Prevention of postoperative peritoneal adhesions: a review of the literature

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Abstract

BACKGROUND: Postoperative adhesions are a significant health problem with major implications on quality of life and health care expenses. The purpose of this review was to investigate the efficacy of preventative techniques and adhesion barriers and identify those patients who are most likely to benefit from these strategies.

METHODS: The National Library of Medicine, Medline, Embase, and Cochrane databases were used to identify articles related to postoperative adhesions.

RESULTS: Ileal pouch–anal anastomosis, open colectomy, and open gynecologic procedures are associated with the highest risk of adhesive small-bowel obstruction (class I evidence). Based on expert opinion (class III evidence) intraoperative preventative principles, such as meticulous hemostasis, avoiding excessive tissue dissection and ischemia, and reducing remaining surgical material have been published. Laparoscopic techniques, with the exception of appendicitis, result in fewer adhesions than open techniques (class I evidence). Available bioabsorbable barriers, such as hyaluronic acid/carboxymethylcellulose and icodextrin 4% solution, have been shown to reduce adhesions (class I evidence).

CONCLUSIONS: Postoperative adhesions are a significant health problem with major implications on quality of life and health care. General intraoperative preventative techniques, laparoscopic techniques, and the use of bioabsorbable mechanical barriers in the appropriate cases reduce the incidence and severity of peritoneal adhesions.

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KEYWORDS: Prevention; Postoperative peritoneal adhesions; Review; Bioabsorbable barriers; Risk factors

Patients undergoing laparotomy for various reasons have a 90% risk of developing intraperitoneal adhesions,1,2 and the incidence of re-admissions directly related to adhesions varies from 5% to 20%.3–6 It is estimated that in the United States there are 117 hospitalizations for adhesion-related problems per 100,000 people and the total cost for hospital and surgeon expenditures is about $1.3 billion.7 In some European countries the direct medical costs for adhesion-related problems were more than the surgical expenditure for gastric cancer and almost as much as for rectal cancer.8,9

In view of the magnitude of the health problems and financial burden related to adhesions, prevention or reduc-
tion of postoperative adhesions is an important priority. Numerous articles on the prevention of postoperative adhesions have been published but several controversies such as the effectiveness of available agents and their indication in general surgical patients still exist. Most of the available literature is based on gynecologic patients. For general surgical patients no recommendations or guidelines exist.

The purpose of this literature review was to assess the efficacy of various described adhesion prevention strategies after emergency and elective general surgery and to identify those patients who are most likely to benefit from these various prevention strategies.

Methods

The National Library of Medicine, Medline, Embase, and Cochrane databases were used to identify articles related to postoperative adhesions. English language citations published from January 1980 to May 2009 were assessed. The references in the identified articles also were reviewed. Case reports, letters to editors, and review articles were excluded.

To specifically identify preventative measures for the development of adhesive morbidity, we used the search terms “abdominal adhesion AND prevention” and “adhesive small bowel obstruction AND prevention.” In addition, specific names of mechanical barriers were entered to identify all studies assessing their ability to prevent postoperative intestinal adhesions and obstruction. The titles and abstracts when available were scrutinized to select relevant controlled studies addressing the safety and efficacy of the use of these agents in abdominal surgery. A total of 39 studies and meta-analyses investigating different mechanical barriers were selected and further evaluated. Of those, 19 prospective randomized trials and 3 meta-analyses were identified and are discussed here in detail.10–31

Pathophysiology

Peritoneal tissue repair is a complex process that involves several different cell types, cytokines, coagulation factors, and proteases, all acting together to restore tissue integrity.32 A complex interaction of biochemical events involved in inflammation, angiogenesis, and tissue repair control the adhesion formation process.33 It is widely accepted that the fibrinolytic system plays a central role in postoperative peritoneal healing. Immediately after surgical injury to the peritoneum there is bleeding and an increase in vascular permeability with extravasation of fibrinogen-rich fluid from the injured surfaces.33–35 Almost simultaneously, an inflammatory response occurs, with migration of inflammatory cells, release of cytokines, and activation of the coagulation cascade.32,35 The activation of the coagulation system results in thrombin forma-

tion, which is necessary for the conversion of fibrinogen to fibrin.35 Fibrinolysis is a key factor in determining the amount of adhesion formation. Early fibrinolysis, within 5 days, encourages healing of the peritoneum without adhesion to the adjunct tissues.36 However, if fibrinolysis does not occur within 5 to 7 days of the peritoneal injury, the temporary fibrin matrix persists and gradually becomes more organized as collagen-secreting fibroblasts and leads to adhesion formation.32,37–39

There are 2 major activators in the fibrinolytic system: tissue plasminogen activator and urokinase-like plasminogen activator. They are the main factors that convert plasminogen into active plasmin, a broad-range protease capable of degrading fibrin.32,34 Plasminogen activator inhibitors inhibit fibrinolysis and encourage adhesion formation (Fig. 1).34,40–42

Inflammatory mediators also may play an important role in adhesion formation. There is experimental evidence that certain mediators, such as transforming growth factor-β and interleukins, decrease the fibrinolytic capacity of the peritoneum and increase the formation of adhesions.33–46

Clinical relevance of adhesion-related complications

Abdominal adhesions pose a significant health problem with major adverse effects on quality of life, use of health care resources, and financial costs. The most common adhesion-related problem is small-bowel obstruction (SBO). Adhesions are the most frequent cause of SBO in the developed world and are responsible for 60% to 70% of SBO.4,47 In addition, adhesions have been implicated as a major cause of secondary infertility.48–50 Pelvic adhesions were found to be responsible in 15% to 40% of infertilities.51,52 It has been suggested that these adhesions may interfere with the ovum pick-up mechanism and gamete transportation. Furthermore, some investigators reported that adhesions are responsible for many cases of chronic abdominal pain although this concept remains a controversial issue.53–56 Finally, the presence of adhesions makes reoperation more difficult, adds an average of 24 minutes to the surgery, increases the risk of iatrogenic bowel injury, and makes future laparoscopic surgery more difficult or even not possible.57,58

Risk factors for adhesion-related problems

The identification of high-risk patients may help in the development and use of adhesion-preventing strategies and advice them on the risk of adhesive SBO before an elective surgery. Review of the literature shows clearly that the most important risk factor for adhesive SBO is the type of surgery and extent of peritoneal damage. Surgeries of the colon and rectum are associated with a
higher risk of adhesion-related problems than surgeries to the small bowel, appendix, or gallbladder. Total colectomy with ileal pouch–anal anastomosis is the procedure with the highest incidence for adhesion-related problems with an overall incidence of SBO of 19.3%. Other high-risk procedures include gynecologic surgeries (11.1%) and open colectomy (9.5%). Table 1 shows the incidence of adhesion-related re-admission after various abdominal surgical procedures. In general, open procedures, with the exception of appendectomy, have a higher risk for the development of adhesions than a laparoscopic intervention.

Other possible risk factors include age younger than 60 years, previous laparotomy within 5 years, peritonitis, multiple laparotomies, emergency surgery, omental resection, and penetrating abdominal trauma, especially gunshot wounds.

Some studies examined possible risk factors for recurrence of SBO. There is evidence that with growing numbers of previous episodes of SBO requiring adhesiolysis, the risk for future re-admission for SBO increases. The same studies identified nonsurgical management of the initial episode as a risk factor for recurrence. A multicenter prospective study of 286 patients with adhesive SBO and a 5-year follow-up period identified age younger than 40 years, the presence of matted adhesions, and surgical complications during the surgical management of the first episode as independent risks for recurrence.

Figure 1 Pathophysiology of peritoneal adhesions. tPA = tissue plasminogen activator; uPA = urokinase-like plasminogen activator; PAI = plasminogen activator inhibitor.
Prevention

In view of the magnitude of the medical problems and financial burden related to adhesions, prevention or reduction of postoperative adhesions is an important priority. Some groups have recognized the importance of the problem and have attempted to educate physicians on this issue. Numerous articles on adhesion barriers have been published but several controversies such as the effectiveness of available agents and their indication in general surgical patients still exist. Most of the available literature is based on gynecologic patients. For general surgical patients no recommendations or guidelines exist.

Any prevention strategy should be safe, effective, practical, and cost effective. A combination of prevention strategies might be more effective but our knowledge on this topic is fairly limited. The prevention strategies can be grouped into 4 categories: general principles, surgical techniques, mechanical barriers, and chemical agents.

General principles

Intraoperative techniques such as avoiding unnecessary peritoneal dissection, avoiding spillage of intestinal contents or gallstones, and the use of starch-free gloves are basic principles that should be applied to all patients.

Starched gloves are a preventable significant risk factor for postoperative adhesions. Several experimental studies have shown that the use of starch-powdered gloves during laparotomy is associated with an increased risk of extensive adhesions.68,69 Examining the association between starched gloves and adhesions in the clinical setting is difficult. Cooke and Hamilton70 found that in most patients with an abdominal surgery who had undergone laparotomy within the previous 2 years, starch granulomas could be detected in peritoneal nodules and adhesions and were responsible for the development of SBO. The investigators suggested that although starch usually is absorbed within 2 years, associated band adhesions may persist.

The role of gallstone spillage in adhesion formation is not clear. Experimental evidence implicates gallstone spillage into the peritoneal cavity in the formation of adhesions.71–73 Infected gallstones were associated with more extensive adhesions.71,72,74 Some investigators suggested that noninfected gallstones do not increase the risk of adhesion formation.74–76 The role of gallstone spillage in adhesion formation in the clinical situation is not as clear as shown in experimental studies. In more than 7% of laparoscopic cholecystectomies there is accidental perforation of the gallbladder and spillage of gallstones and about one third of these patients will be discharged with retained intraperitoneal stones.77 The available literature on the significance of this complication is limited in quantity and quality. Memon et al78 reported no adhesive SBO over a 7-year period in 106 patients who had gallstone spillage during cholecystectomy. Similar results were reported by other smaller series.79,80 In view of the limitations of the available clinical studies and the incriminating findings of experimental studies, every effort should be made to avoid accidental gallstone spillage and retrieve any spilled gallstones.

Surgical techniques

The surgical approach (open vs laparoscopic surgery) plays an important role in the development of adhesive SBO. In most abdominal procedures the laparoscopic approach is associated with a significantly lower incidence of adhesive SBO or adhesion-related re-admission. In a collective review of the literature the incidence of adhesion-related re-admissions was 7.1% in open versus .2% in laparoscopic cholecystectomies, 9.5% in open versus 4.3% in laparoscopic colectomy, 15.6% in open versus 0% in laparoscopic total abdominal hysterectomy, and 23.9% in open versus 0% in laparoscopic adnexal surgery. Only in appendectomies there was no difference between the 2 techniques (Table 1).
The role of surgical handling of the peritoneum during the surgery in adhesion formation is not clear. Many experimental studies have shown that nonclosure of the peritoneum was associated with decreased adhesion formation. However, some studies reported no difference or even decreased adhesion formation with closure. In the clinical setting there are no reliable data regarding the management of the peritoneum after a midline incision. However, there is some class I evidence in obstetrics supporting the theory that suturing the peritoneum increases the risk of adhesions. Komoto et al. randomized 124 women undergoing a cesarean section into 2 groups, closure or no closure of the peritoneum. These patients were evaluated at a second cesarean section for adhesion formation. The study reported that patients who had their peritoneum sutured had a higher incidence of extensive adhesions and required more frequent adhesiolysis. Similar results were reported by Malvasi et al. in a prospective randomized study of women undergoing cesarean sections. At repeat surgery, women with peritoneal closure had a significantly higher incidence of adhesions than those without closure (57% vs 20.6%; P < .05). Microscopy showed increased mesothelial hyperplasia, fibrosis, and neoangiogenesis in the group with peritoneal closure. In view of these findings it is prudent to avoid peritoneal closure during laparotomies.

**Mechanical barriers**

In theory, inert materials that prevent contact between the damaged serosal surfaces for the first few critical days allow separate healing of the injured surfaces and may help in the prevention of adhesion formation. Various bioabsorbable films or gels, solid membranes, or fluid barrier agents have been tested experimentally and in clinical trials. Table 2 summarizes materials for adhesion prevention that the Food and Drug Administration has approved. A significant amount of research has been conducted in gynecologic surgery because a second follow-up laparoscopy after the initial surgery is common, thus allowing the evaluation of the efficacy of the therapeutic agents in reducing adhesions. The most extensively studied bioabsorbable films are Seprafilm (Genzyme Corporation, Cambridge, MA) and Interceed (Johnson & Johnson, New Brunswick, NJ).

**Hyaluronic acid/carboxymethylcellulose**

Hyaluronic acid/carboxymethylcellulose (Seprafilm) is the most extensively tested adhesion prevention agent in general surgery. It is absorbed within 7 days and excreted from the body within 28 days. Its safety with regard to systemic or specific complications, such as abdominal abscess, wound sepsis, anastomotic leak, and prolonged ileus, has been established in many studies, including a safety study of 1,791 patients with abdominal or pelvic surgery. There are concerns about a higher incidence of anastomotic

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of action</th>
<th>Trade name</th>
<th>Reduction of adhesions</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seprafilm (film)</td>
<td>Physical barrier that separates traumatized tissue surfaces, absorbed within 7 days</td>
<td>Effective in gynecologic patients (class I evidence)</td>
<td>Safe and effective in reducing the incidence of adhesions after gynecologic surgeries</td>
<td>Effective in reducing the incidence of adhesions, can be administered laparoscopically</td>
<td>Not studied in general surgical patients</td>
<td>10–18</td>
</tr>
<tr>
<td>Interceed</td>
<td>Physical barrier that forms a gelatinous protective coat to separate injured surfaces, absorbed within 14 days</td>
<td>Effective in gynecologic patients (class I evidence)</td>
<td>Safe and effective in reducing the incidence and extent of adhesions after gynecologic surgeries</td>
<td>Prevention of late SBO remains uncertain</td>
<td>Not studied in general surgical patients</td>
<td>19–29</td>
</tr>
<tr>
<td>Adept</td>
<td>Temporary separation of peritoneal surfaces by hydroflotation as a result of maintaining a fluid reservoir for up to 3–4 days</td>
<td>Effective in gynecologic patients (class I evidence)</td>
<td>Safe and effective in reducing the incidence of adhesions, Ad, not contraindicated in cases involving bowel resection or repair, appendectomy, and in surgical cases with frank abdominopelvic infection</td>
<td>Prevention of late SBO remains uncertain</td>
<td>Adept is contraindicated in cases involving bowel resection or repair, appendectomy, and in surgical cases with frank abdominopelvic infection</td>
<td>30</td>
</tr>
</tbody>
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leaks in cases in which the film is placed directly around the anastomosis. Numerous prospective randomized controlled trials showed efficacy in reducing the incidence and extent of postoperative adhesions. Becker et al. in a prospective, randomized, multicenter, double-blind study of 175 evaluable patients with colectomy and ileostomy pouch procedure, compared Seprafilm with controls. The incidence, extent, and severity of adhesions were assessed laparoscopically by a blinded observer at second surgery 8 to 12 weeks after the initial surgery for ileostomy closure. The Seprafilm group had significantly fewer and less severe adhesions (odds ratio [OR], 0.06; 95% confidence interval [CI], 0.02–0.16).

Tang et al. in a prospective, single-center study randomized 70 patients undergoing an elective rectal resection who needed an ileostomy into a Seprafilm and a control group. The outcomes included severity of adhesions and stomal complications at ileostomy closure at 3 weeks after the initial surgery. The study reported a significant reduction of the mean adhesion scores in the treatment group (5.81 ± 0.5 vs 7.82 ± 0.6; P < 0.05). Also, there was a tendency to easier closure and a lower incidence of perioperative complications.

Vrijland et al. in a prospective multicenter study, randomized 71 patients undergoing Hartmann’s resection into a Seprafilm and a control group. The outcomes included the incidence and severity of adhesions and complications and were evaluated at a second planned surgery by a blinded evaluator. Although the incidence of adhesions did not differ significantly between the study groups (OR, 0.34; 95% CI, 0.06–1.98), the Seprafilm group showed a significant reduction of the severity of adhesions.

Cohen et al. in a prospective multicenter trial, randomized 120 patients with colectomy and ileal pouch surgeries into a Seprafilm and a control group. The outcomes included incidence and severity of adhesions and complications and were assessed laparoscopically by a blinded observer at a second surgery 8 to 12 weeks later for ileostomy closure. Treatment with Seprafilm significantly reduced the incidence and severity of adhesions (OR, 0.23; 95% CI, 0.08–0.62).

Kusunoki et al. in a prospective randomized study of 62 patients who underwent surgery for rectal carcinoma, compared Seprafilm with no treatment. The outcomes included severity of adhesions at the subsequent surgery for ileostomy closure. Seprafilm significantly reduced the adhesions in both the midline incision area and the peristomal area. This was associated with shorter surgical time, reduced blood loss, and smaller incisions for ileostomy closure.

Kumar et al. in a recent Cochrane collective review of 6 randomized trials with nongynecologic surgical patients found that Seprafilm significantly reduced the incidence of adhesions (OR, 0.15; 95% CI, 0.05–0.43; P < 0.001) and the extent of adhesion (mean difference, −25.9%; 95% CI, −40.56 to −11.26; P < 0.001).

The experience with Seprafilm in gynecologic surgeries is fairly limited. Diamond, in a prospective, randomized, blinded multicenter study of 127 women undergoing myomectomy, compared Seprafilm with no treatment. The incidence, severity, and extent of adhesions were assessed laparoscopically at a mean of 23 days after the initial procedure. The incidence, measured as the mean number of sites adherent to the uterine surface, was significantly less in treated patients than in untreated patients (mean ± standard error of the mean, 4.98 ± 0.52 vs 7.88 ± 0.48 sites; P < 0.05), severity and extent of adhesions (mean ± standard error of the mean, 13.2 ± 1.67 vs 18.7 ± 1.66 cm²; P < 0.05) were significantly less in the treated group.

Although there is satisfactory class I evidence that Seprafilm significantly reduces the incidence and severity of postoperative adhesions, there is fairly limited work on the effect of this adhesion reduction on the incidence of SBO. Clinical trials evaluating this specific outcome are difficult to perform because of the need for long-term follow-up evaluation of a large number of patients. Fazio et al. in a prospective, randomized, multicenter, single-blind study of 1,791 patients with intestinal resection compared Seprafilm with no treatment intervention. The mean follow-up time for SBO was 3.5 years. There was no difference between the Seprafilm and control group in the overall incidence of SBO (12% vs 12%). However, the incidence of SBO requiring surgical intervention was significantly lower in the Seprafilm group (1.8% vs 3.4%; P < 0.05). This was an absolute reduction of 1.6% and a relative reduction of 47%. Stepwise multivariate analysis showed that the use of Seprafilm was the only independent factor for reducing SBO requiring reoperation. In both groups, 50% of the first episodes of SBO occurred within 6 months of the initial surgery, with nearly 30% occurring within the first 30 days.

Kudo et al. in a nonrandomized study of 51 patients who underwent transabdominal aortic aneurysm surgery, analyzed the incidence of early SBO in patients who had Seprafilm applied and in control patients with no treatment. The incidence of early SBO was 0% in the Seprafilm group and 20% in the control group (P < 0.05). Early SBO was defined according to Pickleman and Lee: patients who have symptoms of SBO within 30 days after the surgery, symptoms that last for 7 days or more, or symptoms of any duration that occurred 7 to 30 days after the surgery. These symptoms included distension, obstipation, abdominal pain, vomiting, and altered bowel sounds, as well as radiologic findings with dilated small bowel and air fluid levels.

**Oxidized regenerated cellulose**

Oxidized regenerated cellulose (Interceed) is a mechanical barrier that forms a gelatinous protective coat and breaks down and is absorbed within 2 weeks. This product has been studied in numerous prospective randomized studies in open or laparoscopic gynecologic surgeries. It has been shown to be safe and effective in reducing adhesions.
Azziz, in a prospective randomized study of 134 women undergoing adhesiolysis by laparotomy (268 pelvic sidewalls), applied Interceed on one sidewall and left the opposite side uncovered. The incidence and severity of adhesions were evaluated at a second-look laparoscopy 10 days to 14 weeks after surgery. Interceed significantly reduced the incidence and extent of adhesions.

Larsson et al of the Nordic Adhesion Prevention Study group in a multicenter, prospective, randomized, blinded study of 66 women undergoing adhesiolysis of 132 ovaries used Interceed around the adnexa on one side and left the other side uncovered. The incidence and severity of adhesions were assessed at a second-look laparoscopy 4 to 10 weeks after the initial surgery. The study showed that Interceed significantly reduced the incidence, extent, and severity of adhesions.

Other smaller, prospective, randomized studies using the same methodology showed similar efficacy of Interceed application in laparoscopic or open surgery. A meta-analysis of 7 randomized studies showed that Interceed decreased the incidence of adhesions by 24.2% ± 3.3% (P < .001) when compared with untreated sites. A more recent meta-analysis also concluded that Interceed reduced the incidence and severity of adhesions after open or laparoscopic gynecologic surgery.

Expanded polytetrafluoroethylene

Expanded polytetrafluoroethylene (Gore-Tex, Preclude; W.L. Gore & Associates, ’s Hertogenbosch, The Netherlands): It is an inert, nonabsorbable permanent membrane that needs to be removed a few days after application. It has been studied mainly in gynecologic surgeries with favorable results. Its usefulness is limited because of the need to be removed surgically at a later stage.

Bioabsorbable gels

Various agents have been developed and tested, but most have been abandoned or withdrawn because of safety issues or a lack of efficacy. SprayGel (Confluent Surgical, Inc, Waltham, MA) is one of the more extensively tested gels. It is a sprayable hydrogel that adheres to the tissues for a period of 5 to 7 days. After several days it is hydrolyzed into water-soluble molecules and is absorbed. The safety of SprayGel has been shown in a few gynecologic and colorectal studies. Although early preliminary clinical trials showed its effectiveness, a larger-scale study was stopped owing to a lack of efficacy.

Fluid agents

Fluid agents have the theoretical advantage of covering more potential sites of adhesion formation than mechanical barriers. However, the experience is still limited and much more work is needed to show their efficacy.

The most widely studied and the only Food and Drug Administration–approved adhesion-prevention fluid agent in laparoscopic surgery is Adept (Baxter Healthcare, Deerfield, IL). Adept (icodextrin 4% solution) is used as an irrigant fluid throughout surgery and at the end of surgery 1,000 mL is instilled and left in the peritoneal cavity. The fluid remains in the peritoneal cavity for several days and separates the damaged surfaces during the critical period of adhesion formation. A large multicenter, prospective, randomized, double-blind study by Brown et al compared Adept (N = 203) with lactated Ringer’s solution (N = 199), in women undergoing laparoscopic gynecologic surgery for adhesiolysis. The study patients returned for a second laparoscopy within 4 to 8 weeks. Adept was significantly more likely to reduce adhesions and improve fertility scores than lactated Ringer’s solution. There was a higher incidence of labial swelling in the treatment group (6% vs .4%; P = .002).

Intergel solution (Lifecore Biomedical, Inc, Chaska, MN), which contains .5% ferric hyaluronate, is another solution used for adhesion prevention. In preliminary studies it has been shown to reduce the number, severity, and extent of adhesions in peritoneal surgery. However, the use of Intergel in abdominal surgery in which the gastrointestinal tract was opened led to an unacceptably high rate of postoperative complications.

Conclusions

Postoperative adhesions are a significant health problem with major implications on quality of life and health care expenses. General intraoperative preventative techniques, such as starch-free gloves, avoiding unnecessary peritoneal dissection, avoiding spillage of intestinal contents or gallstones, and reducing remaining surgical material, may reduce the risk of adhesions and should be applied in every patient. Laparoscopic techniques are preferable to open techniques whenever possible. In high-risk procedures the use of bioabsorbable mechanical barriers should be considered.

Acknowledgments

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