Adjuvant Therapy for the Reduction of Postoperative Intra-abdominal Adhesion Formation

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BACKGROUND: To review currently available evidence on the use of adjuvant therapy to reduce the formation of postoperative intra-abdominal adhesions.

METHODS: A search on Pubmed and the Cochrane library was undertaken using the keywords “abdominal”, “adhesion”, “postoperative”, “prevention” and “reduction”. Only randomised controlled trials, prospective non-randomised controlled studies and review articles published in the English language between 1990 and 2006 were included.

RESULTS: Two prospective non-randomised controlled studies and 18 randomised controlled trials were included in this review. Adjuvant therapies reviewed included pharmacological agents (streptokinase, recombinant tissue plasminogen activator, vitamin E antioxidant molecules), and mechanical barriers (hyaluronic acid barriers, oxidised regenerated cellulose barriers, nanofibrous barriers and collagen foils). Hyaluronate/carboxymethylcellulose-based bioresorbable membrane (Seprafilm) appeared to be the most efficacious in reducing adhesion formation as well as decreasing the incidence of adhesion obstruction requiring reoperation in clinical studies. Drawbacks to the use of Seprafilm include high cost and complications such as haemorrhage and poor wound healing.

CONCLUSIONS: Only a limited number of adjuvant treatment methods are currently available for the reduction of postoperative adhesions. Seprafilm has been proven to be the efficacious method to reduce adhesions. Investigations into the novel therapies are showing promising results in experimental studies and clinical studies before their wider application. [Asian J Surg 2009;32(3):180–6]

Key Words: abdominal, adhesion, postoperative, prevention, reduction

Introduction

Peritoneal adhesion formation after abdominal and pelvic operations is common and this can be a source of considerable morbidity. The incidence of intraperitoneal adhesions ranges from 67 to 93% after general surgical abdominal operations and up to 97% following open gynaecological pelvic procedures.1 Adhesions form between the wound and the omentum in over 80% of patients and these adhesions may involve the intestines in 50% of patients.1 One of the most serious consequences of adhesion formation is small bowel obstruction. In the United States, up to 70% of small bowel obstructions are due to adhesions.2 Within 2 years of surgery, 14% of patients may develop adhesive intestinal obstruction.3 After a first episode, 53% of patients would go on to develop a second episode of adhesive obstruction, and 83% of these would have chronic symptoms.3 The incidence of small bowel obstruction has been reported to be as high as 10% after appendectomy, 6.4% after...
open cholecystectomy, and 10 to 25% after intestinal surgery. The workload and costs associated with bowel obstruction caused by postoperative adhesions are substantial. Hence, there is an important need to prevent or minimise the formation of postoperative intra-abdominal adhesion.

Surgical trauma to the mesothelial surface of the peritoneum exposes the submesothelial matrix and initiates a process of healing. The coagulation cascade is activated, resulting in fibrin deposition and subsequently fibrinolysis. When there is an imbalance in favour of fibrin deposition, bridges between various unrelated tissue surfaces may develop and adhesions will be formed. Factors associated with this imbalance include surgical trauma, infection, ischaemia and exposure to foreign materials, such as talc and glove powder, lint from abdominal packs, and fibres from disposable paper items.

The main approaches to prevent adhesion formation include the adjustment of surgical techniques, avoidance of foreign material exposure, and the applications of adjuvant treatment. Other effective measures include careful tissue handling, keeping tissues moist, and the use of micro- and atraumatic instruments to reduce serosal injury. The target of most anti-adhesion therapies is the fibrin gel matrix. Applying an agent intra-abdominally at the time of operation bypasses the difficulties of therapeutic homing and minimises potential systemic side effects. The time window for a successful intervention is relatively small (5 to 7 days). An optimal adhesive barrier should be non-toxic, biocompatible, easy to apply, and is ideally dissolved after 1 to 2 weeks. In general, adjuvant therapy falls into two main categories. The first is the administration of drugs that prevent excessive fibrin deposition. The second is the separation of serosal surfaces during the early stages of wound healing by means of mechanical barriers.

This review will focus on pharmacological and barrier adjuvant therapies for preventing or reducing the formation of postoperative intra-abdominal adhesions. The authors aim to review available evidence on different forms of treatment currently in use as well as novel therapies that are still in the experimental stages.

Methods

A literature search using electronic databases, including PubMed and the Cochrane library was performed. Search terms included “abdominal”, “adhesion”, “postoperative”, “prevention” and “reduction”. Two independent investigators screened the abstracts of articles. The inclusion criteria were: (i) randomised controlled trials or prospective non-randomised controlled studies or reviews published in the English language between 1990 and 2006; (ii) articles describing adjuvant therapy for the prevention of intestinal adhesion formation after abdominal or pelvic surgery; (iii) animal experiments or clinical studies. Bibliographies of review articles were searched for potentially relevant studies not identified through the electronic searches. Two independent investigators undertook the data extraction from these articles.

A total of two prospective non-randomised controlled studies and 18 randomised controlled trials were identified (Table 1). Adjuvant therapy for the reduction of adhesion formation may be classified into pharmacological and mechanical barrier methods. Table 2 lists the main modalities of treatment which are to be discussed in the following sections.

Results

Pharmacological adjuvant therapy

Streptokinase

Streptokinase enhances fibrinolysis by increasing the conversion of plasminogen to plasmin, and thereby reduces excessive fibrin deposition which is the key event in adhesion formation. Results from experimental animal studies were, however, disappointing. Several factors may limit the application of pharmacological agents in preventing adhesion formation. Firstly, ischaemic sites liable to adhesion formation are cut off from systemic drug delivery. Secondly, the peritoneum rapidly absorbs and reduces the efficacy of any intraperitoneally administered agents. Thirdly, anti-adhesion agents may affect normal wound healing. A fibrinolytic activity lasting for a minimum of 2 days is needed for the prevention of adhesion formation. The plasma clearance time for streptokinase is 23 minutes and it is expected to completely disappear from the peritoneal cavity after 6 hours. Simply administering streptokinase intraperitoneally therefore showed no significant effect on the prevention of postoperative adhesions.

Repeated injections of fibrinolytic agents or controlled release of them with an infusion pump have been investigated in animal models. It was shown that prolonged
exposure of the peritoneal cavity to streptokinase decreased postoperative adhesion formation. Yagmurlu et al showed in the rat model that continuous use of streptokinase was shown to prevent postoperative adhesion formation in 90% of cases. Biodegradable drug delivery systems such as polyhydroxybutyrate-co-hydroxyvalerate (PHBV) membranes can deliver the streptokinase continuously and had been shown to reduce the extent and severity of the developed adhesions. A lower dose of streptokinase was needed to minimise the harmful side effects such as postoperative haemorrhages.

Recombinant tissue plasminogen activator

Tissue plasminogen activator (t-PA) converts the inactive proenzyme plasminogen into active plasmin, which in turn degrades the fibrin matrix structure. Alteplase or recombinant human tissue plasminogen activator (rt-PA) has several advantages over previously used thrombolytic agents. Animal studies with Alteplase found that the agent did not cause immunogenic reactions, and was readily absorbed into fibrin clots and displayed their effect locally. The incidence of adhesion was less than 31% as compared to 57.2% in the control group. There is a dose-related treatment effect. A further reduction in adhesion formation was found with increasing dosages of rt-PA. There was also a reduction in adhesions from 13.1% after 1 day to 6.9% after 4 days of use. The risk of complications, such as bleeding, systemic fibrinogenolysis and impaired wound healing, was not assessed in the

Table 1. Studies reviewed

<table>
<thead>
<tr>
<th>Authors</th>
<th>Type</th>
<th>Subjects</th>
<th>Therapy studied</th>
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<tr>
<td>Beck 2003</td>
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<td>Human</td>
<td>Seprafilm</td>
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<td>RCT</td>
<td>Animal</td>
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<td>Interceed</td>
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<td>Dunn 1993</td>
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<td>Margenthaler 2006</td>
<td>PS</td>
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<td>Small bowel obstruction</td>
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RCT = randomised controlled trial; PS = prospective non-randomised controlled study.

Table 2. Adjuvant therapy options

1) Pharmacological agents
   (a) Streptokinase
   (b) Recombinant tissue plasminogen activator
       (Alteplase)
   (c) Antioxidants (vitamin E)

2) Mechanical barriers
   (a) Sodium hyaluronate + phosphate-buffered saline
       (Sepracoat, Genzyme, USA)
   (b) Oxidised regenerated cellulose (Interceed, Johnson & Johnson, Canada)
   (c) Sodium hyaluronate + carboxymethylcellulose-based
       biodegradable membrane (Seprafilm, Genzyme, USA)
   (d) Poly(lactide-co-glycolide)-based membranes
   (e) Collagen foils + polypropylene mesh (TissuFoil E, Baxter, Germany)
study.\textsuperscript{11} It was also demonstrated that rt-PA could be delivered as a gel to delay its release and absorption, as similar to streptokinase rt-PA is rapidly absorbed into the peritoneal cavity.\textsuperscript{11} However, there were risks of postoperative haemorrhage and delays in wound healing associated with this approach.\textsuperscript{11} Compared with streptokinase, rt-PA has similar effects on adhesion reduction but streptokinase has lower risks of complications. Both pharmacological agents were only tested on animals and clinical trials are needed to validate its use in humans.

Antioxidants

Reactive oxygen species (ROS) are produced in a hypoxic environment and during the ischaemic/reperfusion process. The ROS activity is deleterious for cells. During laparotomy, the partial pressure of oxygen (150 mmHg) is higher than the intracellular pO$_2$ (5–40 mmHg) and this explains the increase in ROS. ROS scavengers such as antioxidant enzymes and antioxidant molecules can help balance the ROS activity and toxicity.\textsuperscript{15} The use of these ROS scavengers was shown to reduce adhesion formation following open surgery in animal studies.\textsuperscript{15} Vitamin E, an antioxidant molecule, has been shown to exhibit additional anti-inflammatory effects. It also has the ability to inhibit fibroblasts and platelet adhesion and release.\textsuperscript{16} In an experimental model in rats, de la Portilla et al found that intraperitoneal administration of vitamin E reduced 30–90\% of adhesions.\textsuperscript{16} Vitamin E absorption was only 20–60\% orally, but when applied intraperitoneally, there was a reduction in 80\% of adhesions.\textsuperscript{16} The study on ROS leading adhesion formation is in its preliminary stages. The trials available on this subject are limited but the early results are promising.

Mechanical barrier adjuvant therapy

A number of natural and synthetic graft materials have been employed in an effort to reduce adhesion formation between traumatised surfaces. These barriers are placed over traumatised tissues at the conclusion of surgery in order to separate tissue surfaces. The ideal barrier, besides being safe and effective, should persist during the critical remesothelialisation phase, stay in place without sutures or staples, remain active in the presence of blood and be biodegradable. Solid barriers in particular can be used intra-abdominally for haemostasis and has also been examined in the context of adhesion prevention.\textsuperscript{6} These barriers are shown to be efficacious in preventing surgical adhesions. They are primarily designed to prevent adhesions between the bowel and the anterior abdominal incision.\textsuperscript{17}

Sodium hyaluronate combined with phosphate-buffered saline

Hyaluronic acid is a naturally occurring glycosaminoglycan and a major component of the extracellular matrix. It coats serosal surfaces and provides a certain degree of protection from serosal desiccation.\textsuperscript{18} Seprocoat (Genzyme, USA), a combination of hyaluronic acid with phosphate-buffered saline, has been found to effectively reduce serosal damage, inflammation and postsurgical adhesions in animal models.\textsuperscript{19} In a prospective randomised placebo controlled trial on patients who underwent laparotomy for gynaecological procedures and subsequent laparoscopy to assess the severity of intraperitoneal adhesions, Seprocoat was found to significantly decrease the incidence, extent, and severity of de novo adhesions.\textsuperscript{20} Seprocoat significantly increased the percentage of patients who were free of de novo adhesion formation to 13.1\%, compared to 4.6\% in patients treated with a placebo.\textsuperscript{20} The solution is ideal in terms of even distribution and contact with the peritoneal surfaces but in practice, the fluid form is uncomfortable for the patient and is associated with side effects such as pulmonary and perineal oedema.\textsuperscript{6}

Oxidised regenerated cellulose

Oxidised regenerated cellulose or Interceed (Johnson & Johnson, Canada), has been shown in both animal and human studies to reduce adhesion formation by forming a barrier and physically separating adjacent raw peritoneal surfaces. It becomes a gel within eight hours and is completely cleared from the body within 28 days.\textsuperscript{21} Interceed reduced the incidence, extent and severity of postoperative pelvic adhesions but did not completely prevent them.\textsuperscript{22} In an a rabbit uterine horn model, the application of Interceed together with heparin significantly reduced adhesion scores.\textsuperscript{21} However, this reduction did not reach statistical significance when compared to untreated individuals in human studies.\textsuperscript{1} Furthermore, to achieve its optimal effect, the use of oxidised regenerated cellulose barriers requires the absence of free fluid within the peritoneum. Absolute haemostasis and complete removal of excessive peritoneal fluid are the main technical difficulties.\textsuperscript{21,22}
Sodium hyaluronate/carboxymethylcellulose-based biodegradable membrane

Seprafilm (Genzyme, USA) is a biodegradable membrane containing sodium hyaluronate/carboxymethylcellulose. It becomes a hydrophilic gel within approximately 24 hours after placement and provides a protective coat around traumatized tissue for up to 7 days during re-mesothelialisation. The material is completely cleared from the body within 28 days and, unlike Interceed, it can be used in the presence of blood. The effect of the membrane on wound healing, and a series of challenge tests to determine its toxicology, immunogenicity, and biocompatibility was described in an animal study. Sepafilm was found to reduce the number of caecal adhesions significantly. The treated group had a significantly larger proportion of adhesion-free animals (72%) than the untreated group (28%) in post-caecal abrasion or abdominal sidewall injury. Sepafilm maintains its efficacy when used with excessive irrigation solutions, when layered, and under ischaemic conditions. These are the technical advantages that Sepafilm have over Interceed.

The effect of seprafilm on intraperitoneal adhesions was studied in a multi-centre prospective double blind randomised controlled trial on patients who underwent total proctocolectomy and ileal-pouch anal anastomosis with diverting loop ileostomy for ulcerative colitis or familial polyposis. One hundred and eighty-three patients were randomised into the study, 1,791 patients who underwent open resection of the small bowel, colon or rectum were randomised into Sepafilm or no treatment after the operation. Of the 1,701 patients evaluated for the outcome of intestinal obstruction, there was no difference in the incidences of first intestinal obstruction between the two groups (12% versus 12%). However, the incidence of adhesive bowel obstruction which required reoperation was 1.8% in the Sepafilm group while that in the control group was 3.4%. The difference was statistically significant (p < 0.05) and treatment with Sepafilm was the only predicting factor associated with a reduction in the incidence of adhesive obstruction that required reoperation.

Another novel addition to Sepafilm has been studied recently. By adding a glycerol compound to the formula, there was an improvement in the product’s tensile strength and memory. The study involved patients with ulcerative colitis or familial polyposis undergoing restorative proctocolectomy and ileal pouch-anal anastomosis with diverting loop ileostomy. There were fewer patients who developed small bowel adhesions (treated = 53% versus control = 73%) and omentum adhesions (treated = 40% versus control = 65%) when using the novel Sepafilm formula. Furthermore, there was a reduction in the severity of adhesions in the treated group.

Drawbacks to Sepafilm included a higher incidence of fistula formation (Sepafilm group: 2% versus control group: < 1%) when Sepafilm was wrapped around an anastomosis or intestinal suture line. There was also a higher incidence of impaired wound healing and infections (e.g. abscess formation peritonitis) associated with the use of Sepafilm. Wrapping the suture or staple line of a fresh bowel anastomosis with Sepafilm should also be avoided due to an increased risk of an anastomotic leak.

The use of adhesion reducing substance is effective but costly. Although complications due to adhesion formation poses a large economic burden (US$1.18 billion a year), the cost of the barrier methods is also high. There are so far no cost effectiveness studies on the use of these barrier methods.
Poly(lactide-co-glycolide)-based membranes (PLGA)

Currently, there have been studies on the prevention of postoperative abdominal adhesions by novel nanostructured barriers. These electrospun bioabsorbable nanofibrous poly(lactide-co-glycolide)-based membranes (PLGA) are made by electrospinning technology to fabricate unwoven mats or nanofibres. In an animal study with the rats undergoing midline celiotomy, caecal adhesions were reduced from 78% (control) to 50% (PLGA group). Caecal adhesions were further reduced to 22% when using the PLGA with an addition of hydrophilic co-polymer poly(ethylene glycol/poly(D,L-lactide) (PLGA/PEG-PLA). It is postulated that the addition of hydrophilic co-polymer to PLGA can make the barrier more stable because it overcomes the shrinkage problem caused by the hydrophobic nature of PLGA. A locally controlled delivery system of antibiotics further improves the anti-adhesion property. After addition of electrospun antibiotics (cefoxitin sodium in the study), the PLGA group with antibiotics had adhesions in 25% of cases, compared to 50% with PLGA alone. Combination of the PGLA/PEG-PLA with antibiotics was able to achieve a zero adhesion rate. It has been postulated that the use of antibiotics can reduce bacterial load and subsequent inflammation on the wound site. However, this theory is controversial. In fact, the use of intra-abdominal antibiotics may be associated with an increased severity of adhesions.

Collagen foil, TissuFoil E

Collagen foil used in combination with polypropylene mesh for the repair of experimental abdominal wall defects also reduced the formation of adhesions in an animal study. TissuFoil E (Baxter, Germany) showed significantly less severe and also less extensive adhesions when compared with using polypropylene mesh alone. There were less severe inflammatory reactions found histologically after collagen foil was added to polypropylene mesh. Similarly to PLGA membranes, TissuFoil E has significant anti-adhesion properties. However, these membranes have no clinical evidence supporting their use in humans at the moment.

Conclusion

Adjuvant therapy is well studied with the engineering of many novel mechanical barriers. However, only a few barrier methods are currently approved by the Food and Drug Administration (FDA). Seprafilm appears to have the best adhesion reduction results in clinical studies. However, it has significant drawbacks due to its cost and higher complication rates. Many novel pharmaceutical and barrier methods such as slow release streptokinase, antioxidant molecules, poly(lactide-co-glycolide)-based membranes and TissuFoil E were found to reduce adhesion significantly in animal studies but there are as yet no clinical studies to support their use in patients. Further studies will be required to validate these adjuvant therapies but the results based on currently available evidence are promising.

References


