Peritoneal adhesions: Facing the enemy

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**KEYWORDS**

Post-surgical intraperitoneal adhesions

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**Abstract**

Background: Postsurgical adhesions severely affect the quality of life of millions of people worldwide. Numerous attempts have been made to prevent or reduce the incidence of peritoneal adhesions, but with limited success.

Data sources: An extensive Medline search, textbooks, scientific reports and scientific journals are the data sources. We also reviewed reference lists in all articles retrieved in the search as well as those of major texts regarding postsurgical intraperitoneal adhesion formation.

Conclusions: A multifactorial approach including minimizing tissue injury, prophylactic antibiotic usage to reduce infectious morbidity, and biochemical agents with or without biomechanical barriers will reduce the amount and severity of adhesions. However, further research is needed to establish the safety, effectiveness and also the cost/benefit ratio of these substances in human subjects.

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**Introduction**

Abdominal surgery can cause adhesions between tissues and organs. Approximately 93% of the patients who had undergone one or more previous surgeries had intraperitoneal adhesions. Postsurgical adhesions are a consequence of injured tissue surfaces (following incision, cautery, suturing or other means of trauma) fusing together to form scar tissue. Recently it was found that all patients who had undergone at least one prior abdominal surgery developed between one to more than ten adhesions. Postsurgical adhesions severely affect the quality of life of millions of people worldwide, causing small-bowel obstruction, difficult reoperative surgery, chronic abdominal and pelvic pain, and female infertility.

Reoperating through a previous wound can be extremely difficult, risky, and potentially dangerous. Also, adhesiolysis extends operating time, anesthesia, and recovery time and causes additional risks to the patient such as blood loss, visceral damage including injury to the bladder, enterocutaneous fistulas, and resection of damaged bowel.

Numerous attempts have been made to prevent or reduce the incidence of peritoneal adhesions, but with limited success.

**History**

Intra-abdominal adhesions were described at postmortem examination of a patient with peritoneal tuberculosis in 1836. Some studies suggested in 1849 that coagulated lymph...
In 1930, only 7 (3%) of the acute intestinal obstructions were caused by adhesions, but a study during 1942–1945 of 1252 patients with intestinal obstruction suggested that 31% of the acute intestinal obstructions were caused by adhesions. Between 1985–1986, McEntee et al. suggested that in 236 patients with intestinal obstruction, 32% of the acute intestinal obstructions were caused by adhesions. Cox et al. suggested that postoperative adhesions accounted for 64–79% of admissions with small bowel obstruction. Adhesions are the most common cause of large and small intestinal obstructions in the Western world and account for approximately one third to one half of all intestinal and 60–70% of the small-bowel obstructions.

Congenital or inflammatory adhesions rarely give rise to intestinal obstructions, except for malformation. However, between 49 and 74% of the small bowel obstructions are caused by post surgical adhesions. Small bowel obstructions from adhesions are responsible for a large proportion of general surgical admissions and unavoidable operations in current surgical practice. Approximately 1% of all surgical admissions and 3% of laparotomies are the result of intestinal obstruction due to adhesions. In pediatric patients bowel obstruction from adhesions is most prevalent; 8% of neonates undergoing abdominal surgery require a future laparotomy for this complication.

Structure and function of the peritoneum

The peritoneal cavity encompasses the potential space defined by the mesothelial serous membrane and extends superiorly from the diaphragm to the pelvis in its most caudal extent. Anteriorly the peritoneal cavity reflects onto the posterior aspect of the anterior abdominal musculature. Posteriorly the peritoneal lining lies superficial to the retroperitoneal viscera, including the aorta, vena cava, ureters, and kidneys. The anterior and posterior peritoneal layers are described collectively as the parietal peritoneum. The visceral peritoneum represents the mesothelial lining cells that are reflected onto the surface of the viscera, including the stomach, small bowel, spleen, liver, gallbladder, ovaries, uterus, and portions of the bladder, colon, and pancreas. The peritoneum covering the intestine is the serosa of the bowel. The peritoneum also lines the lesser sac, which communicates with the remainder of the peritoneal cavity via the epiploic foramen (foramen of Winslow). In women the peritoneum is reflected onto the fallopian tubes, which communicate through the open fimbriated ends with the uterus and vagina.

The total area of the peritoneum is approximately 1.8 m². It is formed by a single layer of mesothelial cells with an underlying supporting layer of highly vascularized loose connective tissue. Mesothelial cells are organized into two discrete populations: cuboidal cells and flattened cells. Gaps (stomata) between neighboring cells of the peritoneal mesothelium are found only among cuboidal cells. Peritonitis increases the width of these stomata. Beneath the mesothelial cells is a basement membrane of loose collagen fibers, which offers little resistance to diffusion of molecules smaller than 30 kDa. The basement membrane overlies a complex connective tissue layer that includes collagen and other connective tissue proteins, elastic fibers, fibroblasts, adipose cells, endothelial cells, mast cells, eosinophils, macrophages, and lymphocytes.

Peritoneal fluid is secreted by the peritoneal serosa and has the properties of lymph. Diaphragmatic lymphatic channels provide a means for the entry of peritoneal fluid (and any bacteria and proinflammatory mediators) through the thoracic duct into the venous circulation. Inspiration decreases intrathoracic pressure relative to intra-abdominal pressure, creating a pressure gradient favoring fluid movement out of the abdomen.

Under normal circumstances the peritoneal cavity is largely a potential space, as only a thin film of fluid separates the parietal and visceral layers. This fluid layer serves as a lubricant, allowing the abdominal viscera to slide freely within the peritoneal cavity. The capacity of this space is illustrated during peritoneal dialysis, as 2–3 L of fluid are instilled into the peritoneal cavity without any patient discomfort.

Any inflammatory event in the peritoneal cavity results in local peritoneal irritation with loss of regional mesothelial cells. The defect in the mesothelial lining is repaired by "metastasis" of nearby mesothelial lining cells. Peritoneal defects heal everywhere simultaneously. A large peritoneal defect heals in the same amount of time as a small defect, usually 3–5 days. This process is rapid and usually reconstitutes the peritoneal continuity without adhesion formation. The origin of the migrating mesothelial cells remains obscure; they may arise from submesothelial stem cells.

Peritoneal healing and adhesion formation

A peritoneal injury invokes an inflammatory response from the serosal surface with the concurrent loss of the mesothelium. Increased permeability of the blood vessels in the traumatized tissues due to the release of PGE₂ and histamine produces an outpouring of serosanguineous exudates rich in inflammatory cells. This exudate coagulates within a period as short as 3 h. Normally, the majority of fibrinous attachments so formed are lysed within a few days of development. If they persist for 3 days or longer, fibroblastic proliferation may occur within them, causing adhesion formation.

Following surgery, the macrophages increase in number and change function. These postsurgical macrophages are entirely different from the resident macrophages and secrete variable substances, including cyclooxygenase and lipooxygenase metabolites, plasminogen activator, plasminogen activator inhibitor (PAI), collagenase, elastase,
interleukins (IL) 1 and 6, tumor necrosis factor (TNF), leukotriene B₄, prostaglandin E₂ etc.²³–²⁵ Postsurgical intraperitoneal macrophages recruit new mesothelial cells onto the surface of the injury. These mesothelial cells later and in response to cytokines and other macrophage-secreted mediators form small islands which proliferate into sheets of mesothelial remesothelialization.¹⁷

The organization of the fibrin gel matrix is of major importance in adhesion formation. This matrix forms in several steps: from fibrinogen to fibrin monomer, then to soluble fibrin polymer, and finally, by rinsing tissues with irrigating solutions (during surgery), becomes insoluble fibrin polymer. This last product interacts with proteins, including fibronecstin, to form the fibrin gel matrix. This matrix includes leukocytes, erythrocytes, platelets, endothelium, epithelium, mast cells, and cellular and surgical debris. Two damaged peritoneal surfaces coming into apposition while covered with fibrin gel matrix may form an adhesion, not only at the time of surgical injury, but also during the next 3–5 days.²⁶,²⁷ Saed and Diamond suggested that the adhesion fibroblasts develop a specific phenotype which in part is characterized by the over-expression of alpha smooth muscle cell actin.²⁸ The over-expression of alpha smooth muscle cell actin indicates a possible response to peritoneal injury.

Among the earliest factors identified as inducing peritoneal adhesion formation was ischemia.²⁹ Recent investigators have found that the production of ischemic tissue is the most reliable means of inducing adhesion formation for the evaluation of prophylactic modalities. Induction of ischemia by coagulation, ligation, or devascularization as with a free peritoneal graft has all been associated with the induction of peritoneal adhesions. More recent data from a number of investigators²²,³⁰–³⁴ have established that the peritoneum which has been made ischemic loses its spontaneous ability to lyse fibrin. This loss of ability may take as long as 24 h to occur maximally. Moreover, ischemic tissue also inhibits fibrinolysis by adjacent normal tissue.²²

**Weapons of a surgeon to prevent peritoneal adhesions**

**Surgical technique**

Grafting or suturing peritoneal defects increases ischemia, devascularization, and necrosis, predisposing the site to decreased fibrinolytic activity and increased adhesion formation.³⁵ Ryan et al. also reported that normal saline, Ringer’s solution, and Medium 199 were equally ineffective in reducing adhesion formation when fresh blood was dripped intraperitoneally immediately after a wetting procedure.³⁶ Thus, it appears that simply keeping the serosa moist does not prevent a significant impairment of fibrinolytic function. Polubinska et al.³⁷ reported that exposure of the peritoneal mesothelial cells to 0.9% NaCl, Hanks’, Earle’s salts solution, or peritoneal dialysis fluid with high concentration of glucose degradation products results either in reduction of their viability or in loss of their fibrinolytic activity. They also suggested that peritoneal dialysis fluid with low content of glucose degradation products appears to be the optimal solution causing the least damage to mesothelial cells and therefore may be the ideal solution for rinsing the abdominal cavity with low risk of inducing deterioration of the mesothelial cells’ fibrinolytic activity and formation of adhesions.³⁷ They postulated that the hypertonic dialysis fluids may be used for rinsing the abdominal cavity.

Foreign bodies have been found in a large percentage of examined postoperative adhesions.³⁸ Most frequently found are: surface powders from surgical gloves; lint from packs, drapes, or gowns; wood fibers from disposable paper items; and suture materials are also common contaminants. However, recent data suggest that in the absence of an additional peritoneal injury foreign bodies are an infrequent cause of adhesion induction.³⁹–⁴²

Minimizing the production of ischemic tissue remains a crucial concept. If necessary, reperitonealization should be performed with a minimal number of sutures which do not produce significant tension along the suture line. The use of microsutures may be beneficial, because their low tensile strength limits the potential for developing ischemia.⁴¹ The application of free peritoneal or omental grafts is also contraindicated. Precise hemostasis is necessary to limit the amount of tissue rendered ischemic by crushing, ligation, or cautery. The employment of topical hemostatic agents has not been found to increase the incidence of postoperative adhesion formation and may on occasion be advantageous when obtaining hemostasis in areas of generalized oozing.⁴³ Several studies have found that the use of oxidized cellulose (surgicel) actually decreased subsequent adhesion formation.⁴⁴,⁴⁵ Tingstedt et al. suggested that intra-abdominal administration of different charged polypeptides significantly decreased postoperative bleeding and postoperative adhesions in mice.⁴⁶ These polypeptides consisted of a combination of positively charged poly-L-lysine and negatively charged poly-L-glutamate.

Minimal atraumatic handling of tissues is essential for reducing serosal abrasion and is also recognized to reduce fibrinolytic activity. Manipulation of tissues with gloved fingers has been implied by some microsurgeons to be less traumatic than contact with surgical instruments. However, electron-microscopic studies indicate that both produce substantial serosal injury.⁴⁷

In animal models large clots produced adhesion, but small clots did not in the absence of the peritoneal injury.⁴⁸ Hemostasis is essential, and blood should be aspirated in irrigation solution. If pinpoint electrocautery cannot provide adequate hemostasis, then the smallest gauged synthetic suture should be used, with special consideration to avoid tissue strangulation.⁴⁹

The use of the CO₂ laser in gynecologic microsurgery has also been implied to be beneficial.⁵⁰,⁵¹ Sutton and McDonald have been reported that laser laparoscopic adhesiolysis is safe, effective and relatively easy.⁵²

Further studies suggested that compresses, which were moistened with hot saline (over 45 °C), significantly increased intraperitoneal adhesions.⁵³ Also, Smith has found saline warmed to 37 °C to be more effective than room-temperature saline or Hanks’ solution.⁵⁴

The majority of studies indicate that laparoscopy may reduce postoperative adhesion formation relative to laparotomy.⁵⁵–⁵⁷ Brokelman et al. found in a randomized trial that there were no differences in tPA antigen, tPA-activity,
uPA antigen, or PAI-1 antigen concentrations in biopsies taken at the beginning compared to samples taken at the end of the operation. Different intra-abdominal pressures, light intensities and the choice dissection device did not affect any of the measured parameters. They suggested that short-term laparoscopy does not affect the peritoneal fibrinolytic activity. Intra-abdominal pressure, light intensity and choice of dissection device do not affect peritoneal activity during short-term laparoscopy.67

Prophylactic pharmacological modalities

Non-steroidal anti-inflammatory drugs (NSAIDs)
NSAIDs inhibit prostaglandin and thromboxane synthesis by changing cyclooxygenase activities. By this inhibition NSAIDs decrease vascular permeability, plasmin inhibitor, platelet aggregation, and coagulation and also enhance macrophage function. NSAIDs modulate a number of aspects of inflammation and have reduced peritoneal adhesion formation in some animal models.68–70 However, NSAIDs impair wound healing and increase the risk of bleeding.4,61

Glucocorticoids
Corticosteroid therapy attenuates the inflammatory response by reducing vascular permeability and liberation of cytokines and chemotactic factors. They are administered intravenously, enterically or intraperitoneally. This therapy has had mixed results.59 Corticosteroids were studied alone or with antihistamines.61 Antihistamines inhibit fibroblast proliferation and are usually used with corticosteroids. However, corticosteroids have side effects, such as immuno-suppression and delayed wound healing.24,59,61

Progestrone/estrogen
Progestrone prevents adhesion formation in animal models but human studies either failed to confirm this finding or an increase in adhesion formation was noted when medroxyprogesterone acetate was used intramuscularly or intraperitoneally.61 Neither estrogen nor gonadotropin-releasing hormone prevented adhesion formation but fewer adhesions formed than untreated animals.62 It remains unknown whether a hypoestrogenic state leads to less postsurgical adhesions in humans.63

Anticoagulants
In animal models, low molecular weight heparin (LMWH) reduces peritoneal adhesion by increasing the fibrinolysis due to serine esterase activity.64 Many authors suggested that LMWH, at standard treatment doses, prevents postsurgical intraperitoneal adhesions when administered intraoperatively either subcutaneously or intraperitoneally.65,66

Fibrinolytics
Fibrinolytic agents caused hemorrhagic complications, although recombinant tPA, when applied locally, reduced adhesions in animal models without increasing complication rates.24,48,60 A promising approach in postsurgical adhesion prophylaxis was described with the use of tPA. The administration of recombinant tPA succeeded in reducing adhesion formation when studied in the rabbit model. The evidence of further studies suggests that all these approaches have had only limited success, impeded lack of safety, efficacy, and many adverse effects without eliminating the problem of postoperative adhesion formation.17,67–70

Antibiotics
Broad-spectrum antibiotics are commonly used for prophylaxis against postoperative infections and adhesion formation. Less intraperitoneal infection means less intraperitoneal adhesion formation. However, intra-abdominal application causes adhesion formation.60

Vitamin E
Vitamin E theoretically has interesting biological properties and action for the prevention of peritoneal adhesions. In vitro studies have shown that vitamin E has antioxidant, anti-inflammatory, anticoagulant, and antifibroblastic effects, and decreases collagen production. It has been successfully used, administered by the oral route, intramuscularly and especially intraperitoneally, diluted in olive oil, in animal models. Vitamin E was found effective for reducing adhesion formation by some authors.71–73

Methylene blue
Methylene blue is known to inhibit the generation of oxygen radicals such as superoxide by competing with oxygen for the transfer of electrons from flavor-enzymes, primarily xanthine oxidase.74–76 This low molecular weight, partially liposoluble, vital dye, is also a known inhibitor of guanylate cyclase. It organizes the smooth muscle relaxation effects of nitric oxide, blocking its activation by blocking NO binding sites of guanylate cyclase.77,78 In recent studies, it has been suggested that intraperitoneal application of methylene blue can be used as an effective agent in the prevention of postoperative adhesions.79–81 Dinc et al. suggested that methylene blue prevents peritoneal adhesions but causes a significant impairment of anastomotic bursting pressure during the early phase of the wound healing process by its transient inhibitory effect on the nitric oxide pathway.82

Pentoxifylline
Pentoxifylline, a methyl xanthine derivate, enhances plasma fibrinolytic activity, reduces plasma fibrinogen levels, inhibits platelet aggregation and increases erythrocyte and leucocyte flexibility.83–85 Tarhan et al. suggested that pentoxifylline prevents postoperative intra-abdominal adhesions either by intraperitoneal or intravenous administration.86

3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (HMG-CoA-I)
Either Lovastatin or Atorvastatin increases tPA and decreases PAI-1 in human mesothelial cell incubation.87 Aarons et al. suggested that Lovastatin and Atorvastatin reduced adhesion formation by 26% and 58%, respectively, without affecting anastomotic burst pressure, intraperitoneal administration in rats.87

Adjuvant barrier therapy
The ideal barrier, besides being safe and effective, should be non-inflammatory, non-immunogenic, persist during the
critical remesothelialization phase, stay in place without sutures or staples, remain active in the presence of blood and be completely biodegradable. Also, it should not interfere with healing, promote infection, or cause adhesions.27

Barrier solutions
Adept (Shire GmbH and Co. KG) is a 4% icodextrin solution (α-1,4-linked dextrin polymer of glucose) and reduces the extent and severity of adhesion formation in animal models.88–93 It has also been used widely as a peritoneal dialysis solution for several years. Adept is a non-viscous adhesion barrier applied intra-abdominally after surgery. The presence of the polymer creates a constant fluid layer between peritoneal surfaces and acts to reduce adhesion formation by inducing hydroflotation throughout the abdominal cavity for several days. It is reabsorbed gradually through the lymphatic system.94

Hyalobarrier (Baxter GmbH) is a tissue precoating solution and forms a selective barrier made of purified autocrosslinked hyaluronan with increased density, viscosity, and adhesive properties. It remains intra-abdominally for 3–7 days.95,96 It provides lubrication and gliding effects. After surgical trauma, the peritoneal area affected (approximately 25 × 15 mm) was covered to a depth of 3 mm by expelling successive trails of the gel out of the syringe across the surface.97 Martin-Cartes et al. suggested that hyaluronidase gel was moderately superior to obtain reduction of consistency of the adhesion with fibrin glue.98 Hyaluronidase gel also has the advantage of being inexpensive.

Phospholipids in the form of phosphoric acid diesters were defined as a surfactant-like substance in effluent peritoneal dialysis fluid, and possess good release and lubricating properties.99 Experimental results in rat studies with peritoneal instillation of phosphatidylcholine upon abdominal closure seemed to reduce adhesion formation.100–103 It may reduce the risk of adhesion development by diminishing fibrin formation between peritoneal surfaces and defects.99

Solid barriers
Experimental studies have demonstrated that covering lesions of the parietal peritoneum with microsurgically applied autologous peritoneal transplants can completely prevent severe adhesion formation.27 The advantage of a synthetic barrier is that the material does not need to be obtained surgically and can be cut to size outside of the abdomen and then applied without sutures.104

Carboxymethylcellulose is a derivative of cellulose. Carboxymethylation of the glucosidic hydroxyl groups makes the polymer hydrophilic. It is negatively charged at physiological pH and freely soluble. It is spontaneously broken down.63,105 It has heavy molecular weight and slow peritoneal absorption.65 Nevertheless, it cannot completely eliminate postoperative adhesions in all cases.106,107 Mediana et al. suggested that while carboxymethylcellulose film has been shown to decrease adhesions in other models, healing of a rabbit colonic anastomosis even in the presence of an anastomotic defect takes place, further suggesting that the stimulus for adhesion formation can overcome the antiadhesion properties of carboxymethylcellulose.108

Interceed TC7® is made of oxidized regenerated cellulose. It is already in routine clinical use as a “first generation” adhesion barrier.89,109–112 As a mesh like product, it rapidly forms a soft gelatinous mass that provides a protective coating around healing tissue during the first 7–10 days after application.113–115 It is absorbed in the abdominal cavity within 2 weeks.93

Polytetrafluoroethylene (PTFE) is a non-reactive, anti-thrombogenic, non-toxic synthetic fabric with small pores that inhibit cellular transmigration and tissue adherence. A PTFE barrier prevents adhesion formation and reformation regardless of the type of tissue injury or whether hemostasis is achieved.27 It was found that expanded PTFE was associated with fewer postsurgical adhesions to the sidewall than oxidized regenerated cellulose.116

TachoComb H® is a tissue glue-coated collagen sponge. A statistically significant reduction in all adhesion score criteria was found by Schneider et al. in an animal model.117

Poly-DL-lactide (PDLA) is an absorbable copolymer system which has not been formally investigated as a barrier agent for peritoneal adhesions. Wallwiener et al. suggested that PDLA was significantly more effective in preventing adhesions than Ringer’s lactate solution.93

Gene therapy
Hepatocyte growth factor (HGF), also known as scatter factor, exerts multiple effects on a variety of cells, including mesothelial cells. It can stimulate the proliferation and migration of mesothelial cells, inhibit collagen deposition and has a fibrinolytic capacity.118–120 Liu et al. demonstrated that local application of recombinant adenovirus carrying the HGF gene reduces adhesion formation in rat model.121

Conclusion
Strategies to reduce adhesion formation include improving surgical techniques, optimizing laparoscopy conditions, using pharmacologic interventions targeted at the inflammatory response and/or fibrin deposition, and using agents that provide a physical barrier to adhesion formation. While these strategies have provided some success, none have yet proved totally successful in abolishing adhesions. Further research to ensure that adhesion prevention is optimal is therefore essential.

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