Barrier materials for prevention of surgical adhesions: systematic review

Michael Gerard Waldron*, Conor Judge, Laura Farina, Aoife O'Shaughnessy and Martin O'Halloran

Translational Medical Device Laboratory National University of Ireland Galway, Galway, Ireland

*Correspondence to: Michael Gerard Waldron, Translational Medical Device Lab, Galway University Hospital, Newcastle Road, Galway, Ireland H91YR71 (e-mail: waldronucc@gmail.com)

Abstract

Background: Postoperative surgical adhesions constitute a major health burden internationally. A wide range of materials have been evaluated, but despite constructive efforts and the obvious necessity, there remains no specific barrier widely utilized to prevent postoperative adhesion formation. The aim of this study was to highlight and characterize materials used for prevention of postoperative surgical adhesions in both animal and human studies.

Methods: A systematic review was performed of all original research articles presenting data related to the prevention of postoperative adhesions using a barrier agent. All available observational studies and randomized trials using animal models or human participants were included, with no restrictions related to type of surgery. PubMed and Embase databases were searched using key terms from inception to August 2019. Standardized data collection forms were used to extract details for each study and assess desirable characteristics of each barrier and success in animal and/or human studies.

Results: A total of 185 articles were identified for inclusion in the review, with a total of 67 unique adhesion barrier agents (37 natural and 30 synthetic materials). Desirable barrier characteristics of an ideal barrier were identified on review of the literature. Ten barriers achieved the primary outcome of reducing the incidence of postoperative adhesions in animal studies followed with positive outputs in human participants. A further 48 materials had successful results from animal studies, but with no human study performed to date.

Discussion: Multiple barriers showed promise in animal studies, with several progressing to success, and fulfillment of desirable qualities, in human trials. No barrier is currently utilized commonly worldwide, but potential barriers have been identified to reduce the burden of postoperative adhesions and associated sequelae.

Introduction

Postoperative adhesions are scar tissue resulting from trauma of the peritoneal surface and have been documented in 79–90 per cent of individuals after open abdominal or pelvic surgery1–3. Postoperative adhesions are a leading cause of long-term morbidity following surgery4–6, with 27 per cent of patients being re-admitted following abdominal or pelvic surgery for disorders directly related to adhesions within 5 years3. Adhesions are associated with significant morbidity including small bowel obstruction (SBO), chronic pain, infertility, and requirement for a repeat procedure4–6, in addition to the socioeconomic implications7, including the significant financial burden with cumulative direct hospital care costs estimated at 2.3 billion dollars in 2011 in the USA alone8. Postoperative adhesions are characteristic difficulties to treat4, with the severity of formed adhesions and rate of iatrogenic bowel injury during adhesiolysis increasing exponentially with each additional operation7. Adhesive disease has no specific laboratory or radiological finding that are currently in use in common practice, although cine-MRI has shown potential in providing information related to extent, location, and strength of intra-abdominal adhesions9. Prevention or reduction of adhesion formation is a key priority.

A wide range of materials have been evaluated in animal and/or human studies as physical barriers to separate the wound from surrounding tissue in an effort to reduce the rate and severity of postoperative adhesions3,9,11,12; however, despite constructive efforts and the obvious necessity, no specific barrier remains widely utilized in clinical practice to prevent postoperative adhesion formation13. Animal studies remain critical to advancing clinical research, as they are biologically similar to humans, susceptible to similar health issues, and have a shorter life cycle allowing testing over a life span and successive generation14. However, animal welfare and economic funding must be central to any decision to progress with research. The European Union (EU) Directive 2010/63/EU on the protection of animal welfare was produced to harmonize standards of animal research across the EU15. Research using animal models must be carefully designed and relevant, with animal welfare remaining a central concern14. Furthermore, a comprehensive listing of studied barriers in animal and human studies is lacking in systematic reviews to date9,11,12, prompting the need to investigate the breadth of barriers previously published, including those whose investigation was halted after the animal investigation phase.

The aim of this study was to characterize the strengths and shortcomings of each barrier, comparing tissue adherence...
Methods
Selection criteria
A systematic review was performed according to published guidelines from the Cochrane Collaboration16 and is reported according to the PRISMA guidelines17. A study protocol (Appendix S1) was developed to include original research articles presenting data related to the prevention of postoperative adhesions using a barrier agent. Studies involving physical barrier agents and non-physical barriers were included. Studies of non-resorbable barriers (such as polytetrafluoroethylene), where a further interventional procedure would be necessary for removal, were excluded. All published observational studies and randomized trials were included if they met the following criteria: contained original data, used animal or human participants, or evaluated an adhesion barrier(s) in abdominal and/or pelvic adhesions. No date restrictions were applied and there was no restriction on the type of surgery.

Search strategy
A systematic search of the literature was performed in two databases (PubMed and Embase). The databases were searched from inception to August 2019. The search was performed using key terms: (Surg*(Title/Abstract)) AND (adhesion*(Title/Abstract)) AND (prevent*(Title/Abstract)) AND (barrier*(Title/Abstract)). Two reviewers (M.W. and C.J.) independently screened titles and abstracts using the Rayyan web application for systematic review screening18. Full texts were sourced for relevant articles. Inclusion criteria were assessed independently (M.W. and C.J.), and the final list was agreed by consensus with a third reviewer (L.F.). The reference lists of similar review articles were also screened. The systematic review was performed in accordance with the pre-specified protocol, which was prospectively registered on PROSPERO, the international prospective register of systematic reviews (ID CRD42020125090).

Data extraction
Three standardized data collection forms for animal and human studies respectively were used (Appendix S2). For each study, the title, year of publication, barrier type (natural or synthetic), barrier category (categories were finalized after data extraction), generic and brand name (where applicable), and whether the barrier contained a combination of agents, were extracted. The animal model (such as rat, chicken, or rabbit) for animal studies, and the type of surgery performed (such as abdominal or pelvic) for human studies, were recorded. Reviewers (M.W., C.J., and L.F.) independently extracted data, compared for inconsistencies, and merged into a final data set. Discrepancies were resolved following discussion under supervision of the lead author (M.O.H.).

Appraisal of studies
Additionally, desirable barrier characteristics (Appendix S3) including adherence to traumatized tissue, adherence to oozing tissue, application laparoscopically, safety for the patient, cost-effectiveness, postoperative pain, and ease of application were extracted from full-text articles. Pathway to the market characteristics were extracted as listed in Appendix S4. Successful barriers were those where positive outputs have been reported for each of the desirable characteristics in previous literature and potentially successful barriers were those that had positive outcomes but a number of desirable characteristics required further research.

Results
The search of PubMed and Embase databases identified 429 unique articles, with a further six identified from a review of reference listings. A total of 103 articles were excluded on review of titles and abstracts. Sixteen reports could not be retrieved and a further 131 records were removed after full-text review, with 185 remaining for inclusion in the review (Fig. 1).

Characteristics of included studies
The 185 included studies comprised 51 human studies (38 randomized clinical trials and 13 observational studies) and 134 animal studies. The type of surgery or animal respectively, and relative success of the barrier material are described in Appendix S5. Some 96 animal studies were in rat or mouse, 32 in rabbit, four in chicken, and two in pig. Human studies consisted of 26 gynaecological and 25 abdominal surgeries. Full details are described in Appendix S6.

Characteristics of barrier agents
A total of 67 unique adhesion barriers materials were identified, comprising 16 barrier categories. The barrier materials included 37 natural and 30 synthetic products. The characteristics of the 67 barrier agents based on the eight distinctive properties are summarized in Table 1 and described in detail in Appendix S7.

Natural barriers
Algae
Alginate and alginate/hyaluronic acid both had success in animal studies19–22. No human studies were found for any of the materials. The alginate barrier had a higher efficacy compared with a commercialized barrier Interceed in an animal study23. Safety concerns for agar films were identified in an animal study, where there was an increased rate of adverse events24.

Cellulose
Oxidized regenerated cellulose (ORC) and a combination of carboxymethylcellulose (CMC)/hyaluronic acid (HA) had successful animal24–48 and human studies (de novo, reformation, elective, and emergency surgery) after both open and laparoscopic approaches22,26,49–77. ORC showed greater efficacy compared with control in reducing de novo adhesions during laparoscopic myomectomy52 but was inferior to poloxamer 407 in a comparator study25, although poloxamer 407 is only included in a totally haemolysed surface ORC, modified xylitol–xylitol hydrogel, and CMC/HA have very good safety profiles, low levels of postoperative pain, and score highly on ease of application64,73,78.
Chitosan
Six barriers identified had successful animal studies\(^ {79-88}\) but had no human studies performed thus the safety profiles, cost-effectiveness, and levels of postoperative pain remain unknown.

Glycoprotein
Four barrier materials were identified as having successful findings in animal studies\(^ {16,19,40,83-85}\), with only a single human study for fibrin, which was not successful in preventing de novo adhesions after open surgery\(^ {86}\).

Hyaluronic acid
Three barriers were identified which were successful in animal studies\(^ {97-109}\), with HA hydrogel achieving positive results in preventing de novo adhesions following laparoscopic surgery in a single human study\(^ {110,111}\). It can be applied laparoscopically with low levels of postoperative pain\(^ {111}\), although cost-effectiveness remains unknown.

Icodextrin
Icodextrin had positive outcomes in both animal\(^ {29,101,112}\) and human studies (de novo and elective surgery)\(^ {113-117}\). It can be applied laparoscopically and has positive outputs in terms of
safety, cost-effectiveness, levels of postoperative pain, and ease of use\textsuperscript{114,115,117}.

**Starch**

Sterile hydrophilic starch and dextrin had positive results in animal studies\textsuperscript{29,118–120}, but neither material was successful in human studies\textsuperscript{121,122}. Positive outputs have been reported for sterile hydrophilic starch in terms of safety, levels of postoperative pain, and ease of application\textsuperscript{118–121}.

**Miscellaneous**

Twelve barriers in the group were identified with successful animal studies\textsuperscript{102,123–136}, however, only Dextran 70 progressed to have a single successful human study (\textit{de novo} and laparoscopic surgery). Each of the 12 barriers reported were easy to apply\textsuperscript{102,117,124,128,132,136}; however, safety, cost-effectiveness, and levels of postoperative pain remain unknown for each barrier.

**Synthetic barrier**

**Polycaprolactone**

Four barriers had successful animal studies\textsuperscript{137–144}, with no human studies identified. Polycaprolactone/polyhydroxybutyrate, and polycaprolactone/polyethylene glycol (PEG) can be applied laparoscopically and demonstrated good usability\textsuperscript{141,145}.

**Polyethylene glycol**

Four barriers had successful animal studies\textsuperscript{26,38,146–155}, with positive outcomes reported in human studies for PEG (\textit{de novo}, reformation, and elective surgery) and poloxamer 407/alginate (\textit{de novo}) in laparoscopic surgery\textsuperscript{156–168}. No human studies were identified for poloxamer 407. PEG has had positive outputs in terms of patient safety, cost-effectiveness, and level of postoperative pain\textsuperscript{157,159,160}. Poloxamer 407 alginate has been shown to have a high level of patient safety\textsuperscript{165}, but cost-effectiveness, and postoperative pain are unknown.

**Polyglycolic acid**

The polyglycolic acid barrier had no successful animal study\textsuperscript{166} and no human studies have been identified.

**Polylactic acid**

Two barriers identified had successful animal studies\textsuperscript{38,167–172}, with one successful human study performed analysing polylactic acid (PLA)/PEG barrier\textsuperscript{173}. PLA/PEG had reports of high level of patient safety, mixed reports related to postoperative pain, and ease of application\textsuperscript{169–171,173}.

**Polypropylene**

Polypropylene/omega-3 had a single successful animal study\textsuperscript{174}, whereas the remaining three barriers in the category had unsuccessful animal studies\textsuperscript{118,174}. No human studies were identified for any of the materials. Each of the barriers requires sutures to adhere to traumatized and oozing surfaces.

**Polyvinyl alcohol**

Polyvinyl alcohol hydrogel and polyvinyl alcohol/CMC had successful animal studies\textsuperscript{175–181} but no human studies were identified. Characteristics including patient safety, cost-effectiveness, and postoperative pain are unknown for the two barriers.

**Silicone**

Polyisiloxane had no successful animal studies\textsuperscript{182} and no human studies have been performed to date\textsuperscript{118,174,183}.

**Miscellaneous**

Eight further identified barriers except for polyester/collagen had successful animal studies\textsuperscript{118,156,174,184–190}. No human studies were identified for any of the materials. Polyester/collagen has a poor level of safety reported in animal studies\textsuperscript{118,174}, with unknown level of the ease of barrier application. Patient safety and ease of application are unknown for the remaining barriers.

**Pathway to market**

The market potential for each barrier is described in Table 2, based on outcomes from animal and human studies. Six barriers with successful animal and human studies, which are currently available on the market were identified. A further 52 barrier materials with positive outcomes, where further research is required (success in both animal and human studies or success in animal studies without progression to human study) were identified. Fourteen barrier materials with negative outcomes were noted.

**Discussion**

Ten barriers were identified (HA hydrogel, PLA/PEG, poloxamer 407/alginate, and Dextran 70 in addition to the six commercially available barriers) that achieved the primary outcome of preventing adhesions in both animal and human studies, with varying success in attaining each of the optimal characteristics. Furthermore, 48 additional barriers achieved positive outcomes in animal studies but never successfully progressed to a human study. The remaining nine barriers were those with unsuccessful human studies following positive animal studies and those with no successful in animal studies.

Animal models have been the basis of many great discoveries in modern biomedical research\textsuperscript{14}; however, animal welfare must remain a central consideration. The large number of barriers achieving positive outcomes in animal subjects yet failing to progress to human trials questions the investigators’ intentions on progression, appropriateness of model utilized, study design, and reliability of results. Currently, there are six barriers available commercially in Europe comprising ORC (Interceed, Ethicon, Somerville, New Jersey, USA), CMC/HA (Seprafilm, Sanofi, Paris, France), crosslinked HA (CHA) (Hyalobarrier, Nordic group, Paris, France), polyester/collagen (Parietex, Medtronic, Watford, UK), icodextrin 4 per cent solution (Adept, Baxter, Deerfield, Illinois, USA), and PEG (Sprayshield, Integra, LifeSciences, Plainsboro, New Jersey, USA).

The capacity to adhere to traumatized tissue is a fundamental requirement for any barrier to envelope the damaged tissue and partition the aggregated fibrin surface, thereby diminishing adhesion formation\textsuperscript{4}. Overall, only three natural (ORC, CMC/HA, and HA) and two synthetic (PLA/PEG and poloxamer 407/alginate) barriers that were successful in adhesion reduction in animal and human studies demonstrated adequate ability to adhere to traumatized tissue. The barrier was a liquid preparation, except for the PLA/PEG barrier, which requires sutures to impede migration. The PLA/PEG barrier has only been utilized in a single human
| Barrier type | Pathway status | Successful animal test | Followed by human test | Positive outputs | On the market |
|-------------|----------------|------------------------|------------------------|------------------|---------------|
| **Category** |                |                        |                        |                  |               |
| **Barrier name** |                |                        |                        |                  |               |
| **Natural** |                |                        |                        |                  |               |
| **Algae** |                |                        |                        |                  |               |
| Alginates | Yes | Yes | No | No | Yes |
| Agar films | No | No | No | No | No |
| Alginates/hyaluronic acid | Yes | No | No | No | No |
| **Cellulose** |                |                        |                        |                  |               |
| Oxidized regenerated cellulose | Yes | Yes | Yes | Yes | Yes |
| Modified xyloglucan hydrogel | Yes | Yes | No | No | No |
| Carboxymethylcellulose | Yes | No | No | No | No |
| Carboxymethylcellulose/hyaluronic acid | Yes | Yes | Yes | Yes | Yes |
| Carboxymethylcellulose/polyethylene glycol | No | No | No | No | No |
| **Chitosan** |                |                        |                        |                  |               |
| N,O-carboxymethyl chitosan | Yes | No | No | No | No |
| Chitosan | Yes | No | No | No | No |
| Chitosan/carboxymethylcellulose/collagen | Yes | No | No | No | No |
| N,O-carboxymethyl chitosan/hyaluronic acid | Yes | No | No | No | No |
| Chitosan/gelatin | Yes | No | No | No | No |
| N,O-carboxymethyl chitosan/dextran | Yes | No | No | No | No |
| Chitosan/polyglycolic acid | Yes | No | No | No | No |
| **Glycoprotein** |                |                        |                        |                  |               |
| Fibronectin derivative | Yes | No | No | No | No |
| Lactoferrin | Yes | No | No | No | No |
| Fibrin | Yes | No | No | No | No |
| Gelatin/polyglycan | Yes | No | No | No | No |
| Gelatin/proteoglycan | Yes | Yes | Yes | Yes | Yes |
| **Hyaluronic acid** |                |                        |                        |                  |               |
| Hyaluronic acid hydrogel | Yes | Yes | Yes | Yes | Yes |
| Crosslinked hyaluronic acid | Yes | Yes | Yes | Yes | Yes |
| Hyaluronic acid membrane | Yes | Yes | Yes | Yes | Yes |
| **Icodextrin** |                |                        |                        |                  |               |
| Icodextrin | Yes | Yes | Yes | Yes | Yes |
| **Miscellaneous** |                |                        |                        |                  |               |
| Dextran 70 | Yes | No | No | No | No |
| Phosphorylcholine | Yes | No | No | No | No |
| Silk | Yes | No | No | No | No |
| Ancrod | Yes | No | No | No | No |
| Bromelain | Yes | No | No | No | No |
| Xanthan gum | Yes | No | No | No | No |
| Pectin | Yes | No | No | No | No |
| Modified pullulan | Yes | No | No | No | No |
| Liquid paraffin | Yes | No | No | No | No |
| Galls ethyl acetate | Yes | No | No | No | No |
| Ethyl pyruvate | Yes | No | No | No | No |
| Tongfu xiere enteroclysis mixture | Yes | No | No | No | No |
| **Starch** |                |                        |                        |                  |               |
| Sterile hydrophilic starch | Yes | No | No | No | No |
| Dextrin | Yes | No | No | No | No |
| **Synthetic Polycaprolactone** |                |                        |                        |                  |               |
| Polycaprolactone/polyhydroxybutyrate | Yes | No | No | No | No |

(continued)
study of cardiac patients with positive outcomes; however, previous studies have shown that the additional use of sutures entails a heightened opportunity for adhesion formation.

Barrier attachment to oozing surfaces is an important factor to ensure the anti-adhesion effect is maintained, particularly during surgeries that include a high risk of bleeding. Overall, natural barriers seem to maintain more effective anti-adhesion effects on oozing surfaces. HA hydrogel and CMC/HA both highlighted their capabilities in human studies; however, the ORC barrier is of limited effectiveness in the presence of blood or peritoneal fluid. Interestingly, chitosan-based (CS) barriers exhibit haemostatic effects. This prophylactic property, in addition to the ability of the agent to be applied to oozing surfaces, highlights promise as a barrier constituent; however, although positive outputs were achieved in animal studies utilizing CS in combination with other materials, no successful human study exists.

Patient safety is of utmost importance, balancing the utility risks of a barrier with the current standard of care (no barrier). Patients who suffer postoperative adhesions have a longstanding augmented risk of a number of discrete clinical sequelae, including chronic pain, small bowel adhesive disease, increased operating time, increased duration of hospital stay, female infertility, opioid dependency, and reduced quality of life. While, any potential barrier candidate should aim to alleviate or reduce potential patient risks, it is important that the barrier itself does not pose further patient safety concerns.

Table 2 (continued)

| Barrier type | Pathway status | Successful animal test | Followed by human test | Positive outputs | On the market |
|--------------|----------------|------------------------|------------------------|------------------|--------------|
| polycaprolactone/hyaluronic acid | Yes | No | No | No |
| polycaprolactone/polyethylene glycol | Yes | No | No | No |
| polycaprolactone/gelatin | Yes | No | No | No |
| Polyethylene glycol | Yes | Yes | Yes | Yes |
| Polyethylene glycol/collagen/glycerol | Yes | Yes | Yes | No |
| Poloxamer 407 | Yes | No | No | No |
| Poloxamer 407/alginate | Yes | Yes | No | No |
| Polyglycolic acid | Yes | No | No | No |
| Polylactic acid | Yes | No | No | No |
| Polymeric acid/polyethylene glycol | Yes | Yes | No | No |
| Polymeric acid/polycaprolactone | Yes | No | No | No |
| Poly(lactic acid)/modified mesoporous silica/ibuprofen | Yes | No | No | No |
| Polypropylene | Yes | No | No | No |
| Polypropylene/glycolide/polycaprolactone | Yes | No | No | Yes |
| Polydioxanone/polypropylene/carboxymethylcellulose | Yes | No | No | No |
| Polypropylene/titanium | No | No | No | No |
| Polypropylene/omega 3 | Yes | No | No | No |
| Polyvinyl alcohol | Yes | No | No | No |
| Polyvinyl alcohol hydrogel | Yes | No | No | No |
| Polyvinyl Alcohol/carboxymethylcellulose | Yes | No | No | No |
| Silicone | Yes | No | No | No |
| Polyisoxiane | Yes | Yes | Yes | No |
| Polyesterurethane/polydimethylsiloxane | Yes | Yes | Yes | No |
| Miscellaneous | Yes | No | No | No |
| Chitosan/poly(d,l-lactic-co-glycolic acid)/polyethylene oxide | Yes | No | No | No |
| Polyester/collagen | No | No | No | No |
| N-isopropylacrylamide | No | No | No | No |
| C17 glycerin ester | Yes | No | No | No |
| Methylene blue | Yes | No | No | No |
| Dimethyl-sulfoxide | Yes | No | No | No |
| Polyhydroxyethylmethacrylate | Yes | No | No | No |
| Poly(lactic-co-glycolic acid)/epigallocatechin-3-O-gallate | Yes | No | No | No |

Green, on the market; orange, positive outcomes in animal and human study (but not on the market) or successful animal study with no human study to date; red, negative results from animal and/or human studies.
or augment postoperative pain. Overall, the nine barriers achieving the primary endpoint of reducing the extent and severity of postoperative adhesions scored highly on the Likert safety scale. Five barriers achieved positive results regarding extent of postoperative pain, with PLA/PEG barrier having mixed results, whereas poloxamer/alginate and Dextran 70 barriers had no reported outcomes.

The application of ORC during gynaecological surgery decreases the incidence and severity of postoperative adhesions without any significant adverse events. Concerns have been raised that a single adhesion band produced from incomplete cover or on the periphery of a barrier may result in an augmented risk of strangulated SBO; however, the available evidence contradicts these concerns, highlighting that extensive adhesive disease as opposed to isolated areas correlates with incidence of SBO. The CMC/HA barrier has been demonstrated to reduce the rate of SBO in several controlled trials. Furthermore, studies have found a reduction in the incidence of chronic abdominal pain and duration of procedure. Despite predominantly positive outputs for the barrier, safety concerns have been highlighted with augmented risk of abdominal abscess formation on application of the barrier to the region of anastomoses.

The utilization of a laparoscopic approach, where feasible, has consistently demonstrated improved patient outcomes relative to open surgery. Krielen and colleagues analysed a retrospective cohort study of 72,270 patients with adhesion-related readmissions following abdominal surgery, comprising open (n = 50,751) and laparoscopic (n = 21,519) approaches. The study interval encompassed hospital readmissions from 2009 to 2011 utilizing the validated population data for the Scottish National Health Service with a 5-year follow-up. They recorded a statistically significant reduction in the number of readmissions directly related to adhesions (1.7 per cent versus 4.3 per cent; P < 0.0001) and those possibly related to adhesions (16.0 per cent versus 18.2 per cent; P < 0.005) in the laparoscopic group. Of the nine barriers highlighted, each can be applied laparoscopically except for PLA/PEG, where it is unknown and mixed results are reported regarding its ease of application. No studies to date have reported the ease of application of Dextran 70. ORC and CMC/HA are solid membrane barriers and therefore present an augmented challenge in laparoscopic application compared with alternative barriers, which are liquid, gel, or spray preparations. ORC has also been associated with elevated handling issues in comparison with the other preparations.

Postoperative adhesions and related complications accrue substantial healthcare costs, both directly and indirectly. Cost-effectiveness analysis of widespread utilization is an essential prerequisite for any barrier considered for introduction by policymakers. No such analysis assessing the overall cost-effectiveness of a barrier was identified in this systematic review.

The primary strength of the present study is that independent screening and abstraction for both animal and human studies was performed, resulting in the largest systematic review on the topic to date. Ideal characteristics for each barrier were independently reviewed and extracted, allowing potential barriers to be highlighted for further investigation; however, limitations including publication bias and small study bias exist as with all systematic reviews. Additional limitations rely on heterogeneous reporting of characteristics and study success. Furthermore, animal models and human clinical indications were heterogenous. It was not possible to assess the long-term safety and efficacy data of the majority of barriers, as most only included short-term data.

Meticulous surgical technique and increasing performance of minimally invasive procedures have reduced the incidence and severity of the complication, but adhesions remain a significant global burden. Despite a concerted effort and vast investigation over the past two decades, there remains no specific barrier agent in widespread use internationally with only five agents licenced for use in the EU. Positive long-term data on efficacy and safety have been demonstrated for Seprafilm; however, these remain sparse overall. Future research should concentrate on assessing the safety and confirming efficacy observed in animal studies, ensuring that all research is well designed, relevant, and takes into account issues on animal welfare. Outcomes should be reported in a uniform manner based on location of adhesions (such as the modified American Fertility Society endometriosis scale for gynaecology adhesions). Effects on quality of life seem to have been poorly explored to date and require evaluation. Furthermore, before the production of novel barriers, researchers must first ensure compliance with the EU Directive guidance, which puts a clear and explicit obligation on researchers to replace, reduce, and refine studies with animal involvement. Additionally, alignment with clinically based surgeons to identify and assess reluctance and possible concerns with utilization of commercially available barriers, including Seprafilm, is required, and the long-term efficiency and safety data of successful barriers requires evaluation in future research.

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Supplementary material
Supplementary material is available at BJ5 Open online.

Data availability
The data that support the findings of this study are available from the corresponding author, M.W., upon reasonable request.

References
1. Stommel MWJ, ten Broek RPG, Strik C, Slooter GD, Verhoef C, Grünhagen DJ et al. Multicenter observational study of adhesion formation after open- and laparoscopic surgery for colorectal cancer. Ann Surg 2018;267:743–748
antiadhesive barriers for intraperitoneal onlay mesh hernia repair in an experimental model. Br J Surg 2011;98:442–449

39. Hellebrekers BWJ, Trimbos-Kemper CGM, van Blitterswijk CA, Bakkum EA, Trimbos JB. Effects of five different barrier materials on postsurgical adhesion formation in the rat. Hum Reprod 2000;15:1358–1363

40. Arnold PB, Green CW, Foresman PA, Rodeheaver GT. Prevention of de-novo adhesion formation after laparoscopic ovarian surgery with the application of Interceed to one ovary: a prospective randomized controlled study. Hum Reprod 1996;11:992–997

41. Erpek H, Tuncyurek P, Soyder A, Boylu S. Hyaluronic acid/carboxymethylcellulose membrane barrier versus taurodilone for the prevention of adhesions to polypropylene mesh. Eur Surg Res 2006;38:414–417

42. Medina M, Paddock HN, Connolly RJ, Schwartzberg SD. Novel antiadhesion barrier does not prevent anastomotic healing in a rabbit model. J Invest Surg 1995;8:179–186

43. Kelekci S, Yilmaz B, Oguz S, Zergeroglu S, Iinan I, Tokucoglu S. The efficacy of a hyaluronate/carboxymethylcellulose membrane in prevention of postoperative adhesion in a rat uterine horn model. Tohoku J Exp Med 2004;204:189–194

44. Sheldon HK, Gainsbury ML, Cassidy MR, Chu DI, Stucchi AF, Becker JM. A sprayable hyaluronate/carboxymethylcellulose adhesion barrier exhibits regional adhesion reduction efficacy and does not impair intestinal healing. J Gastrointest Surg 2012;16:325–333

45. Hammer RA, Morse AN, Cornella JL, Keller RS, Hentz J, McDonald JA et al. Bringing molecular biology to bear on adhesion prevention: postsurgical adhesion reduction using intraperitoneal inoculation of hyaluronic acid–inducing adenoviral vector in a murine model. J Gynecol Surg 2006;22:7–18

46. Bahadir I, Oncel M, Kement M, Sahip Y. Intra-abdominal use of taurodilone or heparin as alternative products to an antiadhesive barrier (Seprafilm®) in adhesion prevention: an experimental study on mice. Dis Colon Rectum 2007;50:2209–2214

47. Lim R, Morrill JM, Lynch RC, Reed KL, Gower AC, Leeman SE et al. Practical limitations of bioreosorbable membranes in the prevention of intra-abdominal adhesions. J Gastrointest Surg 2009;13:35–42

48. Ryan CK, Sax HC. Evaluation of a carboxymethylcellulose sponge for prevention of postoperative adhesions. Am J Surg 1995;169:154–160

49. Stawicki SP, Green JM, Martin ND, Green RH, Cipolla J, Seamon MJ et al. Results of a prospective, randomized, controlled study of the use of carboxymethylcellulose sodium hyaluronate adhesion barrier in trauma open abdomens. Surgery 2014;156:419–430

50. Greenblatt EM, Casper RF. Adhesion formation after laparoscopic ovarian cauterization for polycystic ovarian syndrome: lack of correlation with pregnancy rate. Fertil Steril 1993;60:766–770

51. Li TC, Cooke ID. The value of an absorbable adhesion barrier (Sepra film®) in gynecologic surgery. Dis Colon Rectum 2000;43:154–945

52. Park CM, Lee WY, Cho YB, Yun HR, Lee WS, Yun SH et al. Sodium hyaluronate-based bioreosorbable membrane (Seprafilm®) reduced early postoperative intestinal obstruction after lower abdominal surgery for colorectal cancer: the preliminary report. Int J Colorectal Dis 2009;24:305–310

53. Kelekci S, Yilmaz B, Oguz S, Zergeroglu S, Iinan I, Tokucoglu S. The efficacy of a hyaluronate/carboxymethylcellulose membrane in prevention of postoperative adhesion in a rat uterine horn model. Tohoku J Exp Med 2004;204:189–194

54. Banker M, Lagrou K, Schildberg FW, Hop WCJ, Jakimowicz JJ, Leguit P. Sodium hyaluronate-based bioreosorbable membrane (Seprafilm®) in surgery for rectal carcinoma: a prospective randomized clinical trial. Surg Today 2005;35:940–945

55. Fazio VW, Cohen Z, Fleshman JW, van Goor H, Bauer JJ, Wolff BG et al. Reduction in adhesive small-bowel obstruction by Seprafilm® adhesion barrier after intestinal resection. Dis Colon Rectum 2006;49:1–11

56. Diamond MP. Reduction of adhesions after uterine myomectomy by Seprafilm membrane (HAL-F): a blinded, prospective, randomized, multicenter clinical study. Seprafilm adhesion study group. Fertil Steril 1996;66:904–910

57. Fazio VW, Cohen Z, Fleshman JW, van Goor H, Bauer JJ, Wolff BG et al. Reduction in adhesive small-bowel obstruction by Seprafilm® adhesion barrier after intestinal resection. Dis Colon Rectum 2006;49:1–11

58. Inoue M, Uchida K, Miki C, Kusunoki M. Efficacy of Seprafilm for reducing reoperative risk in pediatric surgical patients undergoing abdominal surgery. J Pediatr Surg 2005;40:1301–1306

59. Kohanzadeh S, Lugo L, Long JN. Safety of antiadhesion barriers: a prospective randomized clinical trial. Int J Colorectal Dis 2008;23:193–199

60. Merle M, Lallemand B, Lim A, Gantois G. Experimental and clinical evaluation of an absorbable biomaterial inducing an anti-adhesive barrier (Divide®). Eur J Orthop Surg Traumatol 2008;18:255–263

61. Beck DE, Cohen Z, Fleshman JW, Kaufman HS, van Goor H, Wolff BG et al. A prospective, randomized, multicenter, controlled study of the safety of Seprafilm® adhesion barrier in abdominopelvic surgery of the intestine. Dis Colon Rectum 2003;46:1310–1319

62. Suresh A, Celso BG, Awad ZT. Seprafilm slurry does not increase complication rates after laparoscopic colectomy. Surg Endosc 2011;25:2661–2665

63. Hong M-K, Ding D-C. Seprafilm® application method in laparoscopic surgery. JSLS 2017;21:e2016.00097

64. Ota K, Sato K, Ogasawara J, Takahashi T, Mizunuma H, Tanaka M. Prevention of de-novo adhesion formation after laparoscopic myomectomy: a randomized trial to evaluate the effectiveness of an oxidized regenerated cellulose absorbable barrier. Hum Reprod 1995;10:3133–3135

65. Saravelos H, Li T-C. Post-operative adhesions after laparoscopic electrocautery treatment for polycystic ovarian syndrome with the application of Interceed to one ovary: a prospective randomized controlled study. Hum Reprod 1999;11:992–997

66. Nakamura H, Yokota K, Watarai K, Watanabe Y, Tsunoda Y, Kawamura H et al. Prevention of adhesion formation after laparoscopic myomectomy: a randomized trial to evaluate the effectiveness of an oxidized regenerated cellulose absorbable barrier. Hum Reprod 1995;10:3133–3135

67. Nakamura H, Yokota K, Watarai K, Watanabe Y, Tsunoda Y, Yamagami H et al. A sodium hyaluronate carboxymethylcellulose bioreosorbable membrane prevents postoperative small-bowel adhesive obstruction after distal gastrectomy. Surg Today 2010;40:223–227

68. Nakamura H, Yokota K, Watarai K, Watanabe Y, Tsunoda Y, Yamagami H et al. A sodium hyaluronate carboxymethylcellulose bioreosorbable membrane prevents postoperative small-bowel adhesive obstruction after distal gastrectomy. Surg Today 2010;40:223–227

69. Nakamura H, Yokota K, Watarai K, Watanabe Y, Tsunoda Y, Yamagami H et al. Prevention of adhesion formation after laparoscopic myomectomy with an absorbable adhesion barrier. Hum Reprod 1995;10:3133–3135

70. Nakamura H, Yokota K, Watarai K, Watanabe Y, Tsunoda Y, Yamagami H et al. A sodium hyaluronate carboxymethylcellulose bioreosorbable membrane prevents postoperative small bowel adhesive obstruction after distal gastrectomy. Surg Today 2010;40:223–227

71. Nakamura H, Yokota K, Watarai K, Watanabe Y, Tsunoda Y, Yamagami H et al. Prevention of adhesion formation after laparoscopic myomectomy: a randomized trial to evaluate the effectiveness of an oxidized regenerated cellulose absorbable barrier. Hum Reprod 1995;10:3133–3135

72. Nakamura H, Yokota K, Watarai K, Watanabe Y, Tsunoda Y, Yamagami H et al. Prevention of adhesion formation after laparoscopic myomectomy: a randomized trial to evaluate the effectiveness of an oxidized regenerated cellulose absorbable barrier. Hum Reprod 1995;10:3133–3135

73. Nakamura H, Yokota K, Watarai K, Watanabe Y, Tsunoda Y, Yamagami H et al. Prevention of adhesion formation after laparoscopic myomectomy with an absorbable adhesion barrier. Hum Reprod 1995;10:3133–3135

74. Nakamura H, Yokota K, Watarai K, Watanabe Y, Tsunoda Y, Yamagami H et al. Prevention of adhesion formation after laparoscopic myomectomy with an absorbable adhesion barrier. Hum Reprod 1995;10:3133–3135
71. Nordic Adhesion Prevention Study Group. The efficacy of interceed(TC7)* for prevention of reformation of postoperative adhesions on ovaries, fallopian tubes, and fimbriae in microsurgical operations for fertility: a multicenter study. Fertil Steril 1995;63:709–714

72. Franklin R. Reduction of ovarian adhesions by the use of Interceed. Obstet Gynecol 1995;86:335–340

73. Mais V, Ajossa S, Marongiu D, Peiretti R, Guerriero S, Benedettomelis G. Reduction of adhesion reformation after laparoscopic endometriosis surgery: a randomized trial with an oxidized regenerated cellulose absorbable barrier. Obstet Gynecol 1995;86:512–515

74. Wallwiener D, Meyer A, Bastert G. Adhesion formation of the parietal and visceral peritoneum: an explanation for the controversy on the use of autologous and alloplastic barriers? Fertil Steril 1998;69:132–137

75. Keckstein J, Ulrich U, Sasse V, Roth A, Tuttles F, Karageorgieva E. Reduction of postoperative adhesion formation after laparoscopic ovarian cystectomy. Hum Reprod 1996;11:579–582

76. Naito M, Ogura N, Yamanashi T, Sato T, Nakamura T, Miura H et al. Prospective randomized controlled study on the validity and safety of an absorbable adhesion barrier (Interceed®) made of oxidized regenerated cellulose for laparoscopic colorectal surgery: adhesion barrier for colorectal surgery. Asian J Endosc Surg 2017;10:7–11

77. Dupré A, Lefranc A, Buc E, Delpero JR, Quenet F, Passot G et al. Use of bioresorbable membranes to reduce abdominal and peritoneal adhesions in 2-stage hepatectomy of liver metastases from colorectal cancer: results of a prospective, randomized controlled Phase II trial. Ann Surg 2013;258:30–36

78. Zhang E, Li J, Zhou Y, Che P, Ren B, Qin Z et al. Biodegradable and injectable thermoreversible xyloglucan-based hydrogel for prevention of postoperative adhesion. Acta Biomater 2017;55:420–433

79. Krause TJ, Zazanis GA, McKinnon RD. Prevention of postoperative adhesions with the chitin derivative N-O-carboxymethylchitosan. Wound Repair Regen 1996;4:53–57

80. Wei C-Z, Hou C-L, Gu Q-S, Jiang L-X, Zhu B, Sheng A-L. A thermosensitive chitosan-based hydrogel barrier for post-operative adhesions’ prevention. Biomaterials 2009;30:5534–5540

81. Zhang E, Guo Q, Ji F, Tian X, Cui J, Song Y et al. Thermoresponsive polysaccharide-based composite hydrogel with antibacterial and healing-promoting activities for preventing recurrent adhesion after adhesiolysis. Acta Biomater 2018;74:439–453

82. Cheng F, Wu Y, Li H, Yan T, Wei X, Wu G et al. Biodegradable N-O-carboxymethyl chitosan/oxidized regenerated cellulose composite gauze as a barrier for preventing postoperative adhesion. Carbohydr Polym 2019;207:180–190

83. Cai X, Hu S, Yu B, Cai Y, Yang J, Li F et al. Transglutaminase-catalyzed preparation of crosslinked carboxymethyl chitosan/carboxymethyl cellulose/collagen composite membrane for postsurgical peritoneal adhesion prevention. Carbohydr Polym 2018;201:201–210

84. Li L, Wang N, Jin X, Deng R, Nie S, Sun L et al. Biodegradable and injectable in situ cross-linking chitosan-hyaluronic acid-based hydrosols for postoperative adhesion prevention. Biomaterials 2014;35:3903–3917

85. Chen C-H, Chen S-H, Mao S-H, Tsai M-J, Chou P-Y, Liao C-H et al. Injectable thermosensitive hydrogel containing hyaluronic acid and chitosan as a barrier for prevention of postoperative peritoneal adhesion. Carbohydr Polym 2017;173:721–731

86. Shahram E, Sadraie SH, Kaka G, Khoshmohabat H, Hosseinialipour M, Panahi F et al. Evaluation of chitosan–gelatin films for use as postoperative adhesion barrier in rat cecum model. Int J Surg 2013;11:1097–1102

87. Lin L-X, Luo J-W, Yuan F, Zhang H-H, Ye C-Q, Zhang P et al. In situ cross-linking carbodiimide-modified chitosan hydrogel for postoperative adhesion prevention in a rat model. Mater Sci Eng C Mater Biomol Appl 2017;81:380–385

88. Falabella CA, Melendez MM, Weng L, Chen W. Novel macromolecular crosslinking hydrogel to reduce intra-abdominal adhesions. J Surg Res 2010;159:772–778

89. Nilsson E, Björn C, Sjöstrand V, Lindgren K, Münich M, Mattsby-Baltzer I et al. A novel polypeptide derived from human lactoferrin in sodium hyaluronate prevents postsurgical adhesion formation in the rat. Ann Surg 2009;250:1021–1028

90. Oh J, Kuan KG, Tiong LU, Trochsler MJ, Jay G, Schmidt TA et al. Recombinant human lubricin for prevention of postoperative intra-abdominal adhesions in a rat model. J Surg Res 2017;208:20–25

91. Sato D, Takahara M, Narita A, Yamakawa J, Hashimoto J, Ishikawa H et al. Effect of platelet-rich plasma with fibrin matrix on healing of intrasynovial flexor tendons. J Hand Surg 2012;37:1356–1363

92. Komatsu K, Fujii A, Higami T. Haemostatic fleece (TachoComb®) to prevent intrapleureral adhesions after thoracotomy: a rat model. Thorac Cardiovasc Surg 2007;55:385–390

93. Kuschel TJ, Gruszka A, Hermanns-Sachweh B, Elyakoubi J, Sachweh JS, Vázquez-Jiménez JF et al. Prevention of postoperative pericardial adhesions with TachoSil. Ann Thorac Surg 2013;95:183–188

94. Kim E-H, Kim J-W, Han G-D, Noh S-H, Choi J-H, Choi C et al. Biocompatible, drug-loaded anti-adhesion barrier using visible-light curable furfuryl gelatin derivative. Int J Biol Macromol 2018;120:915–920

95. De Clercq K, Schellhout C, Bracke M, De Wever O, Van Bockstal M, Ceelen W et al. Genipin-crosslinked gelatin microosphers as a strategy to prevent postsurgical peritoneal adhesions: in vitro and in vivo characterization. Biomaterials 2016;96:33–46

96. Osada H, Tanaka H, Fujii T, Tsuoda I, Yoshida T, Satoh K. Clinical evaluation of a haemostatic and anti-adhesion preparation used to prevent post-surgical adhesion. J Int Med Res 1999;27:247–252

97. Liu J, Ni B, Zhu L, Yang J, Cao X, Zhou W. Mitomycin C-polylethylene glycol controlled-release film inhibits collagen secretion and induces apoptosis of fibroblasts in the early wound of a postlaminectomy rat model. Spine J 2010;10:441–447

98. Ozgenel GY, Şamil B, Özcak M. Effects of human amniotic fluid on peritendinous adhesion formation and tendon healing after flexor tendon surgery in rabbits. J Hand Surg 2001;26:332–339

99. Tanaka T, Zhao C, Sun Y-L, Zobitz ME, An K-N, Armado PC. The effect of carbodiimide-derivatized hyaluronic acid and gelatin surface modification on peroneus longus tendon graft in a short-term canine model in vivo. J Hand Surg 2007;32:876–881

100. Yeo Y, Highley CB, Bellas E, Ito T, Marini R, Langer R et al. In situ cross-linkable hyaluronic acid hydrogels prevent...
post-operative abdominal adhesions in a rabbit model. Biomaterials 2006;27:4698–4705.

101. Wallwiener M, Brucker S, Hierlemann H, Brochhausen C, Solomayer E, Wallwiener C. Innovative barriers for peritoneal adhesion prevention: liquid or solid? A rat uterine horn model. Fertil Steril 2006;86:1266–1276.

102. Kataria H, Singh VP. Liquid paraffin vs hyaluronic acid in preventing intraperitoneal adhesions. Indian J Surg 2017;79:539–543.

103. Ozmen MM, Aslar AK, Terzi MC, Albayrak L, Berberoglu M. Prevention of adhesions by bioresorbable tissue barrier following laparoscopic intraabdominal mesh insertion. Surg Laparosc Endosc Percutan Tech 2002;12:342–346.

104. Liu Y, Li H, Shu X, Gray S, Prestwich G. Crosslinked hyaluronan hydrogels containing mitomycin C reduce postoperative abdominal adhesions. Fertil Steril 2005;83:1275–1283.

105. Yeo Y, Adil M, Bellas E, Astashkina A, Chaudhary N, Kohane DS. Prevention of peritoneal adhesions with an in situ cross-linkable hyaluronan hydrogel delivering budesonide. J Controlled Release 2007;120:178–185.

106. Mitchell J, Lee R, Neya K, Vlahakes G. Reduction in experimental pericardial adhesions using a hyaluronic acid bioabsorbable membrane. Eur J Cardiothorac Surg 1994;5:149–152.

107. Tsai S-W, Fang J-F, Yang C-L, Chen J-H, Su L-T, Jan S-H. Preparation and evaluation of a hyaluronate-collagen film for preventing post-surgical adhesion. J Int Med Res 2005;33:68–76.

108. Kato T, Haro H, Komori H, Shinomiya K. Evaluation of hyaluronic acid sheet for the prevention of postlaminectomy adhesions. Spine J 2005;5:479–488.

109. Kuo SM, Chang SJ, Wang H-Y, Tang SC, Yang S-W. Evaluation of the ability of xanthan gum/gellan gum/hyaluronan hydrogel membranes to prevent the adhesion of postrepaired tendons. Carbohydr Polym 2014;114:230–237.

110. Hagberg L. Exogenous hyaluronate as an adjunct in the prevention of adhesions after flexor tendon surgery: a controlled clinical trial. J Hand Surg 1992;17:132–136.

111. Koninckx PR, Corona R, Timmerman D, Verguts J, Adamyan L. Peritoneal full-conditioning reduces postoperative adhesions and pain: a randomised controlled trial in deep endometriosis surgery. J Ovarian Res 2013;6:90.

112. Tepetes K, Asprodini EK, Christodoulidis G, Spyridakis M, Kouvaras E, Hatzitheodorou K. Prevention of postoperative adhesion formation by individual and combined administration of 4 per cent icodextrin and dimetindene maleate. Br J Surg 2009;96:1476–1483.

113. Trew G, Pistofidis G, Pados G, Lower A, Mettler L, Wallwiener D et al. Gynaecological endoscopic evaluation of 4% icodextrin solution: a European, multicentre, double-blind, randomized study of the efficacy and safety in the reduction of de novo adhesions after laparoscopic gynaecological surgery. Hum Reprod 2011;26:2015–2027.

114. Köss J, Grönlund S, Utıta-Nieminen M, Crowe A, Knight A, Keränä U. The effect of 4% icodextrin solution on adhesiolysis surgery time at the Hartmann’s reversal: a pilot, multicentre, randomized control trial vs lactated Ringer’s solution. Colo Nicol Dis 2009;11:168–172.

115. di Zerega GS, Verco SJ, Young P, Kettel M, Kobak W, Martin D et al. A randomized, controlled pilot study of the safety and efficacy of 4% icodextrin solution in the reduction of adhesions following laparoscopic gynaecological surgery. Hum Reprod 2002;17:1031–1038.

116. Catena F, Ansaloni L, Di Saverio S, Pinna AD, on behalf of the World Society of Emergency Surgery. P.O.P.A. study: prevention of postoperative abdominal adhesions by icodextrin 4% solution after laparotomy for adhesive small bowel obstruction. A prospective randomized controlled trial. J Gastrointest Surg 2012;16:382–388.

117. Deus C, Kropf S, Kleinstein J. Comparison of 2 different barrier solutions (icodextrin 4% vs. dextran 70) used as adhesion-prevention agents after microsurgical adnexal operations. J Endometr 2014;36:127–132.

118. Winny M, Maelg L, Grethe L, Lippmann T, Jonigk D, Schrem H et al. Adhesion prevention efficacy of composite meshes Parietex®, Proceed® and 4D ryField® PH covered polypropylene meshes in an IPOM rat model. Int J Med Sci 2016;13:936–941.

119. Poehnert D, Abbas M, Kreipe H-H, Klemplnauer J, Winny M. Evaluation of 4DryField® PH as adhesion prevention barrier tested in an optimized adhesion model in rats. Eur Surg Res 2015;55:341–351.

120. Kai M, Maeda K, Tasaki M, Kira S, Nakamura S, Chino N et al. Evaluation of a spray-type, novel dextrin hydrogel adhesion barrier under laparoscopic conditions in a porcine uterine horn adhesion model. J Minim Invasive Gynecol 2018;25:447–454.

121. Blumhardt G, Haas M, Polte S. Effect of 4DryField® PH, a novel adhesion barrier, on recurrence of intestinal adhesions after extensive visceral adhesiolysis. Case Rep Surg 2018;2018:9629742.

122. Kojima Y, Sakamoto K, Okuzawa A. Experience of using a spray-type anti-adhesion barrier in laparoscopic surgery for colorectal cancer. J Surg Case Rep 2019;2019:rrj085.

123. Konovalova MV, Markov PA, Popova GY, Nikitina IR, Shumikhin KV, Kurek DV et al. Prevention of postoperative adhesions by biodegradable cryogels from pectin and chitosan polysaccharides. J Bioact Compat Polym 2017;32:487–502.

124. Konar S, Guha R, Kundu B, Nandi S, Ghosh TK, Kundu SC et al. Silk fibroin hydrogel as physical barrier for prevention of post hernia adhesion. Hernia 2017;21:125–137.

125. Chowdhury SM, Hubbell JA. Adhesion prevention with anacrod released via a tissue-adherent hydrogel. J Surg Res 1996;61:58–64.

126. Sahbaz A, Aynioglu O, Isik H, Ozmen U, Cengil O, Gun BD et al. Bromelain: a natural proteolytic for intra-abdominal adhesion prevention. Int J Surg 2015;14:7–11.

127. Song Z, Zhang Y, Shao H, Ying Y, Chen X, Mei L et al. Effect of xanthan gum on the prevention of intra-abdominal adhesion in rats. Int J Biol Macromol 2019;126:531–538.

128. Giusto G, Vercell C, Jussich S, Audisio A, Morello E, Odore R et al. A pectin-honey hydrogel prevents postoperative intraperitoneal adhesions in a rat model. BMC Vet Res 2016;13:55.

129. Popov SV, Popova GY, Nikitina IR, Markov PA, Latkin DS, Golovchenko VV et al. Injectable hydrogel from pectin and chitosan polysaccharides. J Bioact Compat Polym 2017;32:487–502.

130. Bang S, Lee E, Ko Y-G, Kim WI, Kwon OH. Injectable pullulan hydrogel for the prevention of postoperative tissue adhesion. Int J Biol Macromol 2016;87:155–162.

131. Li X, Zou B, Zhao N, Wang C, Du Y, Mei L et al. A pectin-honey hydrogel prevents postoperative peritoneal adhesions in a rat model. BMC Vet Res 2016;87:155–162.

132. Arslan E, Arslan AS, Artis T, Artis AS, Arslan E, Mutlu F, Akay A, Deniz K. Preventive effect of ethyl pyruvate on postoperative adhesion formation following abdominal surgery. J Invest Surg 2016;29:260–265.

133. Moro-Oka T, Miura H, Mawata T, Kawano T, Nakanishi Y, Higaki H et al. Mixture of hyaluronic acid and phospholipid...
prevents adhesion formation on the injured flexor tendon in rabbits. J Orthop Res 2000;18:835–840

134. Ishiyama N, Moro T, Ohe T, Miura T, Ishihara K, Konno T et al. Reduction of peritendinous adhesions by hydrogel containing biocompatible phospholipid polymer MPC for tendon repair. J Bone Joint Surg Am 2011;93:142–149

135. Soules MR, Dennis L, Bosarge A, Moore DE. The prevention of postsurgical adhesions simultaneously with biodegradable sheath membrane via electrospinning for antiadhesion of rabbits. J Orthop Res 2012;30:829–834

136. Chen YZ, Hao L, Yang HG, Wu JY, Pan YY, Lu WQ

137. Liu S, Zhao J, Ruan H, Tang T, Liu G, Yu D

138. Chen SH, Chen CH, Shalumon KT, Chen JP. Preparation and characterization of antiadhesive barrier film from hyaluronic acid-grafted electrop spun poly(caprolactone) nanofibrous membranes for prevention of flexor tendon postsurgical peritendinous adhesion. Int J Nanomedicine 2014;9:4079–4092

139. Chen SH, Chen CH, Shalumon KT, Chen JP. Preparation and characterization of antiadhesive barrier film from hyaluronic acid-grafted electrop spun poly(caprolactone) nanofibrous membranes for prevention of flexor tendon postsurgical peritendinous adhesion. Int J Nanomedicine 2014;9:4079–4092

140. Wu Q, Li L, Wang N, Gao X, Wang B, Liu X et al. Biodegradable and thermosensitive micelles inhibit ischemia-induced postsurgical peritoneal adhesion. Int J Nanomedicine 2014;9:727–734

141. Fu SZ, Li Z, Fan JM, Meng XH, Shi K, Qu Y et al. Biodegradable and thermosensitive monomethoxy poly(ethylene glycol)-poly(lactic acid) hydrogel as a barrier for prevention of post-operative abdominal adhesion. J Biomed Nanotechnol 2014;10:427–435

142. He T, Zou C, Song L, Wang N, Yang S, Zeng Y et al. Improving antiadhesion effect of thermosensitive hydrogel with sustained release of tissue-type plasminogen activator in a rat repeated-injury model. ACS Appl Mater Interfaces 2016;8:33514–33520

143. Gong C, Yang B, Qian Z, Zhao X, Wu Q, Qi X et al. Prevention of peritendinous adhesions using an electrop spun DegraPol polymer tube: a histological, ultrasonographic, and biomechanical study in rabbits. BioMed Res Int 2014;2014:1–11

144. Hong JH, Choe JW, Kwon GY, Cho DY, Sohn DS, Kim SW et al. The effects of barrier materials on reduction of pericardial adhesion formation in rabbits: a comparative study of a hyaluronan-based solution and a temperature sensitive poloxamer solution/gel material. J Surg Res 2011;166:206–213

145. Mo F, Yue J, Zhang J, Howk K, Williams A. Evaluation of perivascular adhesion formation in New Zealand white rabbits using Crixplex and DuraSeal Xact adhesion barrier system. Int J Spine Surg 2009;3:68–76

146. Ozbalci GS, Sulaimanov M, Hazinedaroglu SM, Torunier A. The effects of hydrophilic polyethylene glycol-based adhesion barrier use to prevent intra-abdominal adhesions in intra-abdominal sepsis model. Indian J Surg 2015;77:398–402

147. Dasiran F, Eryilmaz R, Isik A, Okan I, Somay A, Sahin M. The effect of polyethylene glycol adhesion barrier (spray gel) on preventing peritoneal adhesions. Bratisl Med J 2015;116:379–382

148. Elbert DL, Hubbell JA. Reduction of fibrous adhesion formation by a copolymer possessing an affinity for anionic surfaces. J Biomed Mater Res 1998;42:55–65

149. Gong CY, Wu QJ, Liao JF, Qi TT, Yang B, Wang YJ et al. Prevention of postsurgical cautery-induced peritoneal adhesions by biodegradable and thermosensitive micelles. J Biomed Nanotechnol 2013;9:1984–1995

150. Oh SH, Kang JG, Lee JH. Co-micellized pluronic mixture with thermo-sensitivit y and residence stability as an injectable tissue adhesion barrier hydrogel: co-micellized pluronic mixture as a tissue adhesion barrier. J Biomed Mater Res B Appl Biomater 2018;106:172–182

151. West JL, Hubbell JA. Comparison of covalently and physically cross-linked polyethylene glycol-based hydrogels for the prevention of postsoperative adhesions in a rat model. Biomaterials 1995;16:1153–1156

152. Leach RE, Henry RL. Reduction of posts operative adhesions in the rat uterine horn model with poloxamer 407. Am J Obstet Gynecol 1990;162:1317–1319

153. Park JW, Bak KH, Cho TK, Chun H-J, Ryu JI. Effects of a temperature-sensitive, anti-adhesive agent on the reduction of adhesion in a rabbit laminectomy model. J Korean Neurosurg Soc 2016;59:250

154. Banasiewicz T, Horbacka K, Karoki J, Malinge r S, Antos F, Rudzki S et al. Preliminary study with SprayShield™ adhesion barrier system in the prevention of abdominal adhesions. Wideochir Inne Tech Malinowyzne 2013;8:301–309

155. Johns DA, Ferland R, Dunn R. Initial feasibility study of a sprayable hydrogel adhesion barrier system in patients undergoing laparoscopic ovarian surgery. J Am Assoc Gynecol Laparosc 2003;10:334–338

156. Mettler L, Hucke J, Bojahr B, Tinneberg H-R, Leyland N, Avelar et al. Thermosensitive cross-linked polyethylene glycol-based hydrogels for the prevention of abdominal adhesions. Acta Biomater 2010;6:4079–4092

157. Johns DA, Ferland R, Dunn R. Initial feasibility study of a sprayable hydrogel adhesion barrier system in patients undergoing laparoscopic ovarian surgery. J Am Assoc Gynecol Laparosc 2003;10:334–338

158. Mettler L, Buske J, Bojahr B, Tinneberg H-R, Leyland N, Avelar et al. Thermosensitive cross-linked polyethylene glycol-based hydrogels for the prevention of abdominal adhesions. Acta Biomater 2010;6:4079–4092

159. Johns DA, Ferland R, Dunn R. Initial feasibility study of a sprayable hydrogel adhesion barrier system in patients undergoing laparoscopic ovarian surgery. J Am Assoc Gynecol Laparosc 2003;10:334–338

160. Tjandra JJ, Chan MKY. A sprayable hydrogel adhesion barrier system facilitates closure of defecting loop ileostomy: a randomized trial. Dis Colon Rectum 2008;51:956–960

161. ten Broek RPG, Kok-Krunt N, Verhoeve HR, van Goor H, Bakkum EA. Efficacy of polyethylene glycol adhesion barrier after gynecological laparoscopic surgery: results of a randomized controlled pilot study. Gynecol Surg 2012;9:29–35

162. Tchartchian G, Hackethal A, Herrmann A, Bojahr B, Wallwiener D, Schive K. The effects of hydrophilic polyethylene glycol-based adhesion barrier use to prevent intra-abdominal adhesions in intra-abdominal sepsis model. Indian J Surg 2015;77:398–402

163. Mettler L, Audebert A, Lehmann-Willenbrock E, Jacobs VR, Schive K. New adhesion prevention concept in gynecological surgery. JSLS 2009;7:207–209
166. Pihlajamäki H, Tynninen O, Karjalainen P, Rokkanen P. The impact of poly(glycolic) membrane on a tendon after surgical rejoining. A histological and histomorphometric analysis in rabbits. J Biomed Mater Res A 2007; 81: 987–993

167. Fukuhira Y, Ito M, Kaneko H, Sumi Y, Tanaka M, Yamamoto S et al. Prevention of postoperative adhesions by a novel honeycomb-patterned poly(lactide) film in a rat experimental model. J Biomed Mater Res B Appl Biomater 2008; 86: 353–359

168. Avital S, Bollinger TJ, Wilkinson JD, Marchetti F, Hellinger MD, Jiang S, Zhao X, Chen S, Pan G, Song J, He N et al. Prevention of postsurgery-induced abdominal adhesions by electrospun fibrinous membranes prevents tendon adhesions. Biomaterials 2014; 35: 9920–9929

169. Zong X, Li S, Chen E, Garlick B, Kim K, Fang D et al. Prevention of postsurgery-induced abdominal adhesions by electrospun bioabsorbable nanofibrous poly(lactide-co-glycolide)-based membranes. Ann Surg 2004; 240: 910–915

170. Ozpolat B, Gunal N, Pekcan Z, Ayva ES, Bozdogan O, Gunaydin S et al. Poly(lactic acid and polyethylene glycol) prevent surgical adhesions. Br J Surg Med J 2016; 116: 54–58

171. Hu C, Liu S, Zhang Y, Li B, Yang H, Fan C et al. Long-term drug release from electrospun fibers for in vivo inflammation prevention in the prevention of peritendinous adhesions. Acta Biomater 2013; 9: 7381–7388

172. Lodge AJ, Wells WJ, Backer CL, O’Brien JE, Austin EH, Bacha EA et al. A novel bioresorbable film reduces postoperative adhesions after infant cardiac surgery. Ann Thorac Surg 2008; 86: 614–621

173. Schreinemacher MHF, Emans PJ, Gijbels MJJ, Greve J-WM, Beets GL, Bouvy ND. Degradation of mesh coatings and intraperitoneal adhesion formation in an experimental model. Br J Surg 2009; 96: 305–313

174. Townsend KL, Race A, Keane M, Miller W, Dishaw L, Fisher ER et al. A novel hydrogel-coated polyester mesh prevents post-surgical adhesions in a rat model. J Surg Res 2011; 167: e117–e124

175. Weis C, Oderrmann EK. A-part gel: an efficient adhesion prevention barrier. J Biomed Mater Res B Appl Biomater 2007; 82: 174–182

176. Bae S-H, Son S-R, Kumar Sakar S, Nguyen T-H, Kim S-W, Min Y-K et al. Evaluation of the potential anti-adhesion effect of the PVA/gelatin membrane: PVA/gelatin membrane. J Biomed Mater Res B Appl Biomater 2014; 102: 840–849

177. Weis C, Oderrmann EK, Kressler J, Funke Z, Wehner T, Freytag D. Poly(vinyl alcohol) membranes for adhesion prevention. J Biomed Mater Res B Appl Biomater 2004; 70: 191–202

178. Renn BW, Leitner K, Oderrmann E, Worthley DL, Angele MK, Jauch K-W et al. PGA gel as a potential adhesion barrier: a safety study in a large animal model of intestinal surgery. Langenbecks Arch Surg 2014; 399: 349–357

179. Lang RA, Gruntzig PM, Weisgerber C, Weis C, Oderrmann EK, Kirchner MH. Polyvinyl alcohol gel prevents abdominal adhesion formation in a rabbit model. Fertil Steril 2007; 88: 1180–1186

180. Lalountas M, Ballas KD, Michalakis A, Psarras K, Asteriou C, Giakouvoidis DE et al. Postoperative adhesion prevention using a statin-containing cellulose film in an experimental model. Br J Surg 2012; 99: 423–429

181. Kalem M, Şahin E, Songur M, Zehir S, Armangil M, Demirtaş MA. Role of anti-adhesive barriers following rotator cuff repair surgery: an experimental study. Acta Orthop Traumatol Turc 2016; 50: 227–233

182. Tandon A, Shahzad K, Pathak S, Oommen C, Nunes Q, Smart N. Parietex™ Composite mesh versus DynaMesh®-IPOM for laparoscopic incisional and ventral hernia repair: a retrospective cohort study. Ann R Coll Surg Engl 2016; 98: 568–573

183. Ko JE, Ko Y-G, Kim WI, Kwon OK, Kwon OH. Nanofiber mats composed of a chitosan-poly(l-lactic-co-glycolic acid)-poly(ethylene oxide) blend as a postoperative anti-adhesion agent: chitosan-PLGA-PEO blend nanofibers. J Biomed Mater Res B Appl Biomater 2017; 105: 1906–1915

184. Chou P-Y, Chen S-H, Chen C-H, Chen S-H, Fong YT, Chen J-P. Thermo-responsive in-situ forming hydrogels as barriers to prevent post-operative peritoneal adhesion. Acta Biomater 2017; 63: 85–95

185. Murakami T, Hijiukuro I, Yamashita K, Tsunoda S, Hirai K, Suzuki T et al. Antiadhesion effect of the C17 glycerin ester of isopropenoid-type lipid forming a nonlamellar liquid crystal. Acta Biomater 2019; 84: 257–267

186. El-Sayed N, Galal S, El-Gowelli H, El-Khordagui L. Inhibition of postsurgical adhesions by methylene blue-loaded nanofibers versus cast film matrices. J Biomater Sci Polym Ed 2016; 27: 1029–1044

187. Gunay E, Abuglu HH, Uzunoglu H, Sunamak O, Akyuz C. Efficacy level of dimethyl-sulfoxide (DMSO) in the prevention of peritoneal adhesions: an experimental rat model. Int J Clin Exp Med 2019; 12: 705–711

188. Liu S, Pan G, Liu G, Neves Jd, Song S, Chen S et al. Electrospun fibrous membranes featuring sustained release of ibuprofen reduce adhesion and improve neurological function following lumbar laminectomy. J Control Release 2017; 264: 1–13

189. Shin YC, Yang WJ, Lee JH, Oh J-W, Kim TW, Park JC et al. PLGA nanofiber membranes loaded with epigallocatechin-3-O-gallate are beneficial to prevention of post-surgical adhesions. Int J Nanomedicine 2014; 9: 4067–4078

190. Whitfield RR, Stills HF, Huls HR, Crouch JM, Hurd WW. Effects of peritoneal closure and suture material on adhesion formation in a rabbit model. Am J Obstet Gynecol 2007; 197: 644.e1–644.e5

191. Sekiba K. Use of Interceed®(TC7) absorbable adhesion barrier to reduce postoperative adhesion formation in infertility and endometriosis surgery. The Obstetrics and Gynecology Adhesion Prevention Committee. Obstet Gynecol 1992; 79: 518–522

192. Chung Y-J, An S-Y, Yeon J-Y, Shim WS, Moj-H. Effect of a chitosan gel on hemostasis and prevention of adhesion after endoscopic sinus surgery. Clin Exp Otorhinolaryngol 2016; 9: 143–149

193. Zhou J, Liwski RS, Elson C, Lee TDG. Reduction in postsurgical adhesion formation after cardiac surgery in a rabbit model using N,O-carboxymethyl chitosan to block cell adhesion. J Thorac Cardiovasc Surg 2008; 135: 777–783

194. Li C, Wang H, Liu H, Yin J, Cui L, Chen Z. The prevention effect of poly(l-glutamic acid)/chitosan on spinal epidural fibrosis and peridural adhesion in the post-laminectomy rabbit model. Eur Spine J 2014; 23: 2423–2431

195. ten Broek RP, Bakkum EA, Larhoven CJHM, van Goor H. Epidemiology and prevention of postsurgical adhesions revisited. Ann Surg 2016; 263: 12–19