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Review Article

Prevention of adhesion in laparoscopic gynaecological surgery

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ABSTRACT

Adhesions have important consequences for patients, surgeons, and health services. Peritoneal tissue injury can be prevented by using careful surgical techniques. A large number of anti-adhesion products have been used experimentally and clinically to prevent postoperative adhesions. The current author reviewed the surgical literature published about epidemiology, pathogenesis, and various prevention strategies of adhesion formation. Several preventive agents against postoperative peritoneal adhesions have been investigated. Bioresorbable membranes are site-specific anti adhesion products but may be more difficult to use laparoscopically. Liquids and gels have the advantage of more-widespread areas of action and increased ease of use, particularly during laparoscopic operations. Effective pharmacologic agents that can reduce release of pro-inflammatory cytokines or activate peritoneal fibrinolysis are under development. Their results are encouraging but most of them are contradictory. Many modalities are being studied to reduce this risk; despite initial promising results of different measures in postoperative adhesion prevention, none of them have become standard applications. With the current state of knowledge, preclinical or clinical studies are still necessary to evaluate the effectiveness of the several proposed prevention strategies for avoiding postoperative peritoneal adhesions.

Keywords: Adnexal adhesions, Adhesion prevention, Laparoscopy, Oxiplex/AP gel, Viscoelastic gel

INTRODUCTION

In abdominal and pelvic surgery, adhesion formation regarded as the most common postsurgical complication occurring after 60-90% of procedures.[1] In the majority of patients, adhesions occur as a result of an injury to the lining membranes of the cavities. Peritoneal injury usually occurs as a result of surgery, peritonitis, or a combination of the two events. Pelvic and abdominal adhesions have been associated with significant morbidity, including infertility, chronic pelvic pain, small-bowel obstruction, and difficulty with surgical access or surgical complications in the future. Adhesions result also in a large surgical workload and cost to health care systems.

The Surgical and Clinical Adhesions Research studies (SCAR studies) demonstrated that adhesions are an important issue for the patients and a mounting burden on both the health care system and the surgeons who are faced daily with the treatment of adhesion-related complications. Investigations into the molecular causes of adhesion formation have produced new concepts of adhesion prevention.

New anti-adhesion agents have been developed and existing agents have been evaluated randomised controlled trials or systematic reviews to validate previous data in procedures associated with adhesion formation, surgeons should always inform their patients about the risk of adhesion-related complications. Not only as a precaution against negligence suits but also first and foremost to provide best possible care to our patients, we need to be fully aware now of the extent of the problem and adopt anti-adhesion strategies in our daily routine.

Cofactors contributing to adhesion formation

Ischemia

Ischemia has been proposed as the most important insult that leads to adhesion development. It has been demonstrated that fibroblasts in adhesion tissues have a different phenotype (myofibroblasts) than do the normal peritoneal tissue fibroblasts. More importantly, it has been shown that conversion of these cells from the normal phenotype to the adhesion phenotype can be induced by hypoxia.[2] Compared with peritoneal fibroblasts, adhesion fibroblasts have a significant increase in basal mRNA levels of collagen I, fibronectin, matrix metalloproteinase- 1 (MMP-1), tissue inhibitor of metalloproteinase-1 (TIMP-1), transforming growth factor (TGF)-b1, cyclooxygenase- 2 (COX-2), and interleukin (IL)-10.[2] Tissue plasminogen activator (tPA) and PAI-1 are intracellular enzymes found in the peritoneal mesenchymal cells. These are involved in the intrinsic protective fibrinolytic activity of fibroblasts. The tPA/PAI-1 ratio has been shown to be 80% higher in normal peritoneal fibroblasts than in adhesion fibroblasts. Under hypoxic conditions, this ratio significantly decreases in normal and adhesion fibroblasts.13 MMPs and TIMPs are crucial proteolytic enzymes in the extracellular matrix remodeling process of healing. Hypoxia has been shown to inhibit MMP-1 and MMP-9 and augment TIMP-1 expression. This decrease in the MMP/TIMP-1 ratio during hypoxia may favour an increase in extracellular matrix production, and a decrease in turnover and degradation that may lead to tissue fibrosis and adhesion development. COX-2 has been shown to have an important role in the regulation of inflammation and angiogenesis. In adhesion fibroblasts, the expression of COX-2 is significantly increased, compared with that of normal fibroblasts. COX-2 inhibitors, such as celecoxib, tenoxicam, have been reported to reduce postoperative adhesions through their antiangiogenic, antiinflammatory, and antioxidant effects in animal studies.[3,4]

Pneumoperitoneum

This is a cofactor in adhesion formation, because adhesions have been shown in animal models to increase with the duration of the pneumoperitoneum and with insufflation pressure.[5,6] CO_2 pneumoperitoneum induces adverse effects, such as hypercarbia, acidosis, hypothermia, and desiccation and alters peritoneal fluid and the morphology of the mesothelial cells.[7,8]

Pelvic inflammatory disease and endometriosis

It is recognized that pelvic inflammatory disease and endometriosis are additional potential causes of adhesions. Reactive oxygen species. 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 with an antioxidant system known as ROS scavengers. Recent data also point to a role for ROS in adhesion formation, because the administration of ROS scavengers has decreased adhesion formation in several animal models. ROS activity increases during both laparotomy and laparoscopy.

Tissue drying during surgery

This increases adhesions formation; intentional drying of the tissues, is an otherwise desirable procedure to aid the surgeon's view of the area but increases the risk of adhesion formation. Laparotomy is more likely to produce adhesions than laparoscopy.[9,10]

Types of intra peritoneal adhesions

Two types of adhesion formation are recognized and have been classified are de novo adhesions (type 1) and reformed adhesions (type 2).

METHODS

A literature search was performed using Google, yahoo. Highwire press. The following search term was used: Laparoscopy, viscoelastic gel, adnexal adhesions, adhesion prevention, Oxiplex/AP Gel. Articles were included in the review if the title indicated any relevance to the topic. Statements in the articles were scrutinised by searching the corresponding articles listed in the references sections. The reference lists were also searched for relevant literature.

DISCUSSION

Adhesion formation is a complex process influenced by various factors and resulting in an abnormal deposition of fibrin. After trauma to the peritoneum, fibrin deposition occurs immediately, which is a normal process in peritoneal healing. Usually, there is a balance between fibrin deposition and fibrinolysis so that fibrin is degraded within a few days. However, if this process is impaired in favour of fibrin deposition, fibrin strands occur and stable adhesions are subsequently formed. There are numerous cytokines which influence adhesion formation both directly via the fibrinolytic system and by changing the peritoneal fluid and, hence, the peritoneal healing environment.[11] Further studies into the molecular mechanisms of adhesion formation are essential to the development of future pharmacological anti-adhesion agents. To date, a number of studies have demonstrated the efficacy of various pharmacological approaches to adhesion prevention in animals.[12] In humans, however, none of the promising molecular approaches have led to an effective pharmacological anti-adhesion agent.[13,14] Further research into new uses of such pharmacological agents in humans is awaited. In addition to this purely pharmacological approach, other recent studies have revealed important co-factors which play a role in adhesion formation and could theoretically be targeted in

daily practice. Several animal studies of adhesion formation have demonstrated a pivotal role for the carbon dioxide pneumoperitoneum in laparoscopy. The high pressure of the pneumoperitoneum leads to hypoxia in the peritoneal mesothelial cells. Hypoxia influences adhesion formation in different ways.[15,16] Diamond et al, found increased proliferation and decreased apoptosis in fibroblasts from adhesion tissue compared to fibroblasts from normal peritoneum, where hypoxia leads to an increased rate of apoptosis. Hence, by influencing apoptosis and proliferation in fibroblasts, hypoxia in adhesion tissue during laparoscopy may be an important contributing factor to adhesion reformation after laparoscopic adhesiolysis.[17] In a rodent model, hypoxiainduced adhesion formation was decreased by adding 3% oxygen to the carbon dioxide pneumoperitoneum.[18] Laparoscopy was long regarded as less adhesiogenic than laparotomy due to its less invasive nature. Research as noted above, offers an explanation why this hypothesis must be rejected, because the laparoscopic environment itself unfavourably influences adhesion formation. Another adverse effect of laparoscopy, apart from hypoxia, is desiccation of the peritoneum which is caused by the endoscopic light and dry carbon dioxide and increases adhesion formation. Using warm humidified gas to create the pneumoperitoneum could prevent this effect.[19] The data comparing laparoscopy and laparotomy with regard to their potential for adhesion formation are conflicting. Whereas some authors confirmed that laparoscopy was less adhesiogenic than laparotomy, a comparison of the direct adhesion- related readmissions found no difference between laparoscopy and laparotomy.[20] However, as Ott expressed it: "less adhesion occurrence is still a significant level of adhesion occurrence".[19] Regardless of whether laparoscopy or laparotomy is performed some gynaecological procedures are associated with a higher risk of adhesion development. Ovarian, endometriosis or tubal surgery, myomectomy and adhesiolysis are procedures which lead to more adhesions, whereas Fallopian tube sterilisation is associated with a low risk of adhesion development.[21] Adhesiolysis is a frequently performed high risk procedure. The reformation rate of adhesions after adhesiolysis ranges from 55 to 100% with a mean incidence of 85% regardless of whether adhesiolysis is performed by laparoscopy or laparotomy. As noted above, adhesive tissue is quite different from normal peritoneal tissue and reacts differently to adverse influences like hypoxia. In this case, fibroblasts in the adhesive tissue proliferate, apoptosis of the cells decreases and molecules that influence the fibrinolytic system change so that fibrinolytic activity decreases. Hence, the high reformation rate of adhesions after adhesiolysis might be due to the modified reaction of adhesive tissue to adverse peritoneal environmental influences.[17] Therefore, in high risk procedures like adhesiolysis a systematic anti-adhesion strategy should be used and complemented with an anti-adhesion agent.

In most procedures, it is common to use electrocoagulation and often suturing is needed. In a rodent model, both techniques were identified as important co-factors in adhesion formation if electrocoagulation of the parietal peritoneum was used extensively. Suturing had an additive adverse effect and led to more adhesion formation even if only minimal coagulation was used.[22] All the above-mentioned studies and their findings are of great importance and they underline the complexity of adhesion formation and highlight the influence of many different factors involved. Surgeons always be meticulous in their surgical technique and adopt the principles of microsurgery to reduce adhesion formation. In addition to adhering to the principles of good surgical practice, surgeons should educate themselves about anti-adhesion agents so they can safely use an appropriate agent in situations where high degree of protection against adhesions is necessary. The following sections give an overview of the most common anti-adhesion agents.

Anti-adhesion agents

Anti-adhesion agents should be used in operations which consistently lead to adhesion formation or adhesion reformation. They can broadly be divided into pharmacological and non-pharmacological agents. Anti-adhesion agents must always be used in combination with the principles of microsurgery and they are not capable of compensating for extensive tissue damage. Moreover, the available agents can only reduce adhesion formation; they cannot entirely eliminate their occurrence. In the last decades, considerable research has been conducted into the complex process of adhesion formation and various theoretical and experimental approaches have been investigated to develop appropriate pharmacological agents. Several such agents have also been studied in humans. A number of non pharmacological agents were approved human use, some of which later had to be withdrawn from the market due to safety concerns or lack of efficacy.[14] Hence, complete adhesion prevention remains an unsolved problem and the search for an ideal anti-adhesion agent is still on going. The following subsections provide a brief overview of previous pharmacological and current non-pharmacological anti adhesion agents.

Pharmacological agents

Only a small number of pharmacological agents were ultimately tested in humans; most agents were only tested in animal models. The data from human trials are very limited and were mostly published 20 or more years ago. Based on these data, steroids and heparin cannot be recommended for the pharmacological treatment of adhesion formation, although initially both were promising approaches and were studied in humans. It was presumed that steroids would reduce the peritoneal inflammatory reaction, which enhances adhesion formation, and heparin would prevent the fibrin blood

clot formation, which serves as a matrix for adhesion formation. Unfortunately, none of these agents proved effective in adhesion reduction.[13] Treatment with GNRH analogues to achieve hypo-oestrogenism seemed another promising approach, since oestrogen was known to promote angiogenesis and increase growth factor production. A recent study investigating preoperative treatment with GNRH analogues failed to demonstrate their efficacy in reducing adhesions after myomectomy.[23] All studies have in common that their approaches to preventing adhesions had, of course, successful been tested in animals before. Since cognitions in molecular causes of adhesion formation have led to plenty of theoretical pharmacological approaches to prevent adhesion formation, various pharmacological agents were tested in animal models with an efficient reduction of adhesions. Decreases in adhesion formation of over 90% were observed in a laparoscopic mouse model using reactive oxygen species (ROS) scavengers, calcium channel blockers, phospholipids and dexamethasone in addition to gentle tissue handling, 4% oxygen in the pneumoperitoneum and low temperature.[24] Non-steroidal anti-inflammatory drugs, antihistamines, growth factor inhibitors and vitamin E were among the agents found to be effective in animal models. Even honey was investigated. The list of theoretical options for adhesion prevention is long, and hence the pharmacological agents may be a promising approach for the future. However, to date no effective pharmacological agent has become available for human use.[14]

Non-pharmacological agents

The approach for non-pharmacological agents is to separate the injured tissue from the surrounding organs and the abdominal wall throughout the time of peritoneal healing, i.e. the critical time for adhesion formation. Anti-adhesion agents can be categorised into two groups: site-specific agents forming mechanical or gel barriers and broad-coverage fluid agents.[25] A problem encountered with the first two agents is the necessity to decide intraoperatively where adhesions are likely to occur and, consequently, where to place the agents. The decision may be easy to take when there is only one injured site, as in myomectomy, but may be much more difficult in surgical patients with severe endometriosis. Thus, in the latter case, fluid agents are appropriate which are injected in the peritoneal cavity and remain there for a limited period of time. Due to these differences between agents, it is important for every surgeon to be familiar with the main characteristics of anti-adhesion agents and the limitations to their use.

Site-specific agents

Mechanical barriers Interceed_ (Gynecare, Ethicon, a Johnson and Johnson Company, Somerville, NJ, USA): Interceed is an oxidised regenerated cellulose membrane placed over a suture or a deperitonealised area. No sutures are required to keep Intercede in place; slight moistening after positioning a single layer will make it adhere to the injured site, where it is absorbed within 4 weeks.[26] Interceed has been shown to be effective in various studies, and significantly reduces adhesion formation even in severe endometriosis. Efficacy is limited if complete haemostasis is not achieved, though a modification of interceed, TC 7, was effective in a rodent model even in the presence of blood. Nevertheless, in practice, it is necessary to achieve meticulous haemostasis, as recommended by the manufacturer, before applying interceed, because otherwise adhesion reduction will not be achieved. interceed can be used in laparoscopy easily.

Seprafilm (Genzyme, Cambridge, MA, USA) Seprafilm

It is a hyaluronate-carboxymethyl cellulose membrane, which is placed over a suture or an injured area without stitches and remains in place for 7 days. In contrast to interceed no loss of efficacy in the presence of blood has been reported. Several studies have demonstrated the efficacy of seprafilm mainly in general surgery, especially bowel surgery.[27] Seprafilm is safe with the limitation that there is a risk of anastomotic leaks if a suture of a fresh bowel anastomosis is wrapped with it.[28] In gynaecological surgery, the efficacy of Seprafilm has also been demonstrated for some procedures[29] but it is not easy to use in all procedures. Seprafilm is fragile and therefore difficult to handle particularly in laparoscopy. However, some authors have successfully used Seprafilm in laparoscopy.[30]

Gel barriers SprayShield/SprayGel_ (Covidien Bio-Surgery, Waltham, MA, USA)

SprayShield is a synthetic polyethylene glycol solution which is sprayed over the affected area where it remains for approximately 5-7 days. After that period, it is degraded and absorbed. It consists of two components which react immediately on contact with the tissue to form an adherent layer. One of the components contains a blue food colourant, so there is an intraoperative visualisation of where SprayShield was used[31,32]. Efficacy data are available only for the earlier formulation of SprayShield, SprayGel. However, the two agents differ only in minor details, including a modification of the polyethylene glycol, the use of methylene blue in Spray-Gel_ and faster absorption of SprayShield. In the case of myomectomy a reduction of adhesion formation was demonstrated for SprayGel, but only a small number of patients were investigated.[33] Further research is needed to evaluate the efficacy of SprayShield in multicentre randomised controlled trials.

Intercoat/Oxiplex/AP (FzioMed, Inc., San Luis Obispo, CA, USA)

Intercoat is an absorbable gel composed of polyethylene oxide and sodium carboxymethyl cellulose. Functioning as a mechanical barrier during the healing process,

intercoat is applied as a single layer at the end of the procedures. Since most of the available antiadhesion agents were difficult to use in laparoscopy, intercoat was developed especially for laparoscopic use. Randomised clinical trials of intercoat in laparoscopic adnexal surgery and endometriosis surgery have demonstrated the agent's safety and efficacy.[34,35]

Hyalobarrier gel (Fidia Advanced Biopolymers, Abano Terme, Italy)

Hyalobarrier gel is a highly viscous auto-crosslinked hyaluronate used to separate organs and tissue after surgery. The use of hyaluronic acid agents may decrease adhesion formation and prevent the deterioration of pre-existing adhesions.[13]

CoSeal (Baxter Healthcare Corporation, Deerfield, IL, USA)

CoSeal is a resorbable hydrogel consisting of two polyethylene glycol polymer solutions which are mixed together when applied during surgery. The technology is similar to that seen with SprayShield but in CoSeal the polyethylene glycol esters have a different isomer structure. CoSeal is long available for preventing adhesions in cardiac surgery where its efficacy has already been proved. First researches in women undergoing myomectomy demonstrated safety and efficacy of CoSeal in abdominopelvic surgery.[25,36]

Broad-coverage fluid agents

Adept (Icodextrin 4% solution; Baxter Healthcare, Deerfield, IL, USA)

Adept is a clear solution containing icodextrin at a concentration of 4%. Icodextrin is a 1-4- linked glucose polymer and is responsible for the longer absorption time of Adept compared to the previously used crystalloid instillates like lactated Ringer's solution, which is rapidly resorbed by the peritoneum and therefore not suitable for adhesion prevention. At the end of a procedure, 1,000 ml of Adept is instilled into the abdominal cavity. Instillates separate the injured tissue by hydroflotation and should stay in the abdominal cavity during the first days after surgery. Adept is absorbed by the lymphatic system within 4 days and is metabolised by alpha-amylase to lower molecular weight oligosaccharides. In a large randomised controlled trial Adept showed significantly higher adhesion reduction compared with lactated Ringer's solution. An adverse effect of Adept is the labial or vulval swelling which mostly resolves after a short period. Adept is contraindicated in patients with allergy to cornstarch-based polymers, maltose or isomaltose intolerance or with glycogen storage disease. However, all in all Adept is a safe, effective and affordable antiadhesion agent.[35,37]

CONCLUSION

General recommendations Intrauterine and intraabdominal adhesions are a major cause for infertility. The most recent investigations have demonstrated the potential of intraperitoneal adhesion barriers combined with good surgical technique to reduce adhesion formation. The reduction of postoperative adhesions may be associated with clinically significant benefits such as improved fertility, reduction in pelvic pain, and improved quality of live. Regarding adhesion prevention, available data show some improvement with different approaches. Taking into account data with strong and weak evidence, we have reached the following consensus: Concerning laparoscopic and laparotomic prevention of adhesion also, meticulous surgical technique is of the utmost importance. Residual blood should be avoided, and this can be obtained by careful hemostasis and rinsing with Ringer's lactate with heparin. The proper sutures should be used, and preferably braided sutures are not to be left in the abdominal cavity. Regarding instruments, we advise to avoid unipolar and bipolar cauterization when possible and to replace with ultrasonic or laser energy. The use of floatation barriers does not seem to add substantial benefit in the prevention of adhesions. Gel barriers (Hyalobarrier Gel Endo® or Intercoat®) based on hyaluronic acid is proven to have a significant effect on adhesion prevention and are reimbursed in some procedures. We advocate the proper use of these barriers. As for sheets, there is enough evidence that they prevent adhesions. The use of NSAID in the prevention of pain and/or corticosteroids in the prevention of postoperative nausea is already mainstay after surgery and can be further endorsed in the prevention of adhesions.

To date, only a small number of the various available anti-adhesion agents have been studied in randomised controlled trials. In the future, it will be necessary to test more agents in large trials with endpoints such as pregnancy rates or decreasing incidence of adhesive SBO.

A consistent study design is necessary to enable comparison of studies in systematic reviews. Although large-scale blinded randomised controlled trials are difficult to conduct, they are important for validating the efficacy of anti adhesion agents. At present, it is difficult to determine the extent to which an agent is effective. This could be a challenge for the future. Knowing the real efficacy of an agent will make it easier for surgeons to choose the appropriate agent in their daily routine. Whereas the available agents have been demonstrated to effectively adhesion formation in clinical studies, none of them are able to reduce adhesion formation to a minimum. To achieve this, in combination with good surgical technique, will be the aim in the development of anti-adhesion agents in the future. Further research will reveal new insights into the pathophysiology of adhesion formation and lead us to fully understand how adhesions form, what processes influence them and which patients

will develop them. The possible combination of mechanical barriers and pharmacological agents is another promising field for future research.

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