

Systematic review and meta-analysis of the diagnostic and therapeutic role of water-soluble contrast agent in adhesive small bowel obstruction

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Background: This meta-analysis assessed the diagnostic and therapeutic role of water-soluble contrast agent (WSCA) in adhesive small bowel obstruction (SBO).

Methods: PubMed, Embase and Cochrane databases were searched systematically. The primary outcome in the diagnostic role of WSCA was its ability to predict the need for surgery. In the therapeutic role, the following were evaluated: resolution of SBO without surgery, time from admission to resolution, duration of hospital stay, complications and mortality. To assess the diagnostic role of WSCA, pooled estimates of sensitivity, specificity, positive and negative predictive values, and likelihood ratios were derived. For the therapeutic role of WSCA, weighted odds ratio (OR) and weighted mean difference (WMD) were obtained.

Results: Fourteen prospective studies were included. The appearance of contrast in the colon within 4–24 h after administration had a sensitivity of 96 per cent and specificity of 98 per cent in predicting resolution of SBO. WSCA administration was effective in reducing the need for surgery (OR 0.62; $P = 0.007$) and shortening hospital stay (WMD -1.87 days; $P < 0.001$) compared with conventional treatment.

Conclusion: Water-soluble contrast was effective in predicting the need for surgery in patients with adhesive SBO. In addition, it reduced the need for operation and shortened hospital stay.

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Introduction

Adhesive small bowel obstruction (SBO) is a major cause of postoperative morbidity. In North America, adhesiolysis is responsible for 300 000 hospital admissions annually, accounting for nearly 850 000 days of inpatient care¹.

Patients with signs of bowel strangulation, such as peritonitis, fever and leucocytosis, require emergency surgical intervention². For those without strangulation, however, the best way of predicting which patients can successfully undergo non-operative management has not yet been determined. A number of studies have investigated the diagnostic role of water-soluble contrast agent (WSCA)^{3–9}. It has been suggested that, if oral contrast reaches the colon within 4–24 h after administration, complete obstruction is unlikely and non-operative management is safe^{3,8}.

More recently, several randomized controlled trials (RCTs) have assessed the therapeutic role of WSCA, with conflicting conclusions^{7,8,10–16}. The purpose of this meta-analysis was to examine the diagnostic and therapeutic role of WSCA in the management of adhesive SBO.

Methods

Inclusion criteria

Prospective observational studies or clinical trials were included in the analysis of the diagnostic role of WSCA. Only clinical trials that randomized patients to conventional treatment (nil by mouth, nasogastric aspiration and intravenous fluid rehydration) or conventional treatment plus WSCA were included in the analysis

of the therapeutic role of WSCA. Studies on adhesive SBO, defined as admission to the hospital with abdominal pain, vomiting and abdominal distension with dilated small bowel loops and air–fluid levels on initial imaging, were included². There were no restrictions on age, sex or ethnicity for inclusion in the study.

Exclusion criteria

Case reports, editorial letters, reviews, guidelines and studies that analysed data collected retrospectively were excluded. Non-English-language publications were also excluded. In addition, studies on adhesive SBO that randomized patients to WSCA *versus* non-ionic low-osmolar contrast (OmnipaqueTM; GE Healthcare, Chalfont St Giles, UK) or barium contrast *versus* conventional treatment, or WSCA *versus* surgery were excluded. Data from duplicate studies were analysed once only. Studies of patients who had surgery within 4–6 weeks before the obstructive episode, those with signs of strangulation (peritonitis, fever, tachycardia and leucocytosis), or patients with abdominal malignancy or non-reducible abdominal hernia were also excluded.

Outcome measures

The primary outcome measure used to assess the diagnostic role of WSCA was its ability to predict the need for surgery in adhesive SBO. The primary outcome measures in assessing the therapeutic role of WSCA included at least one of the following: rate of resolution of SBO without surgery, time from admission to resolution of SBO, duration of hospital stay, complications (wound infection, intra-abdominal abscess, fistula, bowel strangulation and resection, thromboembolic events, pneumonia and sepsis) and mortality.

Search strategy

Two investigators independently searched the published literature in the databases PubMed (US National Library of Medicine, Bethesda, Maryland; January 1985 to July 2009), Embase (Reed Elsevier, Amsterdam, Netherlands; January 1985 to July 2009) and the Cochrane Library (2009, Issue 3) for reports of the use of WSCA in adhesive SBO. The search terms were ['adhesion'], ['small bowel obstruction' or 'intestinal obstruction'] and ['water-soluble contrast agent' or 'contrast media' or 'Gastrografin' or 'Urografin']. In PubMed, the 'related articles' algorithm was employed to identify additional articles. Bibliographies of original reports and reviews were scanned for additional references.

Study selection

Two reviewers independently selected studies based on titles and/or abstracts. Studies that met the defined inclusion criteria were selected for article review. If it was not clear from the abstract whether a study fulfilled the inclusion criteria, the full article was retrieved for further evaluation. Any discrepancy between the two reviewers was assessed by a third investigator and resolved by consensus.

Data extraction and quality assessment

The following data elements were extracted from each article: publication year, sample size, patient characteristics, type of intervention and outcomes. For studies that assessed the diagnostic role of WSCA, timing of radiography after contrast ingestion was also extracted. For studies that assessed the therapeutic role of WSCA, additional data extracted included whether the analysis had been done according to the intention-to-treat principle, adequacy of allocation concealment, whether blinded assessment of outcomes had been carried out, and explanation of withdrawals and dropouts. Data were abstracted by one investigator and validated by another.

The quality of each study was assessed independently by two reviewers. Any discrepancy was reviewed by a third investigator and resolved by consensus. For prospective observational studies included in the assessment of the diagnostic role of WSCA, study quality was evaluated using a questionnaire consisting of six components¹⁷: (1) Was the reference standard appropriate? (2) Were the test results and the reference standard independent of each other? (3) Were the readers of the results of the diagnostic test or the reference standard blinded? (4) Did the patient sample include an appropriate spectrum of mild and severe, and treated and untreated patients to whom the diagnostic tests were applied? (5) Were the reproducibility of the test result (precision) and its interpretation (observer variation) determined? (6) Were the methods for performing the test described in sufficient detail to permit replication?

For randomized trials included in the assessment of the diagnostic or therapeutic role of WSCA, study quality was assessed using the Jadad quality scale¹⁸.

Statistical analysis

The guidelines for the Quality of Reporting of Meta-analyses (QUORUM)¹⁹ were followed. Outcomes were synthesized statistically by Reviewer Manager version 5.0.21 (The Cochrane Collaboration, Oxford, UK). To assess the diagnostic role of WSCA, pooled estimates of sensitivity, specificity, positive and negative predictive

values (PPV and NPV respectively), and positive and negative likelihood ratios were derived. For the therapeutic role of WSCA, the rate of resolution of SBO without surgery, complications and mortality were analysed as dichotomous outcomes. The time from admission to resolution of SBO, and the duration of hospital stay were analysed as continuous outcomes. The effect measures estimated were weighted odds ratio (OR) for dichotomous outcomes and weighted mean difference (WMD) for continuous outcomes. DerSimonian and Laird random-effect models were used to derive random-effect estimates and 95 per cent confidence intervals (c.i.) for all outcomes²⁰.

The χ^2 test was used to assess statistical heterogeneity between studies, and the Higgins I^2 statistic to determine the percentage of the total variation across studies owing to heterogeneity. In case of clinical heterogeneity concerning study population ($P < 0.100$), pooling was not performed.

To assess the significance of the estimated effect measures, the location of the 95 per cent c.i. using an *a priori* established zone of clinical indifference was evaluated as follows: c.i. falling within the zone of indifference were considered as established evidence of no effect, whereas those outside the zone of indifference were considered as having an established effect; for c.i. that crossed into the zone of indifference, the effect of WSCA on outcome could not be established²¹. For ratio outcomes,

equivalence testing was carried out for c.i. between 0.9 and 1.1 as the zone of clinical indifference²¹. For mean outcomes, ± 1 day was used as the zone of clinical indifference.

Results

Study selection

After screening 345 abstracts, 60 studies were identified that fell within the scope of this review. After review of full-length manuscripts, 20 studies were found to be potentially eligible. Of these, six were subsequently excluded: two randomized patients to either Gastrografin[®] (Schering, Berlin, Germany) or Omnipaque[™]^{22,23}, one used barium as the contrast agent²⁴, one randomized patients to either Gastrografin[®] or surgery²⁵ and two were duplicate studies^{26,27}. Seven studies were included in the evaluation of the diagnostic role of WSCA³⁻⁹ and nine in the assessment of its therapeutic role^{7,8,10-16}. Two studies were analysed in both diagnostic and therapeutic categories^{7,8} (Fig. 1).

Study quality

Of the seven studies that examined the diagnostic role of WSCA, four were prospective observational studies^{3,5,6,9}

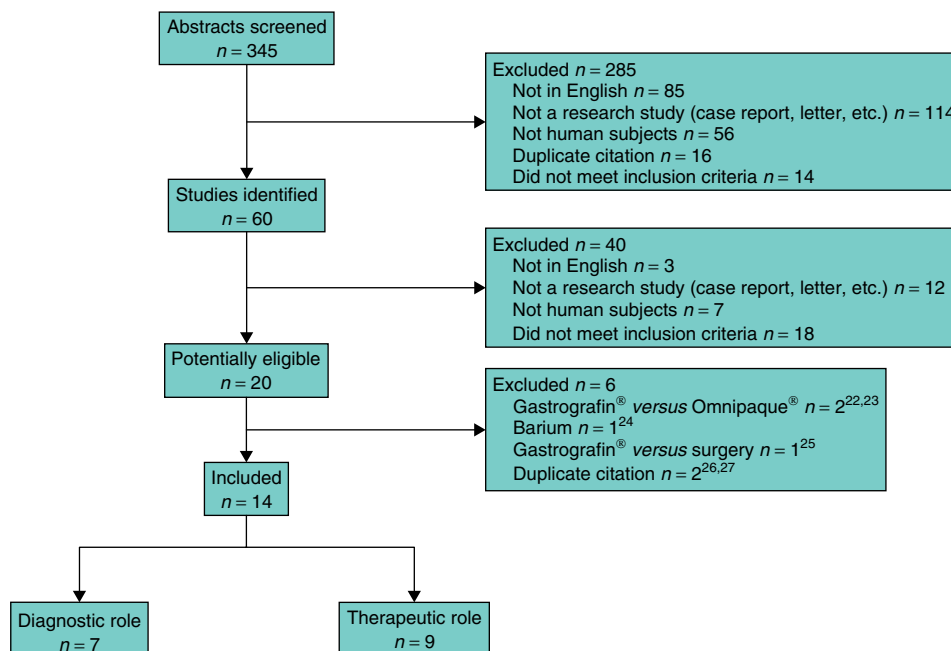


Fig. 1 Study outline. Studies by Biondo and colleagues⁷ and Farid and co-workers⁸ were analysed in both diagnostic and therapeutic roles

Table 1 Studies included in meta-analysis

Reference	Year	Role	Design	Quality	Randomization	Blinding	Withdrawals/ dropouts explained	Allocation concealment
Joyce <i>et al.</i> ³	1992	D	PO	2 (0/0/0/1/0/1)	—	—	—	—
Assalia <i>et al.</i> ¹⁶	1994	T	RCT	2	Unclear	S	Yes	Unclear
Chung <i>et al.</i> ⁵	1996	D	PO	2 (0/0/0/1/0/1)	—	—	—	—
Feigin <i>et al.</i> ¹²	1996	T	RCT	2	Unclear	S	Yes	Unclear
Chen <i>et al.</i> ⁹	1999	D	PO	3 (0/0/0/1/1/1)	—	—	—	—
Fevang <i>et al.</i> ¹³	2000	T	RCT	2	Unclear	S	Yes	Unclear
Onoue <i>et al.</i> ⁶	2002	D	PO	2 (0/0/0/1/0/1)	—	—	—	—
Biondo <i>et al.</i> ⁷	2003	D/T	RCT	2	Unclear	S	Yes	Unclear
Brochwicz-Lewinski <i>et al.</i> ⁴	2003	D	RCT	2	Year of birth	S	Yes	Yes
Lee <i>et al.</i> ¹⁵	2004	T	RCT	3	Computer-generated random number	S	Yes	Yes
Burge <i>et al.</i> ¹⁰	2005	T	RCT	5	Random number	D	Yes	Yes
Di Saverio <i>et al.</i> ¹¹	2008	T	RCT	3	Computer-generated random number	S	Yes	Yes
Kumar <i>et al.</i> ¹⁴	2009	T	RCT	2	Unclear	S	Yes	Unclear
Farid <i>et al.</i> ⁸	2009	D/T	RCT	2	Unclear	S	Yes	Unclear

For the therapeutic role of water-soluble contrast agent, study quality assessment was performed using the Jadad scale. D, diagnostic; T, therapeutic; PO, prospective observational; RCT, randomized controlled trial; S, single blind; D, double blind.

Table 2 Diagnostic role of water-soluble contrast agent: resolution of small bowel obstruction after contrast administration

Reference	<i>n</i>	Timing (h)*	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR ⁺	LR ⁻
3	127	4	112	0	2	13	98	100	100	87	—	0.02
5	45	4	31	1	2	11	94	92	97	85	11.27	0.07
9	116	8	74	0	8	34	90	100	100	81	—	0.10
6	97	24	90	2	1	4	99	67	98	80	2.45	0.04
4	24	4	16	0	0	8	100	100	100	100	—	—
7	44	24	39	0	0	5	100	100	100	100	—	—
8	55	24	7	0	1	47	88	100	100	98	—	0.12
Total	508		369	3	14	122	96 (95, 97)	98 (94, 99)	99 (98, 100)	90 (85, 95)	40.14 (13.12, 112.80)	0.04 (0.02, 0.07)

Values in parentheses are 95 per cent confidence intervals. *Interval between contrast administration and diagnostic radiography. TP, true positive; FP, false positive; FN, false negative; TN, true negative; PPV, positive predictive value; NPV, negative predictive value; LR⁺, positive likelihood ratio; LR⁻, negative likelihood ratio. Significance for testing heterogeneity among the pooled studies was $P = 0.536$ for sensitivity, $P = 0.373$ for specificity, $P = 0.867$ for PPV and $P = 0.519$ for NPV.

and three were RCTs^{4,7,8}. Of the prospective observational studies, one⁹ scored 3 of 6 points and three^{3,5,6} scored 2 in the quality assessment. All RCTs included in the diagnostic role of WSCA scored 2 of 5 points in the Jadad scale. There was no diagnostic standard against which WSCA was compared; patient outcome and need for surgery were regarded as the standard against which WSCA was evaluated.

Of the RCTs examining the therapeutic role of WSCA, the study by Burge and colleagues¹⁰, scored a maximum 5 points in the Jadad scale. It was double blinded with a clear description of randomization methods and allocation concealment. Two studies scored 3^{11,15} and six scored 2^{7,8,12–14,16}; none of these was described as double blinded, and randomization methods and allocation concealment

were unclear. Withdrawals and dropouts were described in all studies and analysis was on the basis of intention to treat (Table 1).

Study characteristics

Studies examining the diagnostic role of WSCA employed 50–100 ml Gastrografin^{®3–8} or 40 ml Urografin[®] (Schering)⁹. Abdominal plain radiographs were obtained after 4 h^{3–5}, 8 h⁹ or 24 h^{6–8}. Patients were considered to have partial SBO if the contrast reached the colon; if not, they were considered to have complete SBO. The decision whether or not to operate was based on the radiological findings.

Table 3 Comparison of 4–8-h and 24-h timing of radiography after contrast administration

Timing	n	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR ⁺	LR ⁻
4–8 h ^{3–5,9}	312	233	1	12	66	95 (92, 98)	99 (96, 100)	100 (99, 100)	85 (78, 93)	68.47 (9.78, 479.62)	0.05 (0.03, 0.09)
24 h ^{6–8}	196	136	2	2	56	99 (97, 100)	97 (91, 100)	99 (97, 100)	97 (91, 100)	26.12 (6.71, 101.72)	0.02 (0.01, 0.06)

Values in parentheses are 95 per cent confidence intervals. TP, true positive; FP, false positive; FN, false negative; TN, true negative; PPV, positive predictive value; NPV, negative predictive value; LR⁺, positive likelihood ratio; LR⁻, negative likelihood ratio.

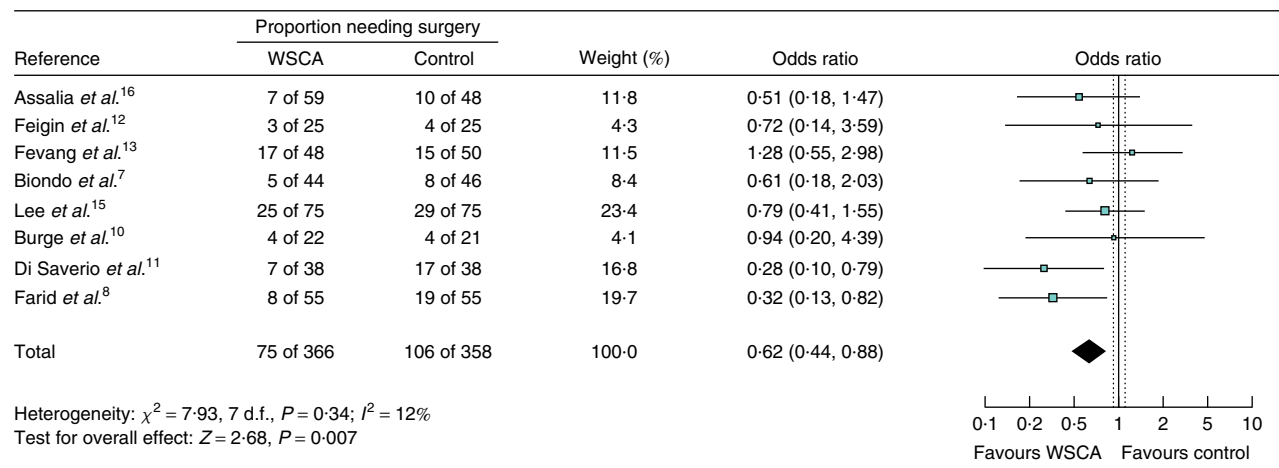


Fig. 2 Effect of water-soluble contrast agent (WSCA) on the need for surgery in patients with adhesive small bowel obstruction. Odds ratios are shown with 95 per cent confidence intervals. Dotted lines indicate the zone of clinical indifference

Studies that examined the therapeutic role of WSCA randomized patients to conventional treatment or conventional treatment plus 100 ml Gastrografin[®]^{7,8,11–14,16} or 50–100 ml Urografin[®]¹⁵, orally or via a nasogastric tube. Burge and colleagues¹⁰ randomized patients to Gastrografin[®] or placebo via a nasogastric tube.

Diagnostic role of water-soluble contrast agent

Seven studies with a total of 508 patients were included^{3–9}. The presence of WSCA in the colon predicted resolution of SBO with 96 (95 per cent c.i. 95 to 97) per cent sensitivity and 98 (94 to 99) per cent specificity. PPV and NPV were 99 (98 to 100) and 90 (85 to 95) per cent respectively. The positive and negative likelihood ratios were 40.14 (13.12 to 112.80) and 0.04 (0.02 to 0.07) respectively (Table 2). There were no differences in sensitivity, specificity, PPV, NPV, and positive and negative likelihood ratios where the timing of radiography was 4–8 h or 24 h (Table 3).

Therapeutic role of water-soluble contrast agent

Resolution of small bowel obstruction without surgery

All nine studies with a total of 765 patients examined the impact of WSCA on the resolution of adhesive SBO^{7,8,10–16}. One study was excluded from meta-analysis because of a protocol violation¹⁴; seven patients who had persistent signs of SBO after 48 h of conservative treatment were not operated on, contrary to the study protocol. A significant reduction in the need for surgery was observed with the administration of WSCA compared with conventional treatment: 76 (20.8 per cent) of 366 *versus* 106 (29.6 per cent) of 358 (pooled OR 0.62, 95 per cent c.i. 0.44 to 0.88; $P = 0.007$). The test for heterogeneity indicated that the studies were amenable to pooling ($P = 0.34$) (Fig. 2). The 95 per cent c.i. of the pooled OR was outside the zone of clinical indifference, thus establishing that WSCA had a significant effect with respect to this outcome measure.

Time from admission to resolution of small bowel obstruction

Five studies reported the time between admission and resolution of obstruction (defined as time to the first

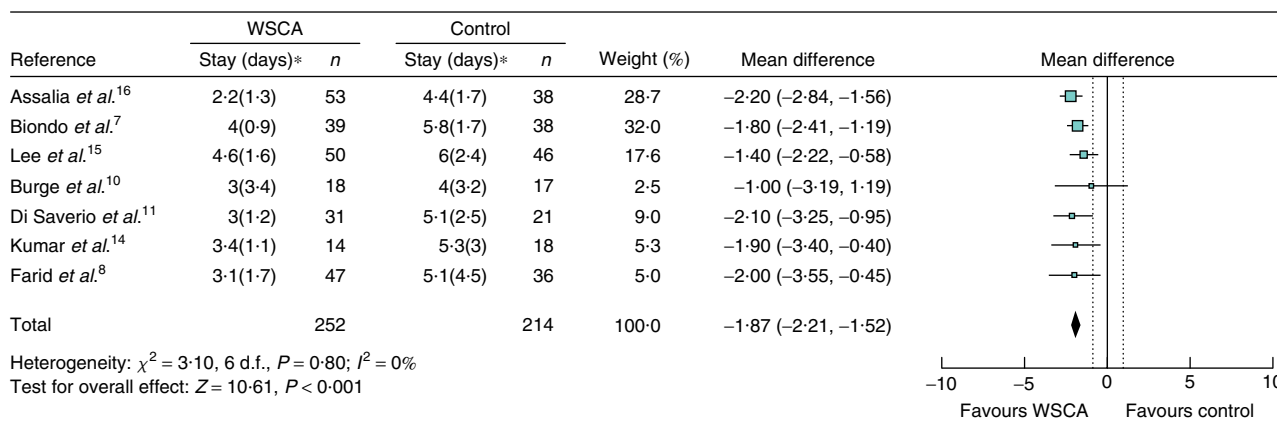


Fig. 3 Effect of water-soluble contrast agent (WSCA) on duration of hospital stay in patients with adhesive small bowel obstruction. *Values are mean(s.d.). Mean differences are shown with 95 per cent confidence intervals. Dotted lines indicate the zone of clinical indifference

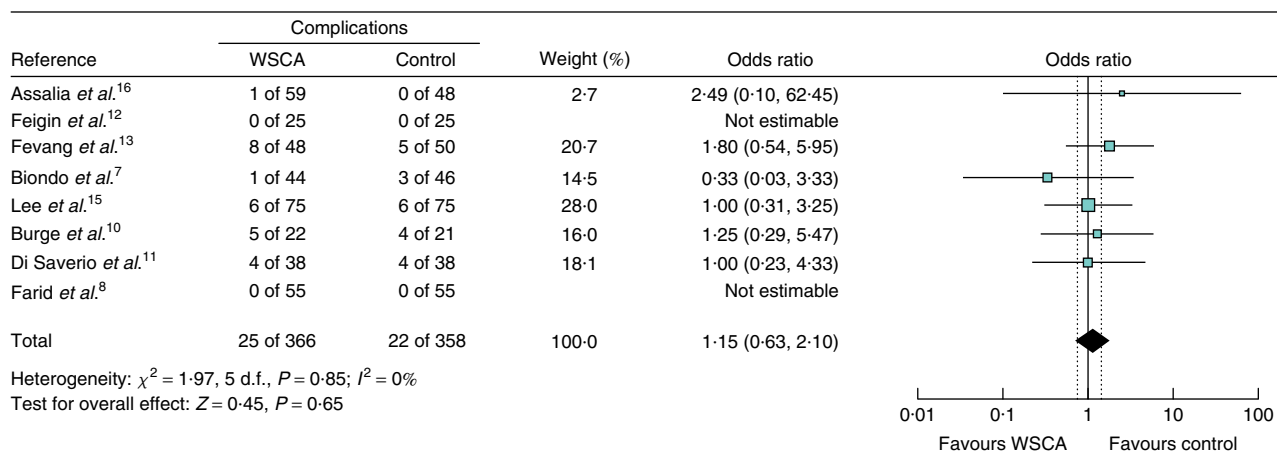


Fig. 4 Effect of water-soluble contrast agent (WSCA) on rate of complications in patients with adhesive small bowel obstruction. Odds ratios are shown with 95 per cent confidence intervals. Dotted lines indicate the zone of clinical indifference

stool passage)^{7,8,10,11,16}. All reported faster resolution of obstruction after administration of WSCA with a pooled WMD of -19.43 (95 per cent c.i. -22.71 to -16.15) h. However, there was significant heterogeneity between the studies and meta-analysis was not therefore performed ($P < 0.001$).

Duration of hospital stay

All nine studies examined this outcome^{7,8,10-16}. The studies by Feigin and co-workers¹² and Fevang *et al.*¹³ did not report standard deviation and were excluded from meta-analysis.

When the results were pooled, patients who had WSCA had a shorter hospital stay, with a WMD of -1.87 (95 per cent c.i. -2.21 to 1.52) days ($P < 0.001$).

No heterogeneity was detected ($P = 0.80$) (Fig. 3). The 95 per cent c.i. of the pooled WMD was outside the zone of clinical indifference, thus establishing that WSCA had significantly reduced hospital stay.

Complications

Eight studies reported complications^{7,8,10-13,15,16}. There were no complications related directly to the administration of water-soluble contrast. The overall rate of complications was 25 (6.8 per cent) of 366 for the WSCA group and 22 (6.1 per cent) of 358 for the conventional management group. The pooled OR was 1.15 (95 per cent c.i. 0.63 to 2.10; $P = 0.65$) (Fig. 4). As the 95 per cent c.i. for the pooled OR crossed the zone of indifference, the difference between WSCA and conventional management

with respect to the complication rate could not be established. More studies and/or more patients are needed for a definitive conclusion.

Mortality

Mortality was reported in seven studies^{7,8,10,12,13,15,16}. The mortality rate was seven (2.1 per cent) of 328 after WSCA and five (1.6 per cent) of 320 for the conventional management group. The pooled OR was 1.37 (95 per cent c.i. 0.43 to 4.38; $P = 0.59$). Because the 95 per cent c.i. for the pooled OR crossed the zone of indifference, no effect of WSCA on mortality rate could be established.

Discussion

For patients presenting with SBO without signs of strangulation, there is good evidence to support non-operative management. Level I data have shown that conservative treatment can be successful in up to 90 per cent of patients without peritonitis¹⁶. Less clear, however, is the way to predict between progression to strangulation or resolution of SBO. Several studies have investigated the diagnostic role of WSCA³⁻⁹.

This meta-analysis supports the use of water-soluble contrast for predicting the need for surgery in patients with SBO. If the contrast reaches the colon within 4–24 h after administration, obstruction will resolve without operation in 99 per cent of patients. On the other hand, if contrast does not reach the colon, the obstruction is unlikely to resolve without operation in 90 per cent of patients. The pooled sensitivity and specificity approached 100 per cent, indicating that WSCA is a very accurate predictor of non-operative resolution. Regarding the optimal cut-off for contrast reaching the colon, there appears to be no advantage in waiting longer than 8 h as the sensitivity, specificity, PPV and NPV were similar at 4–8 h and 24 h, although these were only two false negatives among 196 patients who had a 24-h delay, compared with 12 of 312 patients with a delay of 4–8 h.

Considerable controversy still exists regarding the therapeutic role of WSCA, specifically whether it can reduce the need for operative intervention. Assalia and colleagues¹⁶, in their study of 99 patients with adhesive SBO, showed that there was a lower operation rate in patients who had oral contrast. Similar results were produced by Lee and co-workers¹⁵. Yet when the results of these two studies were pooled with the findings of four additional RCTs in a meta-analysis by Abbas *et al.*²⁸, WSCA did not reduce the need for surgery, although it did significantly reduce the duration of hospital stay. The present review included three additional RCTs in the meta-analysis of therapeutic role of WSCA^{8,11,14}. The result

was a significant reduction in the need for surgery (from 29.6 to 20.8 per cent; $P = 0.007$) and hospital stay (WMD -1.87 days; $P < 0.001$) after the administration of WSCA. The analysis of duration of hospital stay included only patients who did not require operation. Therefore, the bias generated by inclusion of patients who required surgery was avoided. There are an estimated 300 000 hospital admissions for adhesiolysis-related procedures every year in North America, accounting for 850 000 days of inpatient care and an estimated mean hospital expenditure per day of US \$1266¹. The routine use of WSCA as a therapeutic agent could translate into a reduction of 561 000 days of inpatient care and approximately US \$710.2 million in savings.

The present review did not demonstrate any substantial improvement in the time to resolution of obstruction because the studies were not amenable to pooling owing to significant heterogeneity.

With respect to complication and mortality outcomes, using 0.9–1.1 as the zone of indifference, it was not possible to establish a difference between WSCA and conventional treatment. However, although potential complications related to the use of WSCA such as pneumonia, renal failure and anaphylaxis have been reported^{29,30}, no significant complications were seen in the present review.

This review had some significant limitations. Seven studies³⁻⁹ were included in the analysis of the diagnostic role of WSCA, only three of which were RCTs^{4,7,8}. None was described as double blinded and none had a diagnostic standard against which WSCA could be evaluated. The eventual patient outcome (need for surgery and findings at laparotomy or non-operative resolution) was regarded as the standard against which the accuracy of WSCA as a diagnostic tool was evaluated.

To assess the therapeutic role of WSCA, nine RCTs were included^{7,8,10-16}, but only one was described as double blind¹⁰. In this study patients had no further radiological investigations after randomization as abdominal radiography would have revealed to which treatment arm the patient had been randomized. In the other eight randomized trials the decision whether or not to operate could have been influenced by the presence or absence of contrast on follow-up radiographs.

The results of this meta-analysis support both the diagnostic and therapeutic use of water-soluble contrast in patients with adhesive SBO. The presence of contrast in the colon within 4–24 h is predictive of resolution of obstruction. For patients undergoing non-operative management, water-soluble contrast decreased the need for surgery and reduced the length of hospital stay.

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The diagnostic value of silver stool (Thomas' sign)

Heneage Ogilvie first described Thomas' sign in 1955 in the Medical Memoranda of the *BMJ* but unfortunately did not publish a picture. He selflessly admitted that his pathology colleague, Dr Thomas, whom this sign is named after, had pointed out earlier that patients with cancers involving the Ampulla of Vater sometimes pass "silver stools" i.e. motions having the colour of oxidized silver or aluminium paint. The silver stool is a combination of the white stool of obstructive jaundice and the black stool of melaena. He concluded that Thomas' sign is diagnostic of cancer of the Ampulla of Vater, and would enable this eminently curable lesion to be recognized at an early and operable stage.



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