Review

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# Abdominal Adhesion Prevention: Still a Sticky Subject?

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**Key Words**

Adhesions · Peritoneum · Adhesion barrier · Adhesion prevention · Abdominal surgery

**Abstract**

***Background:*** Adhesion formation remains an almost inevitable consequence of abdominal procedures, potentially resulting in significant morbidity and mortality. There is an ongoing need to evaluate current understanding of adhesion formation and products aimed at prevention. Failure to keep up to date with adhesion treatment may subject clinicians to a greater medico-legal risk. ***Design:*** Review of published studies exploring the problem of peritoneal adhesion formation. This encompasses the underlying processes of adhesion formation combined with general approaches to reduce formation. An overview of products trialled to prevent formation in both the animal model and clinical setting describes products of scientific interest and commercial success. ***Results:*** Advances in surgical technique, such as laparoscopic surgery, can help minimize the probability of adhesion formation. Currently barrier products, whilst reducing adhesion formation, have not been shown to reduce the risk of readmission with complications related to adhesions. Hybrid products may improve upon this situation. ***Conclusions:*** No single approach has been wholly satisfactory in reducing adhesions. Research into the processes driving adhesion formation is providing exciting new targets for therapeutic agents. It would seem plausible that with many promising avenues of research a revolutionary agent to reduce the incidence of adhesional small bowel obstruction may result.



## Introduction

Adhesion formation following surgery remains an almost inevitable consequence of most abdominal procedures. Studies have found the incidence of adhesions to be as high as 95% [1]. Though surgeons are aware of adhesions and the problems that can result, it seems that few routinely take measures to reduce their formation. Advances in surgical technique, such as the use of laparoscopic surgery, can help minimize the probability of adhesion formation [2]. However, the significant morbidity and cost associated with adhesion-related disorders continues to be highly prevalent. Estimates on the workload for the treatment of adhesion-related disorders have put the annual cost in the USA at around USD 1.3 billion [3]. Undoubtedly, these figures will continue to increase with the growing cost of health care and medico-legal repercussions of adhesion-related complications. Whilst many methods have been employed in an attempt to reduce the formation of adhesions, no single approach has been wholly satisfactory. A concerted effort is required from all branches of medical science and surgery if the problem of adhesions is to be conquered. Continued ignorance of the subject, or a failure to adopt new practices aimed at adhesion prevention is simply not acceptable in the current litigious healthcare environment.

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## Consequences of Abdominal Adhesions

The development of intra-abdominal adhesions may manifest in a number of ways and can be categorized as primary or secondary. In primary instances, patients who would not have otherwise required operative intervention require surgery to treat adhesive small bowel obstruction [4, 5], volvulus or chronic abdominal pain [6]. In patients with secondary problems from adhesions, future surgery (for abdominal pathology other than adhesions) may be complicated [7] or prolonged [8, 9]. In such cases, the number and density of adhesions will have a direct impact on the second surgical procedure. In female patients, adhesions within the pelvis may result in infertility [10, 11], ectopic gestation [12] and chronic pelvic pain [13, 14].

Patients undergoing surgery for symptomatic adhesions may also require repeat operations, with each instance associated with an increasing risk of morbidity. Repeated bowel resection or enterotomy as a result of adhesion surgery exposes patients to the risk of anastomotic leak and can increase the chances of developing a variety of other chronic conditions such as short bowel syndrome [15] or enterocutaneous fistulae [16]. Recurrent adhesion-forming patients are perhaps the group with the most to gain from adhesion prevention to break the cycle of re-formation.

Although there is a wide spectrum of adhesive response, the clinically relevant outcome is dependent on patient symptoms or the need for operative intervention. It is difficult to identify individual patients with an increased risk of developing symptomatic adhesions since the relationship between adhesion formation and the surgical pathologies that occur as a consequence is somewhat variable. Logic would dictate that a greater number of adhesions should cause more symptoms; however, this is not always the case. Surgeons will be familiar with the scenario of a single band adhesion causing small bowel obstruction in an otherwise unremarkable abdomen.

## Pathogenesis of Adhesion Formation

Adhesions should be considered as highly cellular, vascularized and dynamic structures under the influence of complex signaling pathways. The idea of an adhesion being a simple nonfunctioning scar is an outdated concept [17]. It is now understood why many of the processes occur in response to an initial adhesion-stimulating event. Damage to the peritoneal mesothelium promotes an acute inflammatory response, with subsequent pathways dictating the number and strength of the fibrous adhesions that form (fig. 1). The mechanisms responsible for a change in normal peritoneal healing to those where adhesions propagate are complex.

Fibrinolysis and extracellular matrix remodeling may be as important in regulating the adhesive process as controlling inflammation in the early stages. The difficulty in modulating adhesion formation lies in separating the process of adhesion formation from that of normal wound healing. Studies examining adhesion formation on a genetic level in an animal model have demonstrated that a large number of genes are upregulated at the wound site postoperatively [18]. Further work is required to identify those genes with a specific role in adhesion formation within the profiles already identified.

On a molecular level, the factors determining cell proliferation, migration, differentiation, angiogenesis, apoptosis and host defense will all have an impact on adhesion formation. Targets for the control of these processes include chemokines [19, 20] and matrix metalloproteinases [21]. Vascular endothelial growth factor has also been implicated in having an early role in adhesion initiation [22]. Chemokines trigger a signaling cascade which is responsible for adherence of leukocytes to specific sites in the blood vessels and extravasation into different tissue sites. As such, they can recruit leukocytes into inflammatory areas following surgery. Several cytokines are continuously produced by macrophages and fibroblasts entrapped within the fibrin meshwork [23, 24], including TNF-α, IL-1, PDGF, EGF and MCP-1, which in turn recruit leukocytes and increase collagen synthesis [25]. As long as these conditions persist, adhesions will proliferate. The driving forces for this are the presence of foreign material, persistent infection or trauma.

## Incidence of Adhesions

Assessing the true incidence of adhesion formation is a very difficult task. Asymptomatic adhesions have little chance of being discovered unless the patient has further abdominal surgery, or is noted to have adhesions at autopsy. Numerous studies have looked at the incidence of adhesion formation in isolation; however, the key outcome measure in terms of health care provision is the risk of readmission following the original procedure. This will include patients who may not have undergone further surgery, but have repeated admissions with adhesion-related complications. Of the studies looking at this

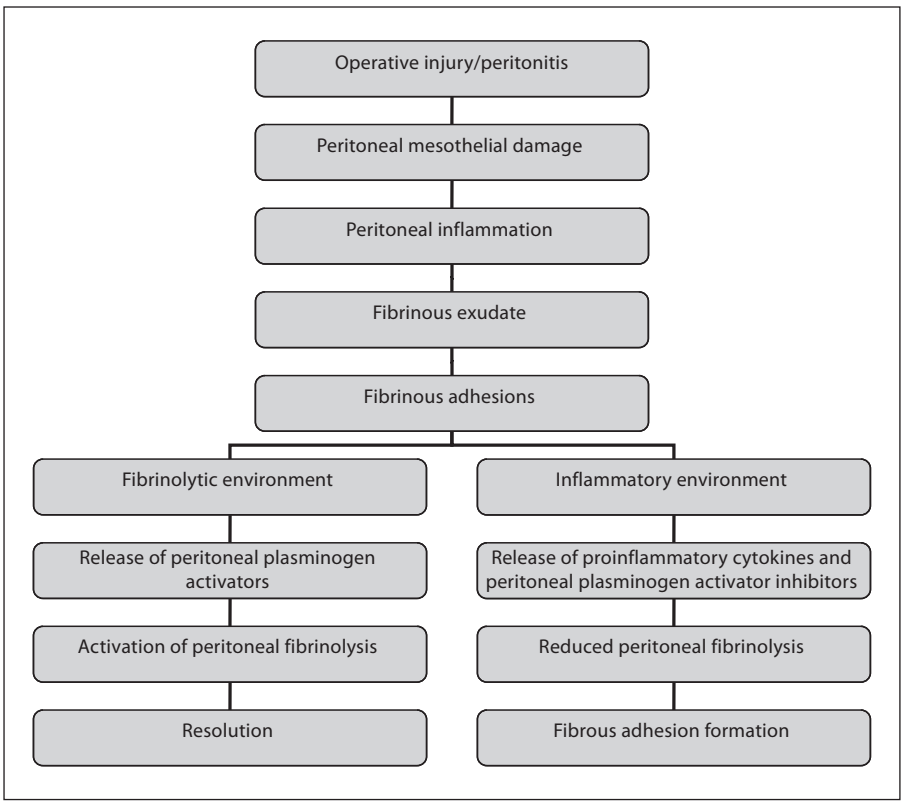


**Fig. 1.** Pathways of adhesion formation or resolution.

risk, the SCAR-3 study [26] is perhaps the best, following a large cohort of patients for an extended period of time. A 5% risk of readmission directly related to adhesions in the 5 years following open abdominal surgery (excluding appendicectomy) was demonstrated. In a retrospective American study investigating readmission rates following open colorectal or general surgical procedures, the readmission rate (with a diagnosis of intestinal obstruction) within 2 years ranged from 12.4 to 17% [4]. Another retrospective study reported proven adhesion-related readmission rates following gynecological surgery at 1.5 to 2% over a 4-year period [27]. When admission data included patients with symptoms not proven to be due to adhesions, the figure is substantially higher ranging from 14.5 to 16.1%. This discrepancy highlights the difficulty in isolating iatrogenic adhesion formation in the presence of non-specific symptoms like pain or with coexisting disease such as pelvic inflammatory disease which can produce de novo adhesions. Coding techniques often differ amongst studies which will also have an effect on reporting of patient morbidities.

A final factor in considering the workload associated with the treatment of adhesions is the ageing population. As the mean survival age increases, the probability of performing more than one surgical procedure on any given patient may also increase.

## Models of Adhesion Formation

The majority of studies investigating adhesion formation utilize an animal model to reproduce surgical insults, although they vary greatly depending on the interests of the investigating party. A lack of uniformity makes collation and interpretation of results between studies difficult. Most models utilize small animals such as the rat or mouse [20, 28–53]; however, the desire to test laparoscopic procedures has necessitated large animal studies [54–56].

The methods used to promote adhesion formation are similarly disparate. Some studies mimic standard surgical procedures on a smaller scale [57], while others use a variety of means to produce much more pronounced adhesions [58]. Although the underlying processes are the same, some stimuli provide a reaction that is unlikely to be replicated in the clinical setting, for example insertion

of large areas of exposed polypropylene mesh [44, 56, 59]. Results from these 'extreme' models therefore need to be interpreted with caution and their use limited solely to a research tool.

A key issue in assessing adhesions in any context (particularly when assessing therapies to reduce adhesions) is the severity scoring criteria used. Although there has been some agreement between committees on the use of a standardized scoring system for the evaluation of adhesions [60, 61], no single method has received widespread acceptance. The two fundamental principles at odds in a method to classify adhesions are those of simplicity versus reproducibility; a scoring system with an infinite number of classifications is unlikely to be popular since it will be difficult to remember, apply and analyze. Conversely, a system that is too simple may fail to demonstrate the difference between treatment arms in adhesion reduction studies, under reporting the true spectrum of disease. Certain criteria would seem essential in the design of adhesion scoring system. The number of sites at which adhesions are present must be recorded as well as noting adhesion length. Further assessment of adhesion strength is necessary, although this can be somewhat subjective. Studies have negated this problem to some degree by using video of procedures to allow an independent observer's interpretation of adhesion strength to be compared with the operating surgeon [62–64]. Typically, the expression of adhesion density starts with filmy adhesions easily taken down by blunt dissection, progressing in density where sharp dissection is required and finally firmly adherent, where no discernable plane is evident.

There are numerous systems based upon these concepts [65–67], although little agreement between studies makes accurate comparison of results difficult. The lack of uniformity between study design and result reporting also makes a meta-analysis of existing data impossible.

## Clinical Studies of Adhesion Formation

Examining adhesion reduction at the surgical site provides a direct measure of the effectiveness of an adhesion prevention regimen; however, few studies have recorded rates of readmission after treatment. To collect accurate data for adhesion-related readmission, the time period needs to be long and the cohort large to demonstrate statistical significance. A study investigating this principle estimated that around 15,000 patients would need to be screened to show a reduced risk of readmission in a trial lasting at least 3.5 years [68]. This is with the assumption that the adhesion reduction product has a 25% efficacy. Clearly, if a product is more effective, then the numbers of patients required to demonstrate statistical significance would be lower.

Adhesion assessment in the clinical setting does not necessarily require an extra procedure as it can be part of a phased reconstruction such as the reversal of a loop ileostomy [69]. Some gynecological treatment algorithms may also involve a second-look laparoscopy [63, 64, 70–72]. In these circumstances, it is possible to directly examine the extent of any adhesions formed.

With the initial use of any new adhesion reduction strategy relook assessment is essential given the quiescent nature of many adhesions. Once the effectiveness of an anti-adhesion agent has been established for a particular surgical operation, longer-term follow-up should confirm the expected effect of a reduced risk of adhesion-related readmission.

## Methods of Adhesion Reduction

The process of adhesion formation can be thought of as a cycle since failed attempts at adhesion prevention may well lead to further surgical intervention (fig. 2). At each point in this cycle, there is the potential to minimize the formation of adhesions which may be influenced by the following methods.

*Surgical Technique*

Since the impact of adhesion-related disorders was realized, there have been numerous attempts to reduce their formation. Changes in surgical technique aim to reduce the trauma associated with a procedure by minimizing tissue handling and practicing meticulous hemostasis. The nidus for persistent inflammation must also be curtailed, including synthetic material such as sutures as well as bacterial soiling, blood or other necrotic material. Aids to achieving these surgical goals include the use of hemostatic agents as well as electrosurgical instruments and laparoscopy. Research investigating the use of specific surgical instruments in isolation have not shown a statistically significant beneficial effect in the reduction of adhesions [73–77]. However, any technique or instrument reducing procedure time, or blood loss, should decrease the physiological insult for the patient, with a reduction in adhesions as a consequence.

Topical products to improve hemostasis have also been shown to provide a beneficial role in reducing adhe-

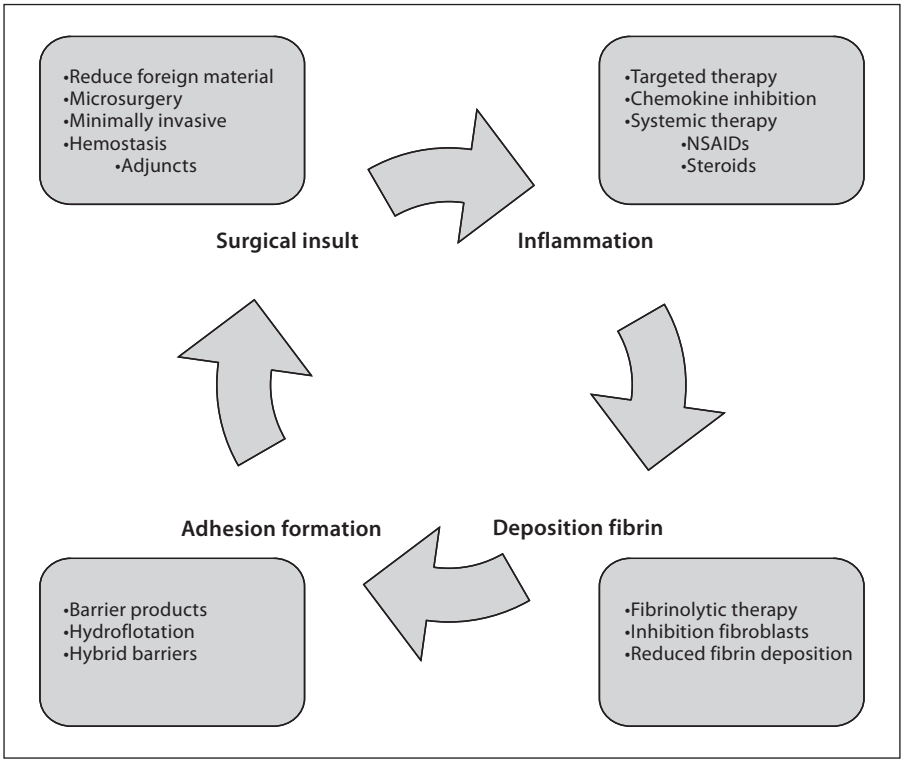


**Fig. 2.** Adhesion cycle and points of manipulation.

sion formation [78]. Many of the early products used to promote hemostasis show similarities in their composition to adhesion prevention treatments. For example Surgicel® (Johnson & Johnson, Somerville, N.J., USA) consists of oxidized regenerated cellulose. Topical thrombin [79–81] and fibrin [81–83] sealants have evidence to show their efficacy in aiding hemostasis and as such can be thought of as adjuncts in an adhesion reduction strategy.

*Laparoscopic versus Open Surgery and Natural Orifice Transluminal Endoscopic Surgery*

There are many benefits to performing a procedure by the minimally invasive method, though adhesion reduction is often not considered. Good evidence exists supporting a reduction in adhesion formation following laparoscopic surgery for a large number of procedures [54, 55, 84, 85]. There are potential disadvantages associated with laparoscopic procedures such as a longer duration of surgery with resulting damage to peritoneal mesothelium from the pneumoperitoneum [28, 29, 86, 87]. This is due to a combination of ischemia, acidosis and desiccation. Amelioration of peritoneal damage may be achieved by heating and humidifying the $CO_2$ as well as reducing gas flow rate and insufflation pressures [88–90]. Although some damage to the peritoneum is inevitable, protective measures such as these may allow quicker resolution of any insult.

A variation in the application of minimally invasive surgery has led to the development of natural orifice transluminal endoscopic surgery [91]. It is conceivable that this method may lead to reduced adhesion formation by virtue of the fact that there are no transabdominal ports. However, there is insufficient evidence to support this concept at present [92].

*Adhesion Reduction Agents – An Overview*

Adhesion reduction agents can be broadly separated into two categories. The first are the pharmacological therapies given around the time of the patient's operation. The second encompasses topical products applied directly to the operative site.

*Pharmacological Therapy*

Many different pharmacological agents have been tried to achieve adhesion reduction [30–43, 93–103]. There is sound logic behind the use of such agents, although their effectiveness has been somewhat limited.

Reports in the literature describe the effective use of a large number of pharmacological agents in experimental animal studies [30–43, 93, 94, 96, 97, 99–103]. However, few agents progress to clinical trials. The focus of this review is to explore the generic classes of drugs based upon their mode of action within the adhesion formation pathways.

Pharmacological agents have also been applied topically in an attempt to enhance the local effects of the drug. Some systemic absorption is inevitable with drugs administered intraperitoneally, although this is a complex process which depends on the properties of the agent in question. The peritoneum is highly permeable to water, small solutes, and proteins and therefore is not a physical barrier [104]. This porosity can lead to rapid absorption of the agent thus limiting any benefit to intraperitoneal application. No strong evidence exists to suggest that the addition of pharmacological agents to fluid left within the abdomen leads to a reduction in adhesions.

Drugs to mediate the inflammatory response following surgery have been trialled extensively. Initial attempts used steroids [30, 93], and nonsteroidal anti-inflammatory drugs [31–33, 94, 95] (NSAIDs). The balance between systemic side effects and adhesion reduction has proved difficult to overcome for this group of agents. The risk of bleeding associated with NSAIDs, or impaired wound healing with steroid use, has limited their use in the clinical setting. More recently, free radical scavengers [34, 96, 97] including methylene blue [105] as well as inhibitors of pro-inflammatory cytokines [35] and antihistamines [36, 37, 72–74] have been trialled. Although there have been promising results from animal studies, no single agent has progressed to widespread clinical use.

Secondary targets include the processes determining fibrin deposition [38, 98] and fibrinolysis [39, 99–103]. Despite low-dose anticoagulation being the accepted standard for deep vein thrombosis prophylaxis in surgery, the use of therapeutic anticoagulation to reduce fibrin deposition has not been shown to have a statistically significant effect on adhesion reduction. Furthermore, this approach is associated with an increased risk of postoperative bleeding. The alternative approach of promoting fibrinolysis has also been met with concern due to the potential for postoperative bleeding [106].

Adhesion reduction by the inhibition of fibroblast proliferation [40, 41] with agents such as mitomycin C has also been trialled, though toxic side effects have limited its use.

Other emerging products include those targeted towards the sites of adhesion formation by inhibition of chemokines. Experimental studies of broad-spectrum chemokine blockade have demonstrated a reduction in adhesion formation in the murine model [42]. Further selective chemokine inhibition such as the prevention of CCL1-CCR8 interaction [43] has also been shown to be effective in experimental models, although clinical trials are awaited.

*Topical Products*

The topical products utilized in prevention of intra-abdominal adhesions can be divided into two basic categories. The first consists of liquids which are instilled to the abdominal cavity at the end of the operation. Liquids rely on the principal of flotation – since the bowel is freely floating within the abdominal cavity and thus separated to some degree. The simplest form of this method was the application of Ringer's lactate or other crystalloid fluid [107]. There is no significant evidence to support adhesion reduction with this method since the fluid is rapidly absorbed before any surgical injury has healed. Modification of this principle led to the addition of solutes to the fluid to decrease the rate at which absorption occurs. The resultant products are similar to peritoneal dialysis solutions, and have shown some promise in adhesion prevention [108, 109].

The second category of topical products consists of gels or films. The basic principle is the separation of the operative surfaces with a mechanical barrier. The barrier must be retained for a suitably long period of time for the surgical insult to heal sufficiently so that adhesions will not form. In order to achieve this, there are certain properties that the product must display. For reabsorbtion to occur, the material must be easily degraded without a fibrous reaction. Popular constituents which meet this criteria include viscous polysaccharides such as cellulose, chitosan, dextran or hyaluronic acid. Interestingly, chitosan, a naturally occurring polysaccharide formed from the deacetylation of chitin, has also been shown to have other beneficial properties that make it a desirable constituent for use in an adhesion prevention product. One aspect is the hemostatic nature of chitosan, with successful use in dressings [110, 111] which are now issued to US army personnel. Another is the antimicrobial action of chitosan to a variety of bacteria, fungi and viruses [112]. Chitosan has shown promising results in animal studies as an adhesion prevention product [51, 58]. Synthetic alternatives include polylactic acid or polyethylene glycol. There is little to choose between these basic materials, although subtle modification of their form may have a significant effect on the polymer properties.

Some crossover exists between gels and films, many of the films taking on more of a gel type consistency during reabsorption. The exception is the application of a PTFE (Goretex®) film between the injured peritoneal surfaces. Whilst results describing the use of PTFE films have been encouraging [113–115], the application of a nonabsorbable foreign body within the abdomen has been criticized. Not only because of the need for later removal (although this has been debated) but also the potential for chronic infection and difficulty associated with fixation of the film to prevent migration.

*Modification of Surgical Materials*

Another challenge to adhesion prevention is the presence of a foreign body such as nonabsorbable sutures or mesh. Coating of the latter has shown some success [44, 56, 59] in applications where a side of the mesh will potentially come into contact with the bowel. Evaluation of six commercially available meshes in an experimental model showed the absorbable layers of Parietex Composite® and C-Qur® were effective at reducing adhesions in the short term. However, as the absorbable layer was phagocytosed from the mesh, the adhesions reduction was seen to diminish [118]. The simple solution is to avoid or minimizes the use of nonabsorbable materials within the abdomen whenever possible. When this is unavoidable, using adhesion reduction products to isolate the operative site may help to reduce adhesions in the immediate postoperative period. However, suture material is frequently found at the site of important vascular or enteric anastomosis, where an adhesion response is essential in order to reduce the probability of subsequent anastomotic leakage. As such, isolation of the area may be the best compromise.

*Evidence-Based Use of Adhesion Prevention Products*

An abundance of published literature describing the use of adhesion reduction products exists; however, the number of good quality randomized control trials is somewhat less. Products that have had the most documented success in humans are the absorbable gels and films. Although the use of some agents is not without certain caveats (such as the avoidance of wrapping the product around any anastomosis, and ensuring complete hemostasis), randomized control trials have shown statistically significant benefits in their ability to reduce adhesion formation [117–125]. As such, the predominance of evidence would suggest that unless there are any contraindications, the surgeon should consider using hyaluronic acid/carboxymethyl membranes. This is of particular relevance in patients undergoing staged surgery. Unfortunately, despite a proven reduction in the incidence, extent and severity of adhesions, a decrease in the incidence of intestinal obstruction or need for operative intervention has yet to be shown [126].

A tabulated summary of those products which have been commercially marketed with proven clinical effectiveness is shown in table 1. This gives the opportunity for a rapid review of a product's constituents, any adverse outcomes, and the evidence supporting its use.

*Considerations for the Use of Adhesion Prevention Products*

The choice of product used may be influenced by the mode of application. Films/solid membranes may prove difficult to apply laparoscopically. An alternative is an in situ cross-linkable hydrogel that can be applied as a liquid which rapidly gels at the desired site of action. There is no one product that is currently available without certain drawbacks. This may be a result of a sensitivity to the product itself, for example with Hyskon® where patients reacted to the antigenic properties of the constituents [127]. Alternatively, the product may increase the incidence of anastomotic leakage or wound dehiscence such as with Intergel®. Adverse outcomes during clinical studies were considered serious enough to cause a product recall [124, 128]. Other instances where an increased risk of anastomotic leakage has been observed are with the use of Seprafilm®. Although the increase in leak rate was relatively low [114], the manufacturers now recommend avoiding wrapping the product around anastomoses. Clinical trials using Interceed® observed that unless complete hemostasis was achieved prior to the application of the product, it may actually precipitate adhesion formation [129].

More minor problems associated with the use of adhesion prevention products center around their application. Many of the more solid sheet preparations require fixation. This makes laparoscopic use a challenge and may necessitate the use of suture material which itself can act as a nidus for adhesion formation. The opposite is true for liquid preparations where the challenge is to keep the solution within the abdomen without leakage from the surgical site. Product storage can be difficult if refrigeration or heating is required prior to use, with specialized applicators using compressed gas or the need for a dedicated light source also deterring routine use.

**Table 1.** Adhesion-reducing products

| Brand name (Company) | Composition and properties | Adverse issues | Current availability | Evidence [ref.] |
|---|---|---|---|---|
| Adcon-P (Gliatech, Inc.) | Gelatin/proteoglycan<br>Hydrophilic, bioresorbable | FDA recalled related product Adcon-L | Animal studies only as of 2003 | 46, 47 |
| Adept (Innovata) | 4% icodextrin solution<br>Hydrophilic, peritoneal residence time >4 days | Leakage of fluid from the surgical wound, and abdominal distension/ discomfort, pulmonary effusion | FDA approved for gynecological laparoscopic procedures in August 2006, marketed in Europe for general and gynecological surgery | 108, 109 |
| FloGel (Alliance Pharm, Co.) | Poloxamer 407<br>Hydrophilic, thermosensitive, bioresorbable | Requires refrigeration | Early clinical trials | 48, 49 |
| FocalGel (Focal) | Polyethylene glycol and polylactic acid<br>Photo-cross-linkable; bioresorbable | Requires dedicated light source | Marketed for general surgical use | 50 |
| Hyskon (Medisan Pharma-ceuticals) | Dextran 70<br>Hydrophilic, bioresorbable | Local and systemic side effects due to osmotic and antigenic properties<br>Not sufficient evidence of clinical effectiveness | Indicated as hysteroscopy fluid | 127, 131–133 |
| Incert (Anika) | Chemically crosslinked hyaluronic acid<br>Hydrophilic, bioresorbable | Difficult laparoscopic application | Pilot human trials in the UK from 2004, Incert-S marketed for spinal surgery | 134 |
| Interceed (Ethicon) | Oxidized regenerated cellulose membrane<br>Hydrophilic, absorbed within 3–10 days | Limited effectiveness in the presence of blood and peritoneal fluids | Marketed for general surgical use | 66, 67, 135, 136 |
| Intergel (Lifecore) | 0.5% ferric hyaluronate gel<br>Hydrophilic, elimination half-life within the peritoneum 51 h | Withdrawn from clinical studies due to high morbidity associated with postoperative peritonitis/anastomotic leak.<br>Clinical study discontinued | Discontinued | 124, 128, 137 |
| NOCC (Kytogenics) | N,O-carboxymethyl chitosan<br>Hydrophilic, bioresorbable | Pilot clinical trial demonstrated no significant difference between treatment and control groups | Phase III clinical trial (2002) | 51, 52, 64 |
| Preclude (W.L. Gore) | Expanded polytetrafluoroethylene membrane<br>Hydrophobic, not biodegradable | Requires strict sterility and fixation; difficult to use laparoscopically and leaves foreign body in the peritoneum | Marketed mainly for gynecological surgery | 113–115 |
| Repel (Life Medical Sciences) | Polyethylene glycol and polylactic acid block copolymer membrane<br>Bioresorbable | Needs fixation; difficult to use laparoscopically | Repel-CV FDA approved in March 2009 for cardiac surgery | 138, 139 |
| Sepracoat (Genzyme) | Sodium hyaluronate solution<br>Hydrophilic, elimination half-life within the peritoneum: 26 h | Insufficient evidence of clinical effectiveness | Marketed in Europe for general surgical use<br>(Not FDA approved) | 140 |
| Seprafilm (Genzyme) | Hyaluronic acid-carboxymethylcellulose membrane<br>Hydrophilic, absorbed within 2 weeks | Requires careful handling at open operation; difficult to use laparoscopically | Marketed for general surgery use | 117–123, 125 |
| Sepragel (Genzyme) | Hyaluronic acid-carboxymethylcellulose gel<br>Hydrophilic, bioresorbable | Sepragel spine withdrawn from clinical trials 2002 | Indicated for ENT surgery as a space-occupying gel | 67 |
| SprayGel (Confluent surgical) | In situ cross-linkable polyethylene glycol gel<br>Hydrophilic, bioresorbable in 6 days | Requires a specialized applicator and air supply | Marketed for general surgery use | 63, 68 |
| Surgiwrap sheet (MAST Biosurgery) | Polylactide membrane<br>Hydrophobic, bioresorbable in 24 weeks | Needs fixation | FDA approved in May 2005, also marketed in Europe for general surgical use | 53 |

## Discussion

Surgery in its essence is a rather 'blunt tool', injuring the tissues and organs at the operative site. In order for the body to recover from this injury, there must be an adequate healing response. For the most part, this response is a normal part of wound healing with a number of factors differentiating between resolution and pathological adhesion formation. Targeted molecular-level therapy provides an attractive panacea to the problem of adhesions; however, the reality may be somewhat different. Overmodulation of the mechanisms driving this response may lead to an inadequate reaction resulting in complications such as bleeding, anastomotic leak or even local cancer recurrence.

Any product designed to reduce adhesions may be overwhelmed if the stimulating adhesive process is on a massive scale, for example gross fecal contamination of the abdominal cavity. In this context, any product used to modulate the formation of adhesions may be ineffective despite attempts to minimize bacterial soiling at the time of the operation. Patients who are systemically unwell often have a number of other clinical problems, such as coagulopathies, which contribute to the difficulty of adhesion reduction in the acute setting. Such extreme circumstances are difficult to replicate in the research setting since animal models will often not survive them.

No product will be a substitute for good surgical technique, and the best approach to adhesion reduction will be a combination of treatments designed to minimize the adhesion-forming process from the outset. Whilst it is not possible to recommend one specific product for every situation, a number of therapies are currently available that have a good evidence base for their use and should be considered by the operating surgeon. Foresight is required to ensure that products are available at the time of elective surgery so that an opportunity to reduce adhesions is not missed. It is a duty of care that surgeons should be aware of a suitable adhesion reduction strategy relevant to their practice. Failing to discuss adhesions with patients during the consent process is to pave the way for potential negligence claims [130].

Continuing research is providing advances in the field which promise more effective products in adhesion reduction. Barrier gels or films can now be modified to include new pharmacological agents [45] further modulating the adhesion-forming process. Such hybrid solutions may provide a synergistic effect to overcome adhesion formation in most settings. As these new therapies emerge, they will clearly require thorough validation in their use to ensure that patient safety is not compromised.

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