International Platform of Registered Systematic Review and Meta-analysis Protocols

INPLASY

Animal models of postoperative adhesions formation for testing of anti-adhesive agents: a systematic review and meta-analysis of 865 studies

INPLASY202620015
doi: 10.37766/inplasy2026.2.0015
Received: 4 February 2026
Published: 4 February 2026

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ADMINISTRATIVE INFORMATION

Support - No funding was received for this study.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202620015

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 4 February 2026 and was last updated on 4 February 2026.

INTRODUCTION

Review question / Objective Postoperative adhesions are the most common cause for long-term complications in abdominal surgery. Numerous animal studies are performed yearly with novel anti-adhesive agents. Most of these agents never progress to the stage of clinical studies. This systematic review aimed to critically evaluate model characteristics, outcome measures and intervention modifications in animal studies of postoperative adhesion formation to identify factors that influence internal validity and translational value.

Rationale Postoperative adhesions remain one of the most frequent and clinically challenging complications following abdominal and pelvic surgery, occurring in up to 93% of patients after open procedures and up to 60% after laparoscopic surgery. Adhesions result from peritoneal injury and aberrant wound healing and are associated with substantial morbidity, including adhesive small bowel obstruction, chronic abdominal pain, infertility, and increased complexity and risk during repeat surgery. Adhesion-related complications account for a considerable proportion of surgical readmissions and healthcare utilization.

Despite their clinical impact, effective prevention of postoperative adhesions remains limited. Surgical adhesiolysis is often required but is associated with a high risk of adhesion reformation, underscoring the need for effective adjunctive anti-adhesion strategies. Several anti-adhesion barriers, including oxidized regenerated cellulose, hyaluronic acid–carboxymethylcellulose membranes, polyethylene glycol hydrogels, and icodextrin solutions, have been evaluated in clinical trials. However, these agents demonstrate variable and often modest clinical effectiveness and present limitations related to handling, applicability, and cost.

Preclinical animal studies form the foundation for the development of anti-adhesion agents, yet

translation from animal models to clinically meaningful benefit has been inconsistent. Although many animal studies report substantial reductions in adhesion scores, corresponding clinical trials frequently fail to demonstrate comparable improvements in patient-centered outcomes. Moreover, numerous interventions showing promising preclinical results never progress to human studies. This translational gap is likely driven by substantial methodological heterogeneity in animal experiments, including variability in injury models, adhesion scoring systems, study design, and outcome reporting, as well as limitations in internal validity and risk of bias.

A comprehensive synthesis of preclinical adhesion research is therefore warranted. This systematic review and meta-analysis aims to evaluate six decades of animal studies on postoperative adhesion prevention, assess methodological quality and risk of bias, quantify baseline adhesion incidence in control groups, and estimate the effectiveness of commonly used anti-adhesion barriers. By identifying determinants of reproducibility and translational relevance, this study seeks to inform evidence-based recommendations to improve the design, reporting, and translational value of future preclinical adhesion research.

Condition being studied Adhesion formation and reformation.

METHODS

Search strategy A systematic literature search was defined to identify animal studies investigating peritoneal adhesion formation. The project was conducted over a longer period of time due to the high number of studies still being published, with the latest update performed October 2024. The search strategy consisted of the same three main components: (1) an anti-adhesion intervention component, (2) a component with terms related to intra-peritoneal surgery and (3) an animal model component (validated animal model filter, created by van der Mierden et al [18]). MesH and Emtree terms were combined with title- and abstract key words in the search string. Studies were identified from PubMed and EMBASE until 13-10-2024.

Participant or population Inclusion criteria were a) studies with a model whereby an injury is performed on the peritoneum, similar for each group, followed by an intervention (gas/gel/film etc.), after which intra-peritoneal adhesions are measured in the abdomen; b) adhesion formation model: model as described above in which the animals are sacrificed after the standard injury. Exclusion criteria were a) human clinical studies or in vitro studies; b) not an original full paper original data; c) Chinese, Arabic and Cyrillic papers; d) studies where animals were sacrificed at different time points between the intervention and control group; e) studies with no numerical or graphical data; f) studies with no formation model; g) studies with groups of animals that were not treated according to the same protocol or adhesion formation model; h) duplicate data.

Intervention Not applicable.

Comparator Not applicable.

Study designs to be included All animals used in experiment meeting our inclusion criteria.

Eligibility criteria Inclusion criteria were a) studies with a model whereby an injury is performed on the peritoneum, similar for each group, followed by an intervention (gas/gel/film etc.), after which intra-peritoneal adhesions are measured in the abdomen; b) adhesion formation model: model as described above in which the animals are sacrificed after the standard injury. Exclusion criteria were a) human clinical studies or in vitro studies; b) not an original full paper original data; c) Chinese, Arabic and Cyrillic papers; d) studies where animals were sacrificed at different time points between the intervention and control group; e) studies with no numerical or graphical data; f) studies with no formation model; g) studies with groups of animals that were not treated according to the same protocol or adhesion formation model; h) duplicate data.

Information sources Studies were identified from PubMed and EMBASE until 13-10-2024.

Main outcome(s) The primary outcome was adhesion incidence. Secondary outcomes are adhesion score, planimetrical data and number of adhesions against ischemic buttons. Additional data collected included experimental model characteristics, such as animal species and sex, adhesion model, abrasion method, day of sacrifice and control group data. The rest of the outcomes can be found in the appendix.

Additional outcome(s) Not applicable.

Data management A Microsoft Access database was built for data extraction and validation.

Quality assessment / Risk of bias analysis For quality assessment of the studies, we created a 4-

point scoring system to grade the risk of bias in the studies based on the following items: a) adequate allocation sequence; b) blinding of treatment allocation; c) blinded outcome assessment; d) incomplete data adequately addressed [19-20]. Each of these were answered as 'yes', 'no' or 'unclear'. Descriptions can be found in Supplementary information C. Subsequently, these items were scored as 'high', 'unclear' or 'low' risk of bias. Here, 'high' risk of bias means that the study did not perform risk mitigation on that item, 'unclear' risk of bias means that it is unclear whether the study performed risk mitigation and 'low' risk of bias means that it clearly did.

Reporting quality was assessed by calculating a custom score for every individual study. This score is based on methods used in previous systematic reviews of animal studies and the ARRIVE guidelines, tailored to experimental investigations of adhesion formation [21-25]. The score consisted of items addressing points of experimental design (randomization and blinding of treatment allocation and outcome assessment), animal characteristics (gender, weight, sample size, housing, feeding), experimental procedures (surgical technique, abrasion method, post-operative analgesia, antibiotics) and ethical considerations (ethical committee approval, humane endpoint, incomplete outcome data). The study could score '1' point for each item, if that item was reported and '0' points for not reported or not applicable. The maximum possible score was 15 points.

Strategy of data synthesis All data will be analyzed and presented graphically using R statistical software. Study characteristics, methodological features and outcome data will be summarized using descriptive statistics. Categorical variables will be reported as frequencies and proportions, while continuous variables will be summarized using means, medians and standard deviations, as appropriate.

Temporal trends in continuous outcomes will be examined using Pearson's correlation coefficient. Trends in binary outcomes will be assessed using logistic regression models, with results reported as odds ratios (ORs) and corresponding 95% confidence intervals (CIs). Statistical significance will be defined as a two-sided p-value < 0.05.

For the assessment of internal validity of animal adhesion models, a single-arm meta-analysis will be performed including negative control groups only (no treatment, placebo, saline, or Ringer's lactate). Adhesion incidence will be pooled using a random-effects meta-analysis with restricted maximum likelihood (REML) estimation on logit-transformed proportions. A continuity correction will be applied to studies reporting 0% or 100% incidence. Between-study heterogeneity will be quantified using Cochran's Q, τ^2 and I^2 statistics. Results will be visualized using binned forest (timber) plots and funnel plots.

To assess translational validity, intervention studies evaluating commonly used anti-adhesion barriers will be analyzed. Pooled relative risks (RRs) of adhesion formation will be calculated using random-effects meta-analyses with REML estimation. When multiple control groups are reported within a study, the control group with the highest adhesion incidence will be selected as reference. Heterogeneity will be assessed using Q, τ^2 and I^2 statistics. Potential publication bias will be evaluated using funnel plots and Egger's regression test. All analyses will be conducted using appropriate meta-analysis packages in R.

Subgroup analysis Subgroup analyses will be conducted to explore sources of heterogeneity in adhesion incidence and intervention effects. Prespecified subgroup analyses will be based on study-level and model-related characteristics, including animal species, adhesion induction method, surgical approach, anatomical site, sample size, and type of adhesion scoring system. Subgroup analyses will be performed using random-effects models with restricted maximum likelihood estimation. Differences between subgroups will be formally tested using univariate mixed-effects meta-regression models, and statistical significance will be evaluated using omnibus Q statistics. Subgroups with very small numbers of studies will be combined into an "Other" category to avoid unstable estimates. Studies with missing subgroup information will be excluded from the respective analyses.

Sensitivity analysis Sensitivity analyses will be performed to assess the robustness of the findings under alternative analytical assumptions. For the single-arm meta-analysis of adhesion incidence, sensitivity analyses will include applying a smaller continuity correction, excluding studies reporting 0% or 100% incidence, and selecting alternative control groups when multiple negative controls are available. For intervention analyses, sensitivity analyses will include selecting the lowest-incidence control group when multiple controls are reported and retaining only one intervention arm per study to reduce within-study clustering. The consistency of pooled estimates and heterogeneity measures across sensitivity analyses will be evaluated.

Language restriction English. Studies published in languages using Chinese, Arabic or Cyrillic scripts will be excluded due to lack of translation resources.

Country(ies) involved Belgium, The Netherlands.

Keywords Animal model; experimental design; tissue adhesions; Seprafilm; Interceed; surgery.

Dissemination plans The results of this systematic review and meta-analysis will be disseminated through publication in a peer-reviewed scientific journal and presentation at relevant national and international scientific conferences. The findings may also inform future preclinical research design and translational strategies.

Contributions of each author

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