancer and emergency operation),[23-25] gastrografin was potentially a key element in a program for ASBO. Nevertheless, use of gastrografin does not reduce the duration of stay or the rate of operative intervention and does not hasten oral refeeding. Furthermore, the patient has to be moved during the abdominal x-ray procedure (with a median of 2 x-rays per patient). The present findings could, however, contribute to early rehabilitation, if one considers the observed time interval (2 days) between oral refeeding and discharge. This knowledge could help the surgeon to estimate the







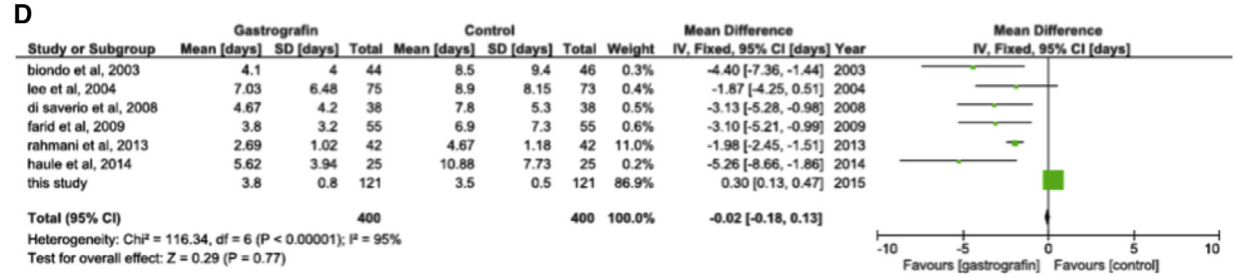


Fig 4. Systematic review and meta-analysis of the use of gastrografin, for the rate of operative intervention (*A*) according to the data from the literature, (*B*) according to the literature pooled with the present study results, and for duration of stay (*C*) according to the literature data, (*D*) according to the literature pooled with the present study results.

discharge date and better manage a patient's hospitalization.

The mortality rate in the present series (2.5%) was still noteworthy. Nevertheless, 2 recent publications (a study of a cohort of 110 patients and a systematic review) reported greater rates (ranging from 3.4–3.6%).[26,27] Accordingly, the mean mortality rate for this benign condition would be around 3%.

Despite its robust design, our study had some limitations. Our study started in 2006 and ended in 2009. The lengthy time interval between the end of the study and the present publication of its results was due to personal considerations by the principal investigator. Despite this time interval, the management of ASBO has not changed since 2009. We chose the rate of operative intervention as our primary end point based on either the absence of flatus or the accumulation of gastrografin in the cecum. We concede that visualization of gastrografin only was possible in the TG arm; however, patients from either arm also could undergo operative intervention on the basis of clinical signs of strangulation or peritonitis. Furthermore, we maximized the probability of avoiding operative intervention by making the decision to operate 48 hours after randomization in both arms. The available series have not shown any difference between a time interval of 24 hours and a time interval of 48 hours.[21] These findings were not integrated into the present series because they were published after the ABOD had been designed. Furthermore, the absence of a significant difference in the duration of stay could have been potentially attributed to the choice of this cut-off (48 hours), as it set a minimum time period before operative intervention in both arms and thus could have increased the duration of stay but with the same impact for both arms. This assumption concealed the fact that either gastrografin or saline solution may have an intrinsic ability to resolve obstruction. Furthermore, this design has been applied to all studies of gastrografin in SBO[12-15,17-22] with the exception of the placebo-controlled, randomized trial performed by Burge et al.[16] We decided to perform a meta-analysis, in order to put the results of the ABOD Study (ie, the study with the largest sample size) into context with regard to the literature data (as it was already done for the DISPACT study).[28] We consider this addition of value, because it updates recent data, increases the ASBO patient population, and confirmed that the meta-analyses findings that gastrografin is not of benefit for the rate of operative intervention or the duration of stay (whatever the meta-analysis [2007, 2010, and 2015] with which the results of our ABOD study were pooled).

Conversely, this ABOD study had several strengths: a) standardization of the control group with saline solution as a comparator, which is closer to a placebo (in contrast with studies that used low-osmolarity contrast medium, the absence of treatment, or operative intervention only as their comparator); b) the choice of a single primary end point, in contrast to a type of composite end point in the meta-analysis of Branco et al[10]; c) the addition of an abdominal x-ray examination at 12 hours, in order to decrease the rate of operative intervention; d) the largest yet sample size, with an exclusion rate of 28%; e) inclusion of all patients on the basis of a CT (thus eliminating other causes, the absence of a true obstruction, or the presence of an obstruction not related to adhesions, etc), and f) consistent results for the lack of benefit of gastrografin after pooling our present data with those of three systematic reviews (from 2015, and data not shown only from 2007–2010).

Despite the robustness of our present results, the treatment of ASBO remains a real issue in clinical practice, because it still is difficult for the surgeon to identify patients who require operative intervention. We reported previously that a biomarker like procalcitonin might be useful in this respect for ASBO.[29]

The results of the present study and those of our systematic review suggest strongly that gastrografin administration is of no benefit in patients with ASBO.

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