Prevention of Abdominal Adhesions – Present State and What's beyond the Horizon?

B. Tingstedt K. Isaksson E. Andersson R. Andersson

Department of Surgery, Lund University, Lund, Sweden

Key Words

Abdominal adhesions · Adhesion prevention · Barriers · Hyaluronic acid · Icodextrin · Polyethylene glycol · Fibrin sealant · Polytetrafluoroethylene · Bioactive polypeptide · Carboxymethylcellulose

Abstract

Intra-abdominal adhesions are normally found after most surgical procedures. Many of the adhesions are asymptomatic, but in about 5% they will lead to readmission due to adhesion-related disorders, such as small bowel obstruction, pelvic pain and infertility. This review discusses possible ways to prevent abdominal adhesions and provides an update as comes to where we stand today in research regarding experimental and clinical use of various antiadhesive agents.

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Introduction

Intra-abdominal adhesions are found in up to 93% of patients who have undergone intra-abdominal surgery [1]. Normally, most adhesions are asymptomatic, but will, however, cause problems in about 5% of the patients. These postsurgical, adhesion-related problems include

small bowel obstruction (SBO), female infertility, pelvic pain and abdominal pain. The formation of adhesions also causes secondary problems like prolongation and endangering future intra-abdominal operations.

Adhesion Pathophysiology

Many types of peritoneal injury have been described that lead to adhesion formation. Mechanical trauma and foreign bodies were the first to be described, but also bacterial infection, desiccation/drying, chemical injury, irradiation, allergic reactions and ischemic injury can lead to injury and subsequent adhesion formation [2].

The fibrinolytic activity in the peritoneum normally degrades fibrin and peritoneal regeneration can take place. The injured area is invaded by inflammatory cells, initially neutrophils but after 24 h mostly macrophages. Chemotactic messengers released by platelets (PDGF, transforming growth factor- β (TGF- β), epinephrine and serotonin), prostaglandins and leukotrienes are hence produced and recruit leukocytes to the site of injury [3]. This attracts mesothelial cells and at 24 h the reperitonealization starts from multiple foci, cell islands, and is finished after 5–7 days [4, 5]. This time range is regardless of the size of the peritoneal wound [4]. The cells are re-

cruited from adjacent tissue, as well as from mesenchymal stem cells and free peritoneal cells [4].

The process continues to healing and/or fibrosis and the subsequent deposition of extracellular matrix containing fibronectin, hyaluronic acid, various glycosaminoglycans and proteoglycans. This deposition is regulated and maintained by growth factors and cytokines (TGF- β , EGF and VEGF) [6]. After the first week and up to a month, the matrix is remodeled and replaced by persistent proteins, such as collagen, and revascularization occurs.

The fibrous exudate, containing both fibrin and inflammatory cells, gradually organizes into a fibrin matrix. If this matrix bridges two surfaces, a fibrinous adhesion is formed. This is more likely to occur when both surfaces are injured [7]. This bridging may occur as long as up to 3 days after the initial surgery/injury [8].

The fibrinous adhesions are lysed if the fibrinolytic activity is adequate, otherwise connective tissue forms and adhesions are developed [9]. Several studies point at the imbalance between fibrin formation and fibrinolysis in the early phase of peritoneal repair as the main determinant in adhesion formation, as demonstrated by studies where decreased fibrinolytic activity increased adhesions [10]. Fibrinolysis stimulators, such as tissue plasminogen factor (t-PA), and urokinase and fibrinolysis inhibitors, such as plasminogen activator inhibitor type-1 (PAI-1), have also been shown to play a role in the adhesion pathogenesis [11]. TGF- β , a key molecular mediator of pathological fibrosis, is also central in adhesion pathogenesis [12].

Further studies are needed to interpret and understand the functions and interrelationships of the involved components in abdominal fibrin formation and fibrinolysis. The field offers most interesting possibilities for intervention and hopefully improved future adhesion prevention.

Modes of Adhesion Prevention

The three main principle pathways to decrease adhesions of today are: (1) decreasing the trauma to the peritoneum; (2) medical interventions in the fibrin formation/degradation balance, and (3) barriers preventing organs from bridging over to other structures in the abdomen and thereby forming adhesions.

The mode of adhesion prevention must also be non-toxic and it can neither intervene in other healing processes, such as wound and anastomotic healing, nor in-

fluence peritoneal immune functions. The study by Wilson et al. [13] states that the cost cannot be higher than GBP 200 to secure cost-effectiveness on national health care.

The adhesive prevention must also be easy to apply to its target (i.e. the injured peritoneum) of its assumed effectiveness. Preferably, it should also be biodegradable and cleared from the peritoneal cavity when it has fulfilled its functions.

Many types of preventive agents have been tried since the 1930s. Only a few have reached clinical application, even though many have shown good experimental results. Adhesion-preventive experimental studies also differ in their designs and evaluation scores, making it difficult to interpret and compare studies. Furthermore, many models have a high standard deviation, which for this reason make the relevance of results with only moderate effects questionable.

Minimized Trauma

The most important factor to reduce adhesions is the introduction of minimal surgical trauma and the absence of powdered gloves [14]. Minimizing the surgical trauma includes avoiding desiccation, gentle handling, reducing foreign body exposure and securing hemostasis. It is also stated that peritoneal defects and the pelvic floor should be left open, since they rapidly reperitonealize and that the anastomosis should be covered with omentum. The omentum should also be pulled down behind the laparotomy incision upon closure. This will lead to a reduced inflammatory response and a decrease in fibrin deposition.

Despite the advances in surgical technique and measurements made for adhesion reduction, there have not yet been any observations of a decrease in the incidence of adhesions according to the SCAR-2 and SCAR-3 studies [15, 16].

Laparoscopic techniques rendered hope since the tissue trauma is reduced and overall traumatizing injury to the peritoneum decreased. However, reports have since concluded that it is not the revelation many thought [17].

Laparoscopy induces new ways of damage to the peritoneal lining, e.g. cooling and drying by carbon dioxide insufflation [18] and also a direct effect on the mesothelial cells by the carbon dioxide per se [19]. The laparoscopic technique seems to decrease the adhesion formation de novo but not the reformation of adhesions [20, 21]. De novo adhesions are defined as new adhesions in previously adhesion-free sites after surgery and reformed adhesions

Table 1. Most common substances tested as biological intervention in adhesion reduction

Biological interventions	Substance	Expected effect	Clinical trials	Reducing adhesions?	Reducing relevant problems? ¹
Anti-inflammatory drugs	NSAID	Varying	No	No	No
	COX-2	Good	No	No	No
Anticoagulants	Heparin	Good	No	No	No
	LMWH	Good	No	No	No
ROS scavengers	Methylene blue	Varying	No	No	No
	Allopurinol	Varying	No	No	No
	Vitamin E	Varying	No	No	No
Proteolytic agents	Trypsin	Reasonable	No	No	No
	Pepsin	Reasonable	No	No	No
	Hypertonic glucose	Reasonable	Yes	Varying	No
	Streptokinase	Varying	Yes	Varying	No
	Urokinase	Varying	No	No	No
	rt-PA	Good	No	No	No
	PRAP-1	Good	No	No	No
Fibrinolysis intervention	Pentoxifylline	Good	No	No	No
	TGF- β antibodies	Good	No	No	No
Other	Antibiotics	Varying	No	No	No
	Chemotherapeutics	Good	No	No	No
	Immunomodulation	Varying	No	No	No
	GnRH α	Good	No	No	No
	Aprotinin (Trasylol®)	Varying	Yes	Yes	No
	Angiogenesis inhibitor	Good	No	No	No
	Nitric oxide	Good	No	No	No

¹ Relevant problems defined as small bowel obstruction, infertility rates and pelvic pain.

are defined as recurrence when located to the same surgical site after adhesiolysis. This terminology is frequent in gynecological literature regarding adhesions. Whether distant adhesions in laparoscopy increase or decrease has not been established [22], but there has not been any effect demonstrable on fibrin balance in laparoscopy as compared to open surgery [23]. No reports on laparoscopic surgery have shown any effect on the incidence of SBO.

Further studies on laparoscopy and postoperative adhesions are needed to establish whether or not there is an advantage on long-term follow-up.

Medical Interventions

Balancing the fibrin formation and degradation is difficult even without taking the potential negative effect on normal wound healing into account. Experiments have

been made on interventions from the coagulation cascade to the formed fibrin matrix. Tested medical interventions are outlined in table 1.

Anti-Inflammatory Drugs

The inflammatory response seems to be a reasonable way to intervene against the formation of adhesions. Anti-inflammatory drugs have been tested experimentally, including corticosteroids, antihistamines, moderate NSAIDs as well as the new COX-2 inhibitors [24–26]. Some experimental results have been achieved, but problems in drug delivery in clinical studies and impaired wound healing raised questions on the feasibility in using anti-inflammatory drugs as prevention against abdominal adhesions.

Anticoagulants

Heparin and its derivatives, as well as low-molecular-weight heparin (LMWH), have been studied extensively.

Experimental results are good, but the dose required for achieving an effect resulted in hemorrhagic diathesis and delayed wound healing, also shown in humans using Ringer's lactate to deliver the heparin [27]. LMWH results show good experimental results, though no clinical studies have been carried out [28]. Using oxidized regenerated cellulose (Interceed®) to deliver the heparin, the preventive effect was increased and side effects diminished, but it failed to prove any effectiveness in a randomized clinical trial [29].

ROS Scavengers

Experiments using ROS scavengers have no convincing results even though significant reductions were found experimentally. Tested substances include methylene blue, allopurinol and vitamin E [30–32]. No data from clinical studies exist.

Proteolytic Agents

The degradation of fibrin is another reasonable and theoretically interesting possibility to solve the problem of abdominal adhesions. Trypsin and pepsin were used in the 1930s, but with side effects such as peritonitis [33]. Hypertonic glucose has fibrinolytic effects through stimulated t-PA synthesis; however, clinical results are conflicting [33, 34].

Streptokinase, urokinase and plasmin were tested with some promising experimental results [33]. Streptokinase even proved to reduce adhesions in a clinical study without impaired wound healing [35], but it has never come to clinical use.

The turning point using proteolytic agents may come with recombinant human t-PA (rt-PA). Several studies have shown promising results with a reduction in adhesions and with few side effects, like absence of negative influence on healing [36]. One pilot clinical trial has been conducted demonstrating a reduction in adhesions [37].

The finding of increased levels of PAI-1 in adhesion-prone objects [38] led Falk et al. [39] to conduct a study with polyclonal rabbit antibodies against PAI-1 (PRAP-1). The result was a significant reduced adhesion rate in mice treated with PRAP-1, which further supports the hypothesis of the crucial role of fibrinolysis in the formation of adhesions.

Fibrous Repair Intervention

Intervening in the formation of fibrosis is another possible way of decreasing adhesion development. Pentoxifylline inhibits collagen and glycosaminoglycan synthesis. Pentoxifylline decreases fibrosis, but its functions are

complex. In one study, pentoxifylline decreased the amount of adhesions, but it is possible that the mechanisms are different than by decreasing fibrosis [40].

TGF- β , a mediator in wound healing and fibrosis, among many other functions, down-regulates t-PA and increases PAI-1 [41]. Reduction of adhesions has also been shown by using antibodies against TGF- β [12] and the use of angiotensin-converting (ACE) inhibitors, which per se decrease TGF- β [42]. A relationship between connective tissue growth factor (CTGF) and fibrosis and angiogenesis suggests CTGF as a potential future target in adhesion prevention [43].

Angiogenesis Inhibitors

Adhesions are vascularized structures. Histologic examination of human adhesions has revealed that they are constituted of collagen fibers, interspersed with adipose tissue and express recognized vascular markers. Expression of the vascular marker CD 105, indicating more immature vessels and presence of vascular growth factor A, suggests a potential for the use of angiogenesis inhibitors [44]. Greene et al. [26] conclude that celecoxib exerts its antiadhesive effect through antiangiogenesis.

Other Medical Interventions

Over the years, a variety of drugs have been tried as antiadhesive agents. Antibiotics have been tried to reduce infection and hereby decrease adhesions [45]. Other authors have, however, seen an increase in adhesions after antibiotic abdominal irrigation [46]. The bactericidal taurolidine has reduced adhesions experimentally [47]. Chemotherapeutics such as 5-FU [48] and mitomycin C [49] have also been evaluated and demonstrated to reduce the extent of adhesions. Immunomodulating drugs (IL-4 and IL-10) were tested in the 1990s, probably inducing their effect via anti-inflammation [50]. Hormone modulation as a mode of reducing adhesions via induction of hypoestrogenism has also been tried [51]. Simvastatin intraperitoneally has also shown experimental reduction in adhesion formation via induction of t-PA activity [52].

Barriers

Hindering adjacent structures from bridging and forming adhesive bands through different strategies, 'barriers' have gained a great interest during the last decades. The idea is not new and the concept was thought of as early as in the beginning of the 20th century. Barri-

Table 2. Most common barriers tested in adhesion reduction

Barriers	Substance	Expected effect	Clinical trials	Reducing adhesions?	Reducing relevant problems? ¹
Polysaccharides	Crystalloid solution	Varying	Yes	Yes	No
	Dextran 70 ^a	Varying	Yes	Yes	No
	CMC	Good	No	No	No
	ORC ^b	Good	Yes	Yes	No
	Icodextrin 4% ^c	Good	Yes	Yes	No
	Fungi polysaccharides	Good	No	No	No
Hyaluronic acid (HA) and derivatives	HA ^d	Good	Yes	Yes	No
	HA+CMC ^e	Good	Yes	Yes	Op. SBO ↓? ESBO ↓?
	Glycerol-HA+CMC	Good	Yes	Yes	No
	Cross-linked ferric HA ^f	Good	Yes	Yes	No
Phospholipids	Phosphatidylcholine	Good	No	No	No
	Unsaturated phospholipids	Good	No	No	No
Polyethyleneglycol	PEG ^g	Good	Yes	Yes	Pregnancy ↑?
Fibrin sealants	Fibrin sealants ^h	Varying	No	No	No
Others	PTFE ⁱ	Varying	No	No	No
	Collagen films ^j	Good	No	No	No
	CMC+polyethylene ^k	Good	Yes	Yes	No
	Polylactic acid	Good	No	No	No
Bioactive polypeptides	pL+pG	Good	No	No	No

^a Hyskon®; ^b Interceed®; ^c Adept®; ^d Incert®, Hyagel®; ^e Seprafilm®; ^f Interigel®; ^g Spraygel®, Adhibit®; ^h Tisseel®; ⁱ Preclude Gore-Tex®; ^j ColCys®; ^k Oxiplex®.

¹ Relevant problems defined as small bowel obstruction, infertility rates and pelvic pain.

ers can be divided into installations creating ‘hydroflotation’, thereby separating adhesion-prone structures, and membranes applied to areas of an injured peritoneum where adhesions were anticipated to develop. Barriers are often applied to protect the incisional scar but are sometimes also applied at other surfaces. This will not hinder all cases of SBO, since approximately one fourth of the cases are linked to small bowel adhesions and incisional scar to small bowel only 5% of the cases [53]. Tested barrier substances are outlined in table 2.

Crystalloid Solutions

Crystalloids have been used for a long time, and proposed to work by hydroflotation, but have, if any effect at all, a negative effect on postoperative adhesions [54]. The volume installed is absorbed rapidly, about 35 ml/h, and to be used within the first 36 h, i.e. a crucial time period in adhesion formation [55].

Polysaccharides

Fluid installation of Dextran 70 demonstrated good antiadhesive results both experimentally and clinically in the early 1980s [56]. However, other studies failed to demonstrate any clinical improvement and instead showed severe side effects such as edema, ascites, and coagulopathy [27].

Carboxymethylcellulose (CMC) has been reported as an antiadhesive agent in experimental models, but not in clinical studies. However, CMC together with LMWH and t-PA has been used as a carrier/vehicle and the combinations have experimentally proved effective against adhesion formation [57, 58]. CMC in membranes together with hyaluronic acid (Seprafilm®) [59] and CMC membranes with polyethylene oxide and calcium chloride (Oxiplex/AP®) [60] has also been reported effective as antiadhesive agents in clinical trials.

Oxidized regenerated cellulose (ORC) reached good preventive results in experimental and clinical models and was used as Interceed during the 1990s [61]. Experimental trials reported, however, poor results in the presence of blood and probably also at coexisting infection [62]. A meta-analysis showed reduction of adhesions using Interceed [63], but no clinical benefits have been reported other than a possible value in infertility surgery and Interceed is not widely used in general surgery today.

Icodextrin is a glucose polymer, used as an antiadhesive agent in a 4% solution, ADEPT®. The icodextrin 7.5% solution has been used as a peritoneal dialysis fluid in totally over 4,000 patient-years. It has antiadhesive effects by separating the damaged tissues and the prolonged resorption (3–4 days) makes it interesting as an antiadhesive agent. The experimental effects have been promising, reducing adhesions without obvious side effects [64, 65]. In a randomized clinical trial, the incidence of adhesions at second-look operation was reduced from 52 to 32% [66]. It has also been reported that ADEPT in a multicenter trial was easy and safe to use [67]. A meta-analysis report on pelvic adhesions, however, could not recommend it for prevention of intra-abdominal adhesions [68].

Interestingly, polysaccharides derived from fungi with well-known anti-inflammatory effects reduced adhesions experimentally and the mechanism seemed to be explained by modulation of t-PA and u-PA [69].

Hyaluronic Acid and Derivates

Hyaluronic acid (HA) is a glycosaminoglycan normally found in various tissues, such as synovial fluid and peritoneal fluid [70]. Having the advantage of being a natural component of the body with biocompatibility and absence of immunologic response, HA seems to be well suited as an antiadhesive agent. HA alone, cross-linked ferric HA and HA combined with the above-mentioned CMC have all proved successful in preventing adhesions [71–73].

HA-based compounds work as a barrier, but they have also been shown to have an anti-inflammatory effect, increase the proliferation rate of mesothelial cells and act as ROS scavengers [74–76].

The most popular product on the market today is Seprafilm, a combination of HA and CMC and two anionic polysaccharides. Seprafilm reduces adhesion formation both experimentally and clinically. This product is, however, expensive and no study today has dealt with cost-effectiveness regarding Seprafilm. One sheet costs

approximately GBP 100 and the normal amount used for the prevention of adhesions is 3.5–4.5 sheets per patient, bringing the total cost well above the GBP 200 calculated by Wilson et al. [13] to ensure cost-effectiveness. Disadvantages of using Seprafilm, apart from the cost, is an increased risk of anastomotic dehiscence and formation of abscesses [77] and case reports of paradox inflammatory reactions [78].

Some reports claim to have decreased the rate of early SBO [79], but Seprafilm has not been shown to reduce SBO in a large multicenter trial [59], though the authors claim to have reduced the number of SBOs that need surgery, a claim that has been debated [80].

Adding glycerol to the HA/CMC membranes has also been shown to reduce adhesions in a randomized evaluator-blinded clinical trial, but infectious rates were still significantly higher [81].

Other products, which include HA, are no longer on the market. The last to fail was Intergel® (cross-linked ferric HA gel), recently shown to result in an increased incidence of postoperative complications, resulting in that an ongoing randomized controlled trial was interrupted [82].

Phospholipids

When the surfactant layer is damaged by surgery, a potential way to prevent adhesion formation could be by the addition of phospholipids, thereby recreating the lubricant layer. Experimental results have been effective using phospholipids, mainly phosphatidylcholine, both in models with 'normal' conditions and peritonitis, and no negative effects were seen on wound healing or anastomosis safety [64, 83]. However, no clinical studies have been conducted.

Polyethylene Glycol

Polyethylene glycol, Spraygel®, is a hydrogel that is formed by spraying two liquid precursors simultaneously. It forms a gel which coats and adheres to tissues, thereby preventing bridging and adhesion formation. Spraygel has shown good experimental results, and randomized clinical studies have demonstrated a beneficial effect in gynecological surgery in preventing adhesions, even though no effect has been noted on pregnancy rates after treatment [84]. A Cochrane meta-analysis though failed to demonstrate evidence for the use of Spraygel in the prevention of adhesions [68]. A development of the spray gel as a one-component gel is Adhibit®, which has been reported promising in a randomized single-blind clinical trial including 71 patients undergoing myomectomy surgery [85].

Fibrin Sealants

Fibrin sealants consist mainly of two components, fibrinogen and thrombin, making them attractive for adhesive reduction. Another reason could also be the fact that bleeding could be decreased, thereby reducing the effect of bleeding on adhesion formation. Fibrin sealants increase both t-PA and PAI-1 expression by human peritoneal cells, which may be of benefit in adhesion prevention [86]. Experimental results are diverging and no clinical data are available yet [87–89].

Expanded Polytetrafluoroethylene (ePTFE)

ePTFE is commonly used in vascular surgery as a barrier and graft. The non-dissolvable membranes are used in the repair of the pericardium or peritoneum and has experimentally prevented adhesions (PRECLUDE Peritoneal Membrane™) [90]. One clinical study has been performed showing a reduction in postsurgical adhesions (Gore-Tex™ surgical membrane) [91], and reports mention less abdominal adhesions using ePTFE as part in composite mesh material (Dual-Mesh®) in hernia repair [92]. ePTFE is not widely used in surgery today.

Bioactive Polypeptides

Bioactive polypeptides are interesting as antiadhesive agents. They are biocompatible and integrated in the peritoneal surface. Their often high viscosity could be used to separate adhesiogenic surfaces. They could thus be used as a barrier, but administered as a hydroflotant, hereby acting not only on localized adhesions but more general on all major and minor areas of peritoneal injury. The strongly positively charged poly-L-lysine (pL) binds to the negative or neutrally charged injured peritoneal surfaces, and then form a matrix with the oppositely negatively charged poly-L-glutamate (pG). pL is known to migrate through lipid bilayers, which further adheres the pL-pG complex to the wound.

The pL-pG compound has experimentally prevented adhesions with no obvious effect on peritoneal macrophages or peritoneal immune function [93] and could furthermore be safely used in an inflamed environment [94]. It has also been demonstrated experimentally to increase anastomotic safety, measured as bursting pressure [94]. Bleeding is decreased following treatment by bioactive polypeptides in another experimental setting [95]. No clinical studies are yet available.

Other Barriers

Collagen films have also in a limited number of experiments shown an effect against adhesion formation,

but no clinical data are available [96]. Thrombin-based hemostatic gelatin decreases tenacity of adhesions [97] and polylactin-acid films decreased them experimentally [96]. Transplantation of an autologous mesothelial cell sheet has recently shown positive experimental results and offers a new interesting platform for future development [98].

Conclusion

Results from the last years in adhesion-preventive research have contributed to the understanding of the complex system of fibrin formation and degradation in adhesion generation. The field offers exciting challenges and hopefully an effective medical intervention will be accessible within a reasonable time.

Antiadhesive agents present today are at best reducing adhesions in the intra-abdominal cavity, but studies have more or less failed to present data regarding reduction of SBO, pain or infertility. The most commonly used are Seprafilm and ADEPT. Both have been reported to significantly decrease adhesions in clinical studies, but the substances have not in a randomized fashion shown that they have an impact on relevant clinical outcome, such as infertility and SBO and possibly pain.

New promising agents are Oxiplex/AP gel and Adhibit working as barriers, mechanically preventing adhesions with preliminary good clinical results, though randomized trials are needed. Of potential future interest are also intervention with differently charged bioactive polypeptides and polylactin films, both with, recently published, good experimental results.

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