Benefits and harms of adhesion barriers for abdominal surgery: a systematic review and meta-analysis

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CRD summary
This review assessed the benefits and harms of four adhesion barriers for abdominal surgery and concluded that evidence suggests that oxidised regenerated cellulose and hyaluronate carboxymethyl cellulose reduce adhesion formation. This was a well conducted review but the evidence base was limited in size and by heterogeneity, which means that the reliability of the findings is unclear.

Authors' objectives
To assess the benefits and harms of four adhesion barriers for abdominal surgery.

Searching
PubMed, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched up to February 2013 without language restrictions. Search strategies were reported. Three databases were searched for grey literature and two trial registries were searched for unpublished studies. Reference lists of identified trials were searched manually.

Study selection
Eligible studies were randomised controlled trials (RCTs) that assessed the benefits and harms of four clinically approved adhesion barriers (hyaluronate carboxymethylcellulose, oxidised regenerated cellulose, icodextrin 4% solution and polyethylene glycol) in patients undergoing any type of abdominal/intraperitoneal surgery. Eligible trials had to include a control group (patients with no adhesion barrier applied). The primary outcome of interest was reoperation for adhesive small bowel obstruction during post-operative follow-up. Secondary outcomes were also stated.

Most trials were of gynaecological surgery, followed by colorectal surgery and one trial each for gastric, hepatic, general paediatric and small bowel obstruction surgery. Nineteen RCTs were multicentre trials. Different surgical procedures (including open or laparoscopic techniques) were performed in patients with various underlying conditions. For some gynaecological surgery trials, patients acted as their own controls. Some trials used Ringer's lactate solution as placebo.

Two reviewers independently screened studies for inclusion; discrepancies were resolved through discussion.

Assessment of study quality
Trial quality was assessed according to the six Cochrane risk of bias criteria. Trials at low overall risk of bias met all six criteria, trials that failed to meet one or more of the six criteria were considered to have unclear or high risk of bias.

Risk of random error and external validity were assessed using Cochrane methods and GRADE approach (as defined in the review).

It seemed that two reviewers independently assessed trial quality; discrepancies were resolved through discussion.

Data extraction
Dichotomous outcome data were extracted to calculate relative risks and 95% confidence intervals. Continuous data were extracted to calculate mean differences and 95% confidence intervals.

It appeared that two reviewers independently extracted outcome data; discrepancies were resolved through discussion.

Methods of synthesis
Meta-analyses were performed on trials that reported complete data for the pre-defined outcomes. Trials that reported on other outcomes or reported incomplete outcome data were mentioned only in tables.
A fixed-effect model (or random-effects where there was evidence of statistical heterogeneity) was used to combine outcome data by type of adhesion barrier. Mantel-Haenszel methods were used to calculate relative risks and 95% confidence intervals. Inverse-variance methods were used to calculate standardised mean differences and 95% confidence intervals. Numbers needed to treat were calculated.

Statistical heterogeneity was assessed using Cochran’s Q test and the $I^2$ statistic. Subgroup analyses were performed based on risk of bias, trial funding and clinical heterogeneity.

Publication bias was assessed using funnel plots.

**Results of the review**

Thirty-three RCTs (5,381 patients) were included in the review and 28 RCTs (5,191 patients) were included in the meta-analysis. Four RCTs had a low risk of bias and 16 RCTs (57%) were industry sponsored. The risk of random error was small for adhesion score in eight RCTs and overall incidence of small bowel obstruction by any cause in one trial.

**Oxidised regenerated cellulose:** There were 11 RCTs in gynaecological surgery (two at low risk of bias). There was no evidence on the primary outcome, reoperations for adhesive small bowel obstruction. For secondary outcomes, oxidised regenerated cellulose statistically significantly reduced the incidence of adhesions (RR 0.51, 95% CI 0.31 to 0.86; NNT=6; three RCTs).

**Hyaluronate carboxymethyl cellulose:** Nine RCTs included six in colorectal surgery and one each in gynaecological, hepatic and gastric surgery (one at low risk of bias). Hyaluronate carboxymethylcellulose statistically significantly reduced incidence of reoperations for adhesive small bowel obstruction (RR 0.49, 95% CI 0.28 to 0.88; five RCTs); separate analyses showed that the differences were not statistically significant for the single trials in hepatic and gastric surgery.

**Icodextrin:** Four RCTs showed no statistically significant differences between treatment groups for reoperation for adhesive small bowel obstruction. There was insufficient evidence to assess the effects of icodextrin on operation time. Icodextrin statistically significantly reduced the incidence of small bowel obstruction (RR 0.20, 95% CI 0.04 to 0.88; one RCT).

**Polyethylene glycol:** Four RCTs (one at low risk of bias) showed no evidence on the primary outcome, reoperations for adhesive small bowel obstruction. There were no statistically significant differences between treatment groups for the incidence of adhesions. Polyethylene glycol showed a beneficial effect on operation time in one trial at low risk of bias in colorectal surgery (SMD -0.84, 95% CI -1.49 to -0.19).

There were no statistically significant differences between any adhesion barrier and controls in the incidence of serious adverse events. Other results were reported in the review, including results from subgroup analyses and findings from trials not included in the meta-analyses.

There was no evidence of publication bias using funnel plots.

**Authors’ conclusions**

Sufficient evidence exists to suggest that oxidised regenerated cellulose and hyaluronate carboxymethyl cellulose reduce adhesion formation.

**CRD commentary**

The review question and inclusion criteria were broad but clearly stated. There was a comprehensive literature search to identify published and unpublished data. The authors formally assessed publication bias for individual outcomes but the small number of trials precluded meaningful interpretation of the funnel plots. Trial quality was assessed using appropriate criteria but only a small proportion were at low risk of bias. It appeared that each stage of the review process was performed in duplicate to minimise bias.

Study and patient details were somewhat limited. The authors acknowledged differences in types of barriers used, clinical heterogeneity and differences in outcome parameters reported. Appropriate methods were used to explore the evidence. The authors acknowledged that despite the large number of trials, outcome comparisons included only a few
This was a well conducted review and the authors’ conclusions reflect the evidence. However, the evidence base was limited in quality, size and by heterogeneity and this makes the reliability of the findings and the authors’ recommendations for practice unclear.

**Implications of the review for practice and research**

**Practice:** The authors stated that the results could be used to develop guidelines for the use of barriers to prevent adhesion-related complications and that routine use of hyaluronate carboxymethyl cellulose was warranted in high risk surgeries for bowel obstruction on the basis of their safety and efficacy results. They also stated that although oxidised regenerated cellulose reduced adhesion formation in fertility surgery, the implications for clinical practice were unclear as none of the trials assessed pregnancy rate.

**Research:** The authors stated that future studies should assess whether oxidised regenerated cellulose reduced reoperation-associated complications.

**Funding**

No external funding.

**Bibliographic details**


**PubMedID**

24075279

**DOI**

10.1016/S0140-6736(13)61687-6

**Original Paper URL**


**Indexing Status**

Subject indexing assigned by NLM

**MeSH**

Abdomen /surgery; Carboxymethylcellulose Sodium /therapeutic use; Cellulose, Oxidized /therapeutic use; Glucans /therapeutic use; Glucose /therapeutic use; Humans; Polyethylene Glycols /therapeutic use; Postoperative Complications /prevention & control; Randomized Controlled Trials as Topic /methods; Tissue Adhesions /prevention & control; Treatment Outcome

**AccessionNumber**

12013055949

**Date bibliographic record published**

27/09/2013

**Date abstract record published**

03/10/2013

**Record Status**

This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.