Review

Water-soluble contrast agent in adhesive small bowel obstruction: a systematic review and meta-analysis of diagnostic and therapeutic value

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KEYWORDS:
Adhesive small bowel obstruction; Intestinal obstruction; Gastrografin; Urografin; Conservative management; Water-soluble contrast agent

Abstract

BACKGROUND: Adhesive small bowel obstructions are the most common postoperative causes of hospitalization. Several studies investigated the diagnostic and therapeutic role of water-soluble contrast agent (WSCA) in predicting the need for surgery, but there is no consensus.

METHODS: A systematic review and meta-analysis was done of studies on diagnostic and therapeutic role of oral WSCA.

RESULTS: WSCA had a sensitivity of 92% and a specificity of 93% in predicting resolution of obstruction without surgery; diagnostic accuracy increased significantly if abdominal X-rays were taken after 8 hours. The administration of oral WSCA reduced the need for surgery (odds ratio .55, P = .003), length of stay (weighted mean difference 2.18 days, P = .00001), and time to resolution (weighted mean difference 28.25 hours, P < .00001). No differences in terms of morbidity or mortality were recorded.

CONCLUSIONS: The administration of WSCA is accurate in predicting the need for surgery; the test should be taken after at least 8 hours from administration. WSCA is a proven safe and effective treatment, correlated with a significant reduction in the need for surgery and in the length of hospital stay.

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waiting for the spontaneous resolution of the obstruction which occurs in the majority of cases, up to 90%. However, some patients with nonresolving obstruction require surgical intervention. A treatment option, recommended in the World Society of Emergency Surgery’s Guidelines on ASBO, is the administration of water-soluble contrast agent (WSCA), a radiopaque hypertonic solution containing diatrizoate meglumine and diatrizoate sodium (66 g and 10 g per 100 mL), through the nasogastric tube. Several studies have investigated the diagnostic and therapeutic role of WSCA in predicting the need for surgery, reducing operation rate, and reducing hospitalization; diagnostic accuracy of the abdominal plain film after 4 to 24 hours from the administration of WSCA was also investigated but no differences in the timing of the test were demonstrated. Three meta-analyses have been published with conflicting results: the role of WSCA in reducing the need for surgery is not clear, with significant results reported only by the most recent review. The aim of this systematic review and meta-analysis is to provide an update with recent data available on the diagnostic accuracy and the therapeutic effect of WSCA in ASBO.

Patients and Methods

Literature search strategy and study selection

Systematic literary research was performed independently by 2 different investigators (M.C. and F.C.) in MEDLINE, EMBASE, PubMed, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews until October 2014. The search terms included the following: “small bowel adhesive obstruction,” “gastrografin,” “urografin,” “water soluble contrast agent,” “meglumine diatrizoate,” “intestinal obstruction,” “randomized trial,” and “prospective study” combined with AND/OR. No search restrictions were imposed. The references of selected articles were also reviewed. Duplicate published trials were considered only in the last or at least in the more complete version. Agreement between the 2 reviewers was measured with the Cohen’s kappa coefficient; all the retrieved articles were selected if they met the inclusion criteria.

Selection criteria

For this meta-analysis, only prospective observational studies and clinical trials were selected and included. For the therapeutic role of WSCA in ASBO, trials were selected where patients were randomized to receive conventional conservative treatment (fasting, i.v. fluid hydration, and nasogastric tube) or conservative treatment plus WSCA (diatrizoate meglumine plus diatrizoate sodium) and analogous prospective studies. For the diagnostic role of WSCA, prospective studies on test accuracy and the interventional arms of the trials with WSCA (if data on test accuracy were reported) were included. No selection on age, sex, or ethnicity was adopted.

Exclusion criteria

Case reports, letters, reviews and meta-analyses, retrospective studies, and non-English language publications were excluded. Studies including both postoperative and non–postoperative small bowel obstruction and studies comparing hyperosmolal vs barium contrast or barium contrast vs traditional treatment were also excluded if subgroup data extrapolation was not possible. Studies where WSCA was administrated after failure of conservative treatment were excluded. Studies regarding only pediatric patients were also excluded.

Data extraction, outcome measures, and quality assessment

The following data were reported for each selected study: year of publication, study characteristics, inclusion and exclusion criteria, patients’ characteristics, sample size, quantity of WSCA, and outcomes. For studies investigating the diagnostic accuracy, the time intervals between WSCA administration and abdominal X-ray execution were reported; the diagnostic abdominal X-rays were considered positive if WSCA reached the colon. The primary outcome was the ability of the WSCA administration to predict the need for emergency surgery in patients with ASBO. The secondary outcome was determining the optimal timing for abdominal X-rays following WSCA administration. Regarding the therapeutic role, the primary outcome was the need for surgery in each group of patients, and the secondary outcomes were time to resolution, length of stay, complications, and mortality. Controversial, missing, and subgroup data were obtained by author correspondence. Quality of randomized trials was evaluated with the Jadad quality scale and prospective studies quality assessment was made using the MINORS scale.

Statistical analysis

The present review and meta-analysis was performed according to the PRISMA statement. Data were analyzed with Review Manager, Version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2011). To study the diagnostic role of WSCA we pooled data on sensitivity (Sn) and specificity (SP); positive predictive value (PPV) and negative predictive value (NPV), positive likelihood ratio (LR+) and negative likelihood ratio (LR−) were calculated and reported with 95% confidence interval (95% CI). Results were divided into 3 time interval–based groups and pooled results were calculated and showed with summary receiver operating characteristic (SROC) curves. To study the therapeutic role of WSCA, we pooled data on the need for surgery; complications and mortality
were expressed as weighted odds ratio (OR) and 95% CI; time to resolution and LOS were expressed as weighted mean difference (WMD) and 95% CI. Outcome were calculated with fixed-effects and random-effects models\(^{12,13}\); statistical heterogeneity was quantified using the \(I^2\) inconsistency test and if statistically significant (\(P < .1\)) were reported only results of random-effects model.

**Results**

**Study selection**

One hundred three abstracts were found using key terms. After an initial review, 26 abstracts were selected and identified as potentially eligible for our study. After a full review of the manuscripts, 5 studies were excluded for the following reasons: the patients were randomized after the conservative treatment failure in 2 studies,\(^ {14,15}\) 1 was a duplicate study,\(^ {16}\) 1 study included non–postoperative ASBO,\(^ {17}\) and in the last study the patients were randomized to a different, nonhyperosmolar WSCA (Gastromiro).\(^ {18}\) Three studies included also patients without previous abdominal surgery, but we have included in the analysis only the subgroups of patients with ASBO.\(^ {19–21}\) Finally, 21 studies were selected and included in this meta-analysis: 12 for the therapeutic role of WSCA\(^ {3,22–32}\) and 13 for its diagnostic role.\(^ {19–22,24,25,31,33–38}\) (Fig. 1). Four studies were considered for both the diagnostic and therapeutic roles.\(^ {22,24,25,31}\) Two prospective studies\(^ {21,36}\) compared the results with a retrospective analysis of an historical cohort of patients: for this reason and for their poor quality, they were not included in the analysis for the therapeutic role of WSCA, but only for the diagnostic role. The agreement between the 2 reviewers, measured with the Cohen’s kappa coefficient, was .928.

**Studies’ quality**

Among randomized studies, only the study by Burge et al\(^ {23}\) was of good quality, reaching the maximum score for the Jadad scale, 5/5; 2 studies scored 3/5, because they were not double blinded\(^ {24,31}\) and the others were of low quality, scoring 2/5.\(^ {3,22,25–30}\) MINOR score evaluates the quality of prospective studies: it is composed of an 8-item questionnaire for all the studies and 4 additional items for comparative studies. Each item should receive 0 points if the item is not reported, 1 if it is reported but inadequate, or 2 if it is reported and adequate. Item numbers 6 and 7 are about the study’s follow-up results evaluating its duration and the “loss at follow-up” rate. For the evaluation of the included studies, these items\(^ {6,7}\) were not evaluable and the maximum score was reduced by 4 points. The maximum score for noncomparative studies was 12 instead of 16: 3 studies scored 7/12,\(^ {33,34,38}\) 3 studies scored 8/12,\(^ {20,35,37}\) and 1 study scored 10/12.\(^ {19}\) The maximum score for comparative studies was 20 instead of 24: 1 study scored 16/20\(^ {32}\) and 2 scored 10/20.\(^ {21,36}\) For complete results regarding studies’ characteristics see Table 1.

**Studies’ characteristics**

All studies analyzed included patients with ASBO after abdominal surgery. Three studies also included patients with non-ASBO,\(^ {19–21}\) but data were extracted only for the subgroup of patients presenting with ASBO.

In all comprised studies, exclusion criteria were the following: patients presenting with peritonitis and strangulation, a large bowel obstruction, early postoperative obstruction (2 to 6 weeks), and allergy to iodine.

In all studies, initial management protocols for the patients were the same: fasting, gastric decompression through nasogastric tube, and i.v. fluids; nasogastric tube after administration of WSCA was closed.

For the diagnostic role, administration of 40 to 150 mL of WSCA was adopted. Plain abdominal films were taken after 2 hours in 1 study,\(^ {33}\) 4 hours in 4 studies,\(^ {19,20,31,36}\) 6 hours in 2 studies,\(^ {33,38}\) 8 hours in 2 studies,\(^ {21,33}\) 12 hours in 1 study,\(^ {37}\) 24 hours in 5 studies,\(^ {22,25,34,35,38}\) and 36 hours in 1 study\(^ {24}\); some studies reported plain abdominal X-ray results at several time points.

For the therapeutic role, administration of 40 to 150 mL of WSCA was adopted, considering that the ASBO was considered resolved if WSCA reached the right colon in the plain abdominal X-rays with clinical improvement or if the patients passed stool. Patients underwent surgery if there

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![Figure 1](https://example.com/image1.png) **Figure 1** PRISMA flow diagram: 4 studies were included for both diagnostic and therapeutic role.\(^ {22,24,25,31}\)
<table>
<thead>
<tr>
<th>Study ID</th>
<th>Year</th>
<th>Number of patients</th>
<th>WSCA</th>
<th>WSCA quantity (mL)</th>
<th>Study’s outcome</th>
<th>Study’s design</th>
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<th>LOS in non operated patients</th>
<th>Time to resolution</th>
<th>Need for surgery</th>
<th>Complications</th>
<th>Mortality</th>
<th>Test accuracy</th>
<th>Study’s protocol</th>
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Gastrografin (Schering, Berlin, Germany); Urografin (Schering NZ Ltd, Auckland, New Zealand).

D = diagnostic role; LOS = length of stay; P = prospective study; R = retrospective study; RCT = randomized study; T = therapeutic role; WSCA = water-soluble contrast agent.

*Subgroup analysis.
was no resolution within 36 to 72 hours in 1 study,24 48 hours in 5 studies,3,22,25,29,32 4 days in 3 studies,23,28,30 and 5 days in 1 study;26; in 2 studies the time for surgical intervention was not indicated.27,31

Diagnostic role

Regarding the diagnostic role of WSCA, 13 studies were included, comprising a total of 947 patients.19–22,24,25,31,33–38 Abdominal X-rays were taken at different time intervals following WSCA administration, ranging between 2 to 36 hours. Results are shown in detail in Table 2.

The presence of WSCA in the right colon in the plain abdominal X-ray in ASBO patients had an Sn of .92 (95% CI .90 to .94), an SP of .93 (95% CI .88 to .96), a PPV of .98 (95% CI .97 to .99), an NPV of .75 (95% CI .70 to .81), an LR+ of 12.78 (95% CI 7.71 to 21.19), and an LR− of .08 (95% CI .06 to .10).

Diagnostic accuracy was calculated by sorting data into 3 different groups: 2 to 6, 8 to 12, and 24 to 36 hours. Results are shown in detail in Table 3. Three different

Table 2  Different timing of the test

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<th>FN</th>
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<td>.56</td>
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<tr>
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Table 3  Test accuracy at different timing

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<th>Timing (hours)</th>
<th>n</th>
<th>TP</th>
<th>FP</th>
<th>FN</th>
<th>TN</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
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<th>LR−</th>
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<td>355</td>
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<td>4</td>
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<td>69</td>
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<td>[.77–.86]</td>
<td>.95</td>
<td>[.89–.99]</td>
<td>.98</td>
<td>[.96–1.00]</td>
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<td>115</td>
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<td>3</td>
<td>40</td>
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<td>[.95–1.00]</td>
<td>.89</td>
<td>[.78–.98]</td>
<td>.96</td>
<td>[.92–.99]</td>
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<tr>
<td>24–36</td>
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<td>[.98–1.00]</td>
<td>.93</td>
<td>[.88–.99]</td>
<td>.99</td>
<td>[.97–1.00]</td>
</tr>
</tbody>
</table>

Data are expressed as [95% confidence interval].

FN = false negative; FP = false positive; LR+ = positive likelihood ratio; LR− = negative likelihood ratio; PPV = positive predicting value; NPV = negative predicting value; TN = true negative; TP = true positive.
interpolated SROC curves were generated from these results (Fig. 2).

**Therapeutic role: need for surgery**

This analysis included 1,216 patients from 12 studies\textsuperscript{3,22–32}: 653 treated with WSCA and 563 with conservative management. Administration of WSCA resulted in a significant reduction in the need for surgery (OR .55, 95% CI .37 to .32, \( P = .003 \)). Excluding the prospective study\textsuperscript{32} and selecting only the randomized studies similar results were obtained (OR .6, 95% CI .39 to .91, \( P = .002 \); Fig. 3).

**Therapeutic role: length of hospital stay in nonoperated patients**

Data were collected from 7 studies\textsuperscript{3,22–25,29,31} and included 464 patients: 252 treated with WSCA and 212 treated conservatively, where obstruction resolved without operation. Among these patients, WSCA administration resulted in a significant decrease in length of stay (WMD \(-2.12\) days, 95% CI \(-2.63\) to \(-1.60\), \( P < .00001 \); Fig. 4).

**Therapeutic role: time to resolution**

Four studies reported data about the time to resolution in patients who did not undergo surgery\textsuperscript{3,24,25,28}: the analysis included 264 patients, 153 treated with WSCA and 111 treated conservatively. WSCA resulted in a significant reduction in the time to resolution of the obstruction, interpreted as passing of first stool (WMD \(-28.25\) hours, 95% CI \(-40.13\) to \(-16.37\), \( P < .00001 \); Fig. 5).

**Therapeutic role: overall length of stay**

Data about the overall length of stay were available for analysis in 6 studies.\textsuperscript{22,24,25,28,30,31} Five hundred fifty-eight patients were included, 279 for each group: the administration of WSCA resulted in a significant reduction in the length of stay (WMD \(-2.18\) days, 95% CI \(-2.61\) to \(-1.74\), \( P < .00001 \); Fig. 6).

**Therapeutic role: complications and mortality**

Data about complications and mortality were reported in all the 12 selected studies\textsuperscript{3,22–32} and included 1,216

Figure 2  Summary receiver operating characteristic curves at 3 different time points after administration of WSCA.
patients: 653 in the WSCA group and 563 in the control group. The administration of WSCA did not increase complications significantly, OR 1.3, 95% CI .64 to 2.62, \( P = .47 \) either with the fixed-effects model or OR 1.29, 95% CI .63 to 2.62, \( P = .49 \) with the random-effects model (Fig. 7). Mortality did not change significantly relative to the control (OR 1.26, 95% CI .42 to 3.81, \( P = .68 \)) with both the fixed-effects (OR 1.26, 95% CI .42 to 3.81, \( P = .68 \)) and the random-effects model (Fig. 8). Excluding the prospective study the results did not vary significantly.

**Comments**

Our meta-analysis confirms the results of the last meta-analysis by Branco et al\(^1\): the administration of WSCA reduces the need for surgery in patients with ASBO with a significant reduction in the time to resolution, length of stay in nonoperated patients, overall length of stay, and the mean length of stay. The administration of WSCA is a safe therapeutic strategy with no significant differences in complications or mortality.
The treatment of ASBO, after the exclusion of the need for an urgent operation, should be conservative. Surgery should be reserved for patients showing no resolution because the majority of the obstruction episodes resolved with conservative treatment only, as recommended by the guidelines on the management of ASBO, promoted by the World Society of Emergency Surgery. To date, 3 meta-analyses have been published on this issue and demonstrated that the administration of WSCA had a very good diagnostic accuracy in predicting the need for surgery and reducing the length of stay; only the most recent study by Branco et al, published in 2010, demonstrated a significant reduction in the need for surgery. Regarding the diagnostic accuracy of the WSCA, past studies did not identify disparities among tests taken at different time points, particularly with no differences between 4 to 8 and 24 hours.

The aim of this meta-analysis was to update this investigation with recently published articles to investigate the diagnostic and therapeutic role of administration of hyperosmolar WSCA in the management of ASBO. Moreover, different from the previously published meta-analysis, particular attention to the inclusion criteria was adopted. Also, some studies included in the previous meta-analysis were not included. This meta-analysis investigates the role of hyperosmolar WSCA administered in patients with postoperative (at least 4 weeks) ASBO: for this reason, 2 studies were included in the analysis only for the subgroup’s data about patients who had previously undergone surgery.

The administration of WSCA had both diagnostic and therapeutic effects. The diagnostic effect may be a direct consequence of the therapeutic one. The presence of WSCA in the right colon indicates with high Sn and Sp the resolution of the small intestine obstruction; as presumed by several authors, high osmolarity, approximately 6 times that of extracellular fluid, increases the pressure gradient across an obstructive site, promotes shifting of fluid into the bowel lumen, decreases bowel edema, and enhances bowel motility leading to the resolution. The previous meta-analysis included, for the diagnostic role of WSCA, the randomized study by Brochwicz-Lewinski et al where a nonhyperosmolar WSCA (Iopamidol - Gas-tromiro, Merck Pharmaceuticals, Kenilworth, NJ, USA) was administrated: for the abovementioned reasons we exclude it from the meta-analysis.

Different from the last meta-analysis by Branco et al, we have decided to include in the systematic review the randomized study by Kumar et al: this study has a well-described partial protocol violation, because 7 patients from the control group demonstrated only a partial clinical improvement within 48 hours and, despite the study protocol, they did not undergo surgery; these obstructions resolved with conservative treatment. Data from this study were included on intention-to-treat analysis principle.

We also included the prospective study by Yagci et al: it is prospective but not randomized; inclusion and exclusion criteria were the same as that of other studies, it has a large study population (317 patients), and is a good
quality study. However, all the analyses have been performed by both including and excluding this study, showing no significant differences in results. Two prospective studies\textsuperscript{21,36} were excluded because they were prospective studies with an historical control cohort. For these 2 studies, only data on diagnostic accuracy were collected.

This meta-analysis confirms that the presence of WSCA in the right colon (4 to 36 hours) has high Sn (92%) and high Sp (93%) in predicting the resolution of the small bowel obstruction without surgery, with very high PPV (98%), LR\textsuperscript{1} and LR\textsuperscript{2} (12.75 and .08), and an acceptable NPV (75%). The great variability in time points of the test and the greater number of included studies could justify the difference between our results and the previous meta-analysis where Sn and Sp were 96% and 98%, respectively.\textsuperscript{5}

Results were sorted based on the different time points of abdominal X-rays, and 3 periods were individuated as shown in Table 3: 2 to 6, 8 to 12, or 24 to 36 hours from the administration of WSCA. To date, there is no evidence to determine the best timing for the abdominal X-rays after the administration of WSCA. The previous meta-analysis by Abbas et al.\textsuperscript{6,7} and Branco et al.\textsuperscript{5} did not show any significant difference in terms of accuracy between tests taken after 4 to 8 and 24 hours. Guidelines on the management of ASBO\textsuperscript{4} recommend the administration of WSCA in conservatively treated patients and set the limit for the appearance of WSCA in the right colon within 24 hours.

Our meta-analysis demonstrated a significant increase in terms of accuracy among tests taken after 8 to 12 hours relative to tests taken after 2 to 6 hours: Sn increased from .82 (95% CI .77 to 0.86) to .97 (95% CI .95 to 1.00). Test accuracy did not vary significantly among tests taken after 8 to 12 or 24 to 36 hours with similar and comparable results as shown by the SROC curves in Fig. 2. This finding suggests that abdominal X-ray should not be taken earlier than 8 after the administration of WSCA, allowing WSCA to carry out its therapeutic effect; waiting this time can reduce the number of patients requiring an operation for ASBO.

This meta-analysis has some limitations. In patients with ASBO, the presence of WSCA in the right colon seems to indicate the resolution of the obstruction with a good diagnostic accuracy; however, there is no diagnostic gold standard for ASBO. In all the included studies the decision on whether the patient should undergo surgery was determined clinically by the surgeon if there were no improvements after a given time interval ranging from 4 hours to 5 days among the included studies. At the moment, despite the several classification attempts,\textsuperscript{40–42} there does not exist an intraoperative finding that could confirm or reject the surgical indication: the decision of the surgeon to operate or not is the gold standard, and this is a great source of bias. Moreover, all the included studies for the diagnostic value of WSCA were not double.
blinded and were of poor quality. Guidelines on ASBO\(^4\) recommend that conservative treatment, in the absence of strangulation or peritonitis, can be prolonged up to 72 hours but with a poor level of evidence (level 2b, recommendation grade C). Among the included studies, there is a great variability in the study’s protocols, as shown in Table 1. Because the conservative treatment (with or without WSCA) was considered failed after different time intervals ranging from 12 hours to 5 days, studies with restricted conservative treatment time could have overestimated the need for surgery in ASBO patients treated both conservatively or with WSCA.

Data about the length of stay in nonoperated patients and time to resolution also showed a significant statistical heterogeneity probably because of the difference in studies’ protocol.

Conclusions

This meta-analysis confirms that the administration of WSCA in ASBO is safe and has a therapeutic role, significantly reducing the need for surgery, the length of stay (both in nonoperated and in the overall patients), and the time of resolution. The administration of WSCA also has a diagnostic role in predicting the need for surgery; the WSCA test has a better diagnostic accuracy if it is taken after at least 8 hours from the administration of the contrast agent.

Acknowledgments

We would like to give a special thanks to Ms Franca Boschini, Papa Giovanni XXIII Hospital’s library, who helped us with the bibliographic research; to Chiara Falcone, Fondazione per la Ricerca Ospedale Maggiore-Bergamo, for the statistical revision; and to Josephine Napoli, University of Hawaii, Manoa, Hawaii, for the native English speaker language revision.

References


