Postoperative adhesion prevention a sticky problem

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Abstract:

OBJECTIVES: To investigate various agents for adhesion prevention when used as adjuvants during pelvic surgery.

SEARCH STRATEGY: The following databases were searched: the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and SCOPUS.

Intra-abdominal adhesions may occur after most surgical procedures, and are of major clinical, social and economic concern. In most instances the adhesions are asymptomatic, but in about 5% they will lead to adhesion-related disorders, such as small bowel obstruction, pelvic pain and infertility. Although minimal access surgery has been shown to be less adhesiogenic than traditional open surgery, with regard to certain procedures, it does not totally eliminate the problem. Consequently, attempts have been made to further reduce adhesion formation and reformation following endoscopic procedures. A wide variety of strategies, including surgical techniques, and the use of pharmacological agents and mechanical barriers have been advocated. There does not seem to be any single modality that has proven to be effective in preventing post-operative adhesion formation following laparoscopic or hysteroscopic surgery. Since meticulous surgical technique alone is insufficient, further research is needed on adjunctive therapies for the prevention and/or reduction of adhesion formation following laparoscopic procedures. This review discusses ways to reduce abdominal adhesions, and provides an update on current practices, and future research regarding experimental and clinical use of various anti-adhesive agents.

Key words: endoscopy, laparoscopy, surgical adhesion prevention.

Introduction:

Post-operative adhesions have long been recognised as a complication of general and gynaecological surgery. As the frequency of abdominal and pelvic surgery has increased, the incidence of pelvic adhesions has risen in direct proportion (1). Post-surgical adhesions occur in 60%–90% of women who had undergone major gynaecological surgery (2, 3, 4). The morbidity of adhesion formation, and its economic costs are substantial (5, 6, 7, 8.) (Table 1).

Table1. Incidence of post-surgical adhesions (6, 7, 8)

Adhesiolysis	76%
Surgical treatment of endometriosis	82%
Ovarian surgery	75%
Myomectomy	68%
Tubal surgery	76%

In an analysis of the burden of postoperative adhesions studies showed that 35% of women having had open gynaecological surgery were readmitted on average 1.9 times in the following 10 years for reoperation due to adhesions (9). Adhesions are the largest single cause of intestinal obstruction, accounting for 30%–41% of all cases requiring further surgery (10). Further, it is estimated that 15%–20% of cases of infertility in women are secondary to adhesions (11). Despite long-standing controversy regarding the association between adhesions and pelvic pain, there is increasing evidence to support such a relationship (12).

Surgical research in the prevention of postsurgical adhesions and its preventive strategies goes beyond a century (13). Historically, there has been difficulty in analyzing the literature on adhesion-formation, since there is no single consistent model of adhesion formation, and no standard and reliable means of measuring its formation. Further, there has been marked variability in the results from animal models, and between the various means of inducing peritoneal injury. A lack of standardization has made the comparison of studies difficult (14).

Peritoneal healing and adhesion formation

Healing of the peritoneum following surgery is different from healing of the skin following injury. In the peritoneum, islands of regenerated peritoneum occur over the entire surface at once. This means that large peritoneal wounds heal as quickly as small ones. During surgery, the mesothelial injury exposes a denuded and acellular surface that serves as the nidus for wound healing and/or tissue-tissue adhesion. This submesothelial damage and exposure of the submesothial matrix occurs with simultaneous activation of the coagulation cascade and deposition of fibrin at the site of injury. Under normal conditions, this fibrinous exudate serves as a platform for the progress of proper healing, but under certain circumstances, the deposited fibrin can instead serve as a bridge between unrelated, neighboring tissues. Within a short period of time, the wound and its surrounding area are invaded by inflammatory cells that migrate from the peritoneal vasculature or from the peritoneal fluid. The inflammatory exudate is initially composed of neutrophils, by 24 h the predominant cell is the macrophage. Next, the injured wound surface is evenly reperitonealized by the combined effort of multiple foci of proliferating mesothelial cells. Reperitonealization continues for 7 to 10 days during which time the entire surface becomes covered by a contiguous sheet of mesothelium. This process differs from the annular ingrowth of peripheral epithelial cells that occurs cutaneous wound healing. In the abdomen, the

speed of reperitonealization remains the same (7–10 days), regardless of the initial wound size, since it is not limited by the rate of migration of cells from the periphery. The presence of mesothelial cells at the wound site corresponds to progressive wound healing and/or fibrosis and the deposition of an extracellular matrix (ECM) composed of fibronectin, hyaluronic acid, various glycosaminoglycans, and proteoglycans. The process of ECM deposition is directed by and maintained through the action of various growth factors and cytokines. Finally, the deposited matrix is strengthened and remodeled over time (1 week to 1 month). As the cells realign, the temporary ECM molecules are replaced by more permanent proteins such as collagens, while revascularization continues (15).

The balance between fibrin deposition and degradation is critical in determining normal peritoneal healing or adhesion formation. If fibrin is completely degraded, normal peritoneal healing will occur. In contrast, if fibrin is not completely degraded, it will serve as a scaffold for fibroblasts and capillary ingrowth. Fibroblasts will invade the fibrin matrix and ECM will be produced and deposited. This ECM is normally completely degraded by matrix metalloprotease, leading to normal healing. If this process is inhibited by tissue inhibitors of matrix metalloprotease, peritoneal adhesions will form. In addition to fibroblast invasion and ECM deposition, the formation of new blood vessels has been universally claimed to be important in adhesion formation (16).

Co- factors that contribute to adhesion formation

The effects of CO2 pneumoperitoneum have come under increased scrutiny. CO2 pneumoperitoneum induces adverse effects such as hypercarbia, acidosis, hypothermia and desiccation (17,18). It alters peritoneal fluid and the morphology of the mesothelial cells (19, 20). Pneumoperitoneum is a cofactor in adhesion formation since adhesions increase with the duration of the pneumoperitoneum and with the insufflation pressure in animal models (21, 22). It is recognised that pelvic inflammatory disease and endometriosis are additional potential causes of adhesions (23)The amount of raw peritoneal surfaces left following excision surgery may help us anticipate the likelihood of adhesion formation (24). It has been demonstrated that the pneumoperitoneum used during laparoscopy is a cofactor in adhesion formation. Reactive oxygen species (ROS) are produced in a hyperoxic environment, and during the ischemia/reperfusion process. ROS activity is injurious to cells, which protect themselves by an antioxidant system known as ROS scavengers. Recent data also point to a role for ROS in adhesion formation since the administration of ROS scavengers decreases adhesion formation in several animal models (16). ROS activity increases during both laparotomy and laparoscopy.

Drying of tissues during surgery increase adhesion formation, a situation remedied by paying attention to the arid conditions and correcting them during the procedures. Intentional drying of the tissues, by applying gauze, is an otherwise desirable procedure to aid the surgeon’s view of the area, but because of increased adhesions, it must be minimized. Laparotomy is more likely to produce adhesions than surgery performed via laparoscopy (25, 26).

Adhesion prevention strategies:

Surgical technique:

There is no substitute for meticulous surgical technique. This includes minimizing injury to tissues through the careful use of atraumatic instruments that do not crush tissue or leave denuded surfaces. Preventing blood loss is important, as intra-abdominal blood can increase the chances of adhesion formation. Copious irrigation helps to remove any remaining intra-abdominal blood. In addition, the judicious selection of sutures may help prevent foreign body reactions. Non-reactive suture material such as polyglycolic acid (Dexon), polyglactin (Vicryl), or polydioxanone (PDS) should be used; whereas using reactive material, such as catgut, should be discouraged.The surgical principals of adhesion prevention must be adhered to, ie. the gentle handling of tissues, meticulous control of bleeding, avoidance of foreign materials, excision of necrotic tissue; minimization of ischemia and desiccation; and prevention of infection (27).

Peritoneal closure
Several randomized trials have demonstrated that closure of the parietal or visceral peritoneum is not necessary. Peritoneal closure is associated with slightly longer operating times and greater postoperative pain and cause more adhesions (28). In a study by Tulandi et al. (29), the rate of adhesion formation after laparotomy with peritoneal closure was 22.2%, compared with 16% without closure.

Access
The issue of whether laparoscopic surgery resulted in fewer adhesions as compared to open laparotomy has been assessed. Diamond et al. (30), found that the incidence of de novo adhesion formation was lower when surgery was performed laparoscopically as compared to laparotomy. Similar finding were reported by Lundorff et al. (31). While the concept of reduction in adhesion formation holds true in theory, there are few trials to support this in practice (32).

Adhesion protectors
An ideal adhesion barrier should be non-reactive, but protect tissue at risk during the critical wound healing period before being resorbed and cleared; it should remain adherent to the target tissue; and it should be easily applicable during laparoscopic procedures performed on adhesiogenic organs such as ovaries and adnexa (33). Other properties of an ideal barrier are shown in table 2.

Table 2. Properties of an ideal adhesion protector

Non-cytotoxic Non-hemolytic Non-toxic Non-sensitizing Non-irritating Non-genotoxic Non-pyrogenic Should not potentiate infections Should be easy to use at laparoscopy

Liquids

Crystalloids

Historically, crystalloids such as normal saline and Ringer's lactate were used to produce a 'hydroflotation' effect by instilling 500ml to 3 litres of fluid into the peritoneal cavity at the end of surgery in an attempt to prevent adhesion formation. Irrespective of the volume instilled, the absorption rate by the peritoneum ensures that all the fluid is reabsorbed into the vascular circulation in 24-48 hours, too short an interval to prevent adhesion formation (32).

Besides pure crystalloids, others have tried adding pharmacologic agents such as antihistamines, promethazine, heparin, and steroids to the solutions, either singly, or in combination; based on animal studies. However, none of these were shown to reduce the incidence of adhesion formation in randomized controlled human trials (34). Most studies that looked at using corticosteroid drugs to help prevent adhesions reported little success. The pharmacologic properties of corticosteroids suggest that they would be helpful in adhesion prevention. However, this is not the case; one possibility is that peritoneal surgery overwhelms the therapeutic benefits of the dose. If a higher dose is used, the effect on other organs, such as immunosuppression and delayed wound healing, would outweigh any positive benefit (35).

Non-steroidal anti-inflammatory drugs (NSAIDs) are a class of drugs that ease the post-surgical inflammatory response. Some studies have shown a marked reduction in adhesion formation in animal models when the drug was given peri-operatively (36). Others have not found them to be beneficial for that indication (34). Areas devascularized by surgery are hypoxic, thus permitting fibrin persistence and adhesion formation as devascularized sites are prime adhesion candidates. However, these sites are not readily available to drugs given systemically.

Recently, several liquid products have been developed in an attempt to combine hydroflotation, barrier, and pharmacologic agents in a single product.

Dextran

Dextran is a water-soluble glucose polymer originally used as a plasma expander. The weight most often considered in adhesion studies is a 32% solution of dextran 70 suspended in glucose. Hyskon® is the best known brand name. Hyskon® is slowly absorbed in five to seven days. It was proposed that by producing a 'siliconizing' effect, hydroflotation, and effects on the clotting cascade, it would reduce adhesion formation. In studies, use of Hyskon® produced mixed results. Some found that patients treated

with Hyskon® had fewer and less severe adhesions than patients treated with saline (Ringer's lactate). Other studies found no differences between treatments (32). Hyskon® carries with it side-effects that include temporary weight gain, vulvar edema, leg edema, pleural effusion, and coagulopathy. Rarely, a patient may be allergic to it. Its use in gynecologic reconstructive surgery has been virtually eliminated.

Icodextrin solution

One of the most recently developed peritoneal instillates is 4% icodextrin solution (Adept®, Baxter BioSurgery). Adept® is hypothesized to provide prevent formation of adhesions by providing a physical separation of the peritoneal surfaces during the early phases of natural healing. Adept® is a single use, sterile, clear, and colorless to pale yellow fluid for intraperitoneal administration containing icodextrin. Icodextrin is an α-1, 4-linked glucose polymer (P050011, Volume 1, page 20), provided at a concentration of 4% w/v in an electrolyte solution. Icodextrin (glucose polymer) used in this device is generated via hydrolysis of corn starch. Adept®'s ability to draw and maintain a reservoir of fluid in the peritoneal cavity is by the process of colloidal osmosis, which is achieved through the presence of molecular weight species of icodextrin that are not rapidly absorbed across the peritoneal membrane.

It is FDA-approved for the reduction of adhesion reformation after laparoscopic adhesiolysis. In a randomized study during laparoscopic gynecologic surgery, it was found that instillation of 4% icodextrin solution decreased adhesion formation and reformation (37).

Hyaluronic acid

Intergel® (Lifecore, Johnson & Johnson, Gynecare) is a cross-linked compound of hyaluronic acid with ferric ion. Intergel® provides a transient, viscous, lubricant coating on peritoneal surfaces following surgical procedures. It reduced the extent of adhesion formation following abdominal surgery (38). However, the product was withdrawn from the market after reports of late-onset postoperative pain requiring surgery.

Seprafilm® and Sepracoat®

Seprafilm® (Genzyme BV, Naarden, Netherlands) is a sterile translucent membrane comprising sodium hyaluronate and carboxymethylcellulose which temporarily separates potentially adherent surfaces, turning to a gel within 24 hours, and cleared from the abdominal cavity in 7 days. While it degrades very rapidly in a few days, it is difficult to manipulate. It is fragile and brittle and impossible to use through a trocar in association with laparoscopy. Finally, it progressively loses its initial adherence and can migrate some distance, thereby leaving the wound unprotected. Sepracoat® (HAL-C Bioresorbable Membrane, Genzyme Corp) is a solution of hyaluronidase in phosphate buffered saline, reabsorbed from the body cavity and excreted in 5 days. Its mechanism of action includes the reduction of tissue desiccation In animal models and patients, these agents reduced adhesion formation by about 44% without any apparent increase in adverse events. However, it did not receive FDA approval for clinical use, and was withdrawn from the market in 1997. (39, 40, 41).

Hydrogel

A novel technique of substance delivery into the abdominal cavity is by combining 2 streams of liquid polymers, delivered via a catheter to the target tissue. When combined, the 2 streams produce a bright-blue solid polymer within minutes. Sprayable hydrogel (SprayGel®, Confluent Surgical) can be easily applied at laparoscopy; the solid polymer acts as an adhesion barrier. SprayGel® is a synthetic hydrogel which forms an absorbable, flexible, adherent gel barrier when two polyethylene glycol-based liquids are sprayed onto target tissue (Figure 1). It remains intact where applied for approximately five to seven days, protecting the target tissue during wound healing, and then is hydrolyzed gradually into polyethylene glycol constituent molecules that are resorbed and rapidly cleared by the kidneys.

Figure 1. Laparoscopic Sprayer

SprayGel is applied to the surgical site through the SprayGel Laparoscopic Sprayer, designed for site-specific delivery. The SprayGel Laparoscopic Sprayer connects to the SprayGel Air Pump, which is a reusable, self-contained air pump.

In a European multicenter, randomized study, Mettler et al. (42), evaluated 66 women who underwent myomectomy with or without SprayGel® application. When compared with initial surgery, the mean adhesion tenacity score of adhesions seen at second-look laparoscopy was 64.7% lower in patients receiving adhesion barrier than in control patients (0.60 vs 1.7). Compared with initial surgery, mean adhesion extent score at second-look laparoscopy was 4.5 vs 7.2 cm2, and mean adhesion incidence score was 0.64 vs 1.22. There were no adverse effects attributed to the adhesion barrier.

A similar product is a sprayable selfpolymerizing gel called Adhibit® (Angiotech). Adhibit® is a spray gel applied at the time of surgery that binds directly to the tissue and creates a temporary barrier, preventing contact and adhesions from forming between tissue surfaces. Adhibit is a synthetic, self-polymerizing liquid hydrogel that is metabolized by the body in less than 30 days. A randomized, controlled, single-blind study of 71 women who had surgery to remove uterine fibroids (myomectomy) reported that 48 women who received Adhibit (0.8±2.0) had a reduction in adhesions compared with 23 women in a control group who did not receive the gel (2.6±2.2, p=0.01). Adhesions were measured eight to 10 weeks after the surgery, using the modified American Fertility Society score (43).

AdSurf® (Britannia Pharmaceuticals) is a new clinical approach to the prevention of surgical adhesions. It is administered as a sterile dry powder via aerosol prior to surgical closure, giving it a distinct ease of application. The powder melts at just below normal body temperature and coats the internal surface tissues, preventing the formation of adhesions. Furthermore, when applied to the tissues, AdSurf® disperses throughout the peritoneal cavity, creating a better chance for the prevention of adhesions. AdSurf® is a unique formulation of the naturally occurring phospholipids Dipalmitoylphosphatidycholine (DPPC) and Phosphatidyl Glycerol (PG)

Adhesion barriers

Barrier Agents

Barrier agents include mechanical barriers and viscous solutions. Many different mechanical barriers have been tried, but they are generally inadequate because they interfere with the blood supply or produce foreign body reaction. The original 'barriers' consisted of peritoneal and omental grafts placed over traumatized surfaces and sewn in place. This practice placed a layer of dead necrotic tissue on top of traumatized peritoneal surfaces providing an abundant supply of substrate for adhesion formation. Subsequent animal studies have shown that placing devascularized tissue over damaged peritoneal surfaces increases, rather than decreases adhesion formation. Although no human randomized trials have been performed, this practice has been abandoned.

Oxidized regenerated cellulose

One of the first barriers to be evaluated was Interceed® (Gynecare, Johnson & Johnson), a mesh-like product designed to be placed over or between injured surfaces. A review published by Larsson in 1996 (44), concluded that Interceed is 'safe and effective in all controlled human clinical trials'. Unfortunately it did not eliminate adhesions in all patients and in all clinical situations. Some of the reviewed studies showed no benefit. It has been shown that the product was efficacious in limited situations, where injured areas or structures can be completely covered with the material. In addition, the entire area must be completely blood-free. The presence of blood in the matrix of the material completely negated any benefit (32). Postoperative adhesions may be induced by its application if adjacent tissues (e.g., ovary and tube) and structures are coapted or conjoined by the device, or if it is folded, wadded or layered. Care must be taken to apply Interceed® in single layers, interposed between adjacent anatomic structures at risk for adhesion formation. It is the easiest adhesion barrier to use at laparoscopy.

Expanded polytetrafluoroethylene, or ePTFE

Gore-Tex surgical membrane, constructed of ePTFE (Preclude®, WL Gore), is a nonabsorbable barrier, and produced in thin sheets (0.1 mm), with an average pore size of less than 1 μm. It is sutured to the tissue so that it overlaps the incision by at least 1 cm. It prevents adhesion formation, and reformation, independent of the type of injury. It is also effective in the presence of blood. In a randomized trial, ePTFE decreased postmyomectomy and pelvic sidewall adhesions (45, 46).

It is not widely used, however, because it is non-absorbable and has to be fixed to the tissue. This product must be sewn in place and is usually removed during a second surgical procedure. Its usefulness is limited by the nature of the product, in that, it must be sutured in place and removed at a subsequent surgery. It is very difficult to apply at laparoscopy (32).

Newer agents in development include CMC and polyethylene oxide (PEO) composite gel (Oxiplex/AP, FrizoMed) and polylactide (PLa): copolymer of 70:30 Poly (L-lactide-co-D,L-lactide) film (SurgiWrap, Mast Biosurgery). More recently, recombinant human tissue plasminogen activator has been evaluated for its effectiveness in the prevention of post-operative adhesions. This group of agents holds significant promise. The

development of new aids to prevent postsurgical adhesion formation is encumbered by the way the peritoneum heals, access to the peritoneal cavity, limitations of extrapolating results in humans as compred to animal models, and the complexities of interperitoneal circulation and transperitoneal transport. When barrier methods are used in conjunction with excellent surgical technique, meticulous hemostasis and careful tissue handling, the risk of adhesion formation is reduced, but not completely eliminated. There are three devices approved by the FDA for adhesion prevention: the site-specific Interceed® and Seprafilm®, and the broad-covering Intergel®. These devices are FDA-approved for laparotomy use. There are no approved devices in the United States for adhesion prevention by laparoscopic instillation.

The future

Improved surgical training and tools are important considerations. Research designed to define the peritoneal wound environment would identify target molecules. This information could be used to design devices carrying wound-modifying factors to alter the wound healing process. There is growing literature on the visualization and quantification of adhesions, that would greatly facilitate our ability to compare various interventional modalities. A study correlating functional cine magnetic resonance imaging (MRI) studies with later operative observations demonstrated the ability of this noninvasive imaging technique to visualize adhesions (47). Another active and potentially useful field of inquiry is into the origin and behavior of the premesothelial or stem cells responsible for reperitonealization. The discovery of tissue-derived stem cells in the adult has focused on the possibility of stem cell reactivation as a driving force for patterned tissue regeneration and healing. There may be cell-driven approaches to adhesion prevention involving stem cell therapies which theoretically would prevent denuded surfaces from adhering to one another. The possibility of a serum marker for adhesion formation could facilitate investigations of adhesion formation. The correlation of the presence of a marker protein in the serum for the formation of peritoneal adhesions, would facilitate a way of predicting who would form adhesions, and thereby a means of non-invasively measuring the efficacy of any given intervention. As yet there is no consistent correlation between protein levels and the presence or severity of adhesions.

Conclusion

The current evidence for the use of fluid and pharmacological agents for the prevention of adhesions is limited. There is insufficient evidence for the use of steroids, icodextrin 4%, SprayGel and dextran in improving adhesions following surgery. There is some evidence that hyaluronic acid agents may decrease the proportion of adhesions and prevent the deterioration of pre existing adhesions. However, due to the limited number of studies available, this evidence should be interpreted with caution and further studies are needed (34).

There has been a wide range of adhesion-reducing substances evaluated in animal models. However, in clinical situations, no adhesion-preventing substance, material, or barrier is unequivocally effective (48). One key challenge is that these physical agents may reduce adhesions where they are placed, but do not prevent adhesions developing elsewhere in the abdomen. The ideal adhesion-reduction agent should be easy to use

in all types of surgical procedures, and be capable of reducing adhesion formation at the operation site and throughout the peritoneum. A direct cause-and-effect relationship between adhesion prevention and outcome measures is difficult to establish. Screening of potential tools is time consuming and expensive. Besides, a disparity between preclinical animal results and clinical trials in humans is disappointing and costly. We are just beginning to understand the intricate role of the mesothelium in the early formation of adhesions and how mesothelial cells regulate the peritoneal fibrinolytic environment. More basic research into the mechanisms of adhesiogenesis is needed so that we can identify new opportunities for therapeutic intervention.

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