

## Review Article

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# Prevention and treatment of peritoneal adhesions in patients affected by vascular diseases following surgery: a review of the literature

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**Abstract:** Intra-abdominal adhesions are the most frequently occurring postoperative complication following abdomino-pelvic surgery. Abdominal and pelvic surgery can lead to peritoneal adhesion formation causing infertility, chronic pelvic pain, and intestinal obstruction. Laparoscopy today is considered the gold standard of care in the treatment of several abdominal pathologies as well as in a wide range of vascular diseases. Laparoscopy has several advantages in comparison to open surgery. These include rapid recovery times, shorter hospitalisation, reduced postoperative pain, as well as cosmetic benefits. The technological improvements in this particular surgical field along with the development of modern techniques and the acquisition of specific laparoscopic skills have allowed for its wider utilization in operations with fully intracorporeal anastomoses. Postoperative adhesions are caused by aberrant peritoneal healing and are the leading cause of postoperative bowel obstruction. The

use of anti-adherence barriers is currently being advocated for their prevention. The outcome of the investigation showed adhesion formation inhibition without direct detrimental effects on anastomotic healing. Poor anastomotic healing can provoke adhesions even in the presence of anti-adhesion barriers. This review gives a short overview on the current evidence on the pathophysiology and prevention of peritoneal adhesions.

**Keywords:** Peritoneal adhesions, Laparoscopy, Vascular Surgery, Pain, Anti-adhesive barriers.

## 1 Introduction

Adhesions are bridges of collagen tissue that form due to the deposition of fibrin, which attaches between the serous of the viscera or between the latter and the parietal peritoneum. Peritoneal adhesions are a common complication of surgery and still represent a major burden to clinicians and researchers in various types of surgery especially in multiple surgical approach like in vascular diseases. The formation of adhesions documented in the literature occurs in about 55-100% of cases [1]. From a clinical perspective, up to 30% of cases of mechanical ileus are due to adhesion syndromes, and could reach up to 74%, considering those involving the small intestine [2]. At the moment, peritoneal adhesions represent the cause of about 1% of all hospital admissions and the reason for several laparotomies performed in the department of surgery. In particular, it has highlighted the role played in fibrin exudation by the fibrinolytic system activation, and by the stimulation of cytokines and growth factors on fibroblast migration and proliferation. These processes are of fundamental importance in the formation of adhesions. There is no doubt that any pharmacological and technological proposal aiming to limit and control peritoneal adhesion formation, has to incorporate the

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recent advancements in understanding both the pathogenesis and pathophysiology of adhesions [3]. It is generally acknowledged that the best prevention of peritoneal adhesions is based on meticulous surgical technique that aims to minimize peritoneal trauma through delicate manoeuvres, constant bathing of the tissues with physiological saline or Ringers-lactate, and maintenance of haemostasis, including suitable suture materials and prostheses, avoidance of infection and tissue ischemia, and tension sutures. The importance of minimal invasive surgical techniques is also widely recognized and is becoming increasingly common. Some surgeons have switched to the intraperitoneal instillation of drugs or substances of differing nature (fibrinolytics, anticoagulants, antibiotics, anti-inflammatories, lipid compounds, silicone, dextran, carboxymethylcellulose, hyaluronic acid, etc). Others have preference for the use of various barriers both the endogenous (omentum, peritoneal grafts, fetal membranes, etc.) and the exogenous (gelatin, oxidized cellulose and optionally regenerated, photo-polymerizable gels, membranes and non-absorbable material, etc.) ones.

## 2 Postoperative adhesions

The occurrence of postoperative adhesions is closely linked to several predisposing factors. A summary of these factors is reported in Table 1. The first predisposing factor is the type of organ surgically treated. For instance, after operations on the uterus and small intestine, the incidence of adhesion formation is about 60-100%, whereas after operations on ovary-fallopian tubes and the colon/gallbladder, adhesion formation is about 25% and 15% respectively [2]. The explanation for this difference is attributed to the differing amount of integrins present in the serous tissue of intraperitoneal organs and peritoneum. Integrins are  $\text{Ca}^{2+}$ -dependent molecules that facilitate essentially, but not exclusively, the adhesion of cells to the extracellular matrix. It has been recently demonstrated that  $\text{Ca}^{2+}$  signalling machinery is also related to the so-called endothelial colony forming cells (ECFCs), and in particular their regenerative outcome in therapeutic settings [4- 23].

The physiological levels of integrin alpha-v beta-3 are greater in the serosa of the uterus and small intestine, and lesser in other intraperitoneal organs. Tissue insult can result inevitably in inflammation, whether diffused or circumscribed, and consequently the formation of adhesions, especially in tissues where the levels of integrins are higher [24]. Therefore, integrin alpha-and beta-3

are certainly involved in intraperitoneal adhesions and neo-angiogenesis. However, further studies are required to better understand their role in the scope of post-surgical adhesions syndromes.

Operation type is also a cause of intraperitoneal adhesions [24]. The most destructive operations are the urgently performed especially for neoplastic diseases, leading to the formation of a more serious adhesions syndrome. The advent of laparoscopy represents not only a huge technical innovation but has also led to a number of benefits including a reduction of approximately 50% of post-surgical adhesions compared to open surgery [25-31]. The materials used are involved in these processes. Monofilament sutures reduce the risk of adhesions, as they cause a lesser insult. The same author accords importance to the thickness of the suture used. A broad diameter suture generates an inflammatory stimulus greater than that of a lighter calibre braided suture, exacerbating the risk of infection. Nevertheless, according to the same author, a network of smaller calibre rather than a mono-filament suture would always cause an increased risk of adhesions [32,33]. A comparison was also made between absorbable and non-absorbable but the evidence on this in the literature is controversial, since on one hand a non-absorbable suture generates a stimulus phlogogenic that is almost constant, while on the other hand it is now universally accepted that the neogenesis of adhesions reaches its peak at about 48 hours after the insult, then decreases and remains constant for about three months thereafter. Thus, the difference between the absorbable and non-absorbable material should may not be relevant. In light of the above, it would be preferable

**Table 1**

1. The organ treated
2. Operation type
3. Materials used
4. Degree of surgical manipulation
5. Surgical complications
6. Use of drainage tubes and their time of stay
7. Collection formation
8. Subjective reactivity to the inflammatory stimulus

to use monofilament sutures of a smaller calibre. The titanium coated clips used in laparoscopy are biologically inert and therefore reduce the inflammatory insult compared to sutures [34], hence, resulting in a lower risk of adhesions. It is essential that the intraperitoneal tissues and viscera are treated with extreme care to avoid vascular damage [35], maintain meticulous debridement and peritoneal detachment and avoid unnecessary viscerolysis. Whenever there is a complication of surgery (dehiscence, abscesses), the possibility of a fibrinous reaction and therefore of adhesion formation is extremely high even if it might facilitate the resolution of the complication with time, but it could cause disorders of transit. In the event where there is already a circumscribed or generalized peritonitis the resultant fibrinous reaction that attempts to circumscribe the process has a very high likelihood of adhesion formation. The use of drainage tubes which are foreign bodies can provoke an inflammatory response, therefore, its usage should be limited to times when they are absolutely necessary. As much as possible, drains should be left in place only for a shorter time (not more than 48 h) and should be flexible, of small calibre and siliconized [35]. This is perhaps the most frequent cause of formation of adhesions and so every surgery should be conducted in the best possible manner; the use of hemostasis must be very precise and as thorough as possible. Unfortunately, there is a varying degree of predisposition of patients to developing adhesions to the same stimulus, pathology and surgery. This is controlled by adjusting multiple factors including: the balance between subjective fibrinogenesis and fibrinolysis, and in particular role of mast cells in the formation and degradation of the extracellular matrix [36-38].

### 3 Management and preventive strategies for adhesions

The need to reduce the development of postoperative surgical adhesions is high. More than 440,000 abdominal and pelvic adhesions interventions for removal are performed each year in the United States, creating a number of risks to the health of the patient at a cost of \$ 1.2 billion /year [1,2,24]. The propensity to form adhesions appears to be patient-specific. Several individual factors, such as nutritional status, diseases such as diabetes, and the presence of concomitant infectious processes that alter the functions of leukocytes and fibroblasts, affect the formation of adherence. The research of effective methods

for adhesions prevention, has proposed a variety of techniques and pharmacological agents useful both for the primary prevention and for the secondary ones. The main approaches in the prevention of adhesions include:

- improvement of surgical techniques,
- limitation of the intra-abdominal organs trauma,
- application of adjuvant agents to reduce the formation of adhesions.

The post-surgical adhesions by coalescence will be formed only when both contact surfaces of the peritoneum have undergone a surgical trauma. Techniques that minimize peritoneal trauma, and the reduction of materials that constitute foreign bodies in the abdominal cavity may lead to a reduction of the formation of adhesions. The delicate manipulation of tissue and meticulous haemostasis are necessary in order to avoid the presence of free blood in the abdomen and prevent tissue ischemia, and are both responsible for the deposition of fibrin. Consequently the formation of adhesions lead to the release of thromboplastin, with subsequent activation of coagulation cascade. More effective preventive measures include the careful and delicate methodical handling of the intestine in order to reduce the trauma, and keep the tissues moist with constant bathing. It is also necessary to avoid carrying out large abdominal incisions and dissections where not necessary, and instead use small and atraumatic tools to not damage the serosa. Adjuvant therapy is characterized by the administration of drugs that interfere with the inflammatory cascade that leads to adhesion. Pharmacological agents may be directed against a variety of aetiologies and various components of the inflammatory process and / or training tack. A number of obstacles must be overcome before that these drugs can act to prevent the formation of adhesions. First, the ischemic sites, susceptible to adhesion formation, are to be cut off from the bloodstream, and then, from systemic circulation of the drug. Second, the peritoneal membrane has an extremely rapid adsorption mechanism, which greatly reduces the half-life of drugs dispensed. Third, some agents directed against adhesions need to act specifically against the formation of 'adherence and not towards the normal repair processes of wound healing; This is because processes that lead to the formation of the 'grip and mesothelium reconstruction also use the same cascade of events [60]. The available pharmacological therapies are the: *Nonsteroidal anti-inflammatory drugs (NSAIDs)*

They work by altering the normal metabolism of the 'arachidonic acid with the inhibition of the activity of cyclooxygenases, thereby inhibiting the formation of the final products, including prostaglandins and thromboxanes. Through the inhibition of prostaglandin and

thromboxane, NSAIDs decrease vascular permeability, inhibitors of plasmin, platelet aggregation, coagulation and increase macrophage activity. NSAIDs modulate different aspects of inflammation and reduce the formation of adhesions in most animal models [39]

### 3.1 Glucocorticoids and antihistamines

Therapy with corticosteroids attenuates the inflammatory response with the reduction of the vascular permeability and the release of cytokines and chemotactic factors. This therapy has yielded several results [40]. Corticosteroids, such as the dexamethasone, hydrocortisone, and prednisolone, were tested alone or with antihistamines, such as promethazine, intraperitoneally [41]. Antihistamines, often used in combination with glucocorticoids, inhibit the proliferation of fibroblasts. The possibility of emergence of side effects, such as immunosuppression or delayed wound healing, have led to limited use of these drugs which must be done with extreme caution [42].

### 3.2 Progesterone / Estrogen

Progesterone has shown a reduction of adhesion formation in an animal model. However, human studies have shown an increase in the formation of adhesions with intramuscularly or peritoneally administered medroxyprogesterone acetate [43]. Estrogen was shown to be associated with increased adhesion formation in animal models. In these animal studies, there were less fatty degeneration and fibrotic transformation in anastrogenic subjects. Those primates that were treated with agonists of G-rh had less adhesions compared to their untreated counterparts, suggesting that estrogen works by promoting the formation of adhesions although it is unknown how ipoeostrogenic condition can lead to the formation of a smaller number of adhesions in humans.

### 3.3 Anticoagulants

Bathing of tissue with isotonic crystalloid containing heparin sulfate reduces intra-abdominal adhesion formation possibly by inhibiting the coagulation of fibrin. But the use of heparin has been reported to be associated with bleeding and delayed wound healing. Irrigation with low-dose heparin (2,500 / 5,000 U / l) showed no benefit in reducing adhesions [44].

### 3.4 Fibrinolytics

Fibrinolytic agents can cause bleeding complications, however, the recombinant form t-PA, when applied topically, reduces adhesions in animal models with no net increase in complications [45]. A promising approach in the prevention of postsurgical adhesions has been described with the use of t-PA. The effectiveness of the rt-PA obtained by recombinant DNA techniques, has been studied in the prevention of primary adhesions and relapses. As previously mentioned, it is thought that the decreased activity of plasminogen activators (PAA) could be a possible pathogenic factor in the development of adhesions. In experimental models, this activity is reduced in the presence of thermal or mechanical trauma, ischemia, and inflammatory factors, known to cause the formation of adhesions. However, the administration of rt-PA resulted in reduced formation of adhesions in rabbits. The aim of current research is to establish the degree of safety and effectiveness accompanying the use of RT-PA in humans. The overall evidence from clinical trials and animal studies suggests that all of these approaches have only a minimal success, limited by poor safety and efficacy, without the complete elimination of postoperative adhesions [46].

### 3.5 Antibiotics

Broad-spectrum antibiotics are commonly used for prophylaxis against postoperative infections and the formation of adhesions. Antibiotics found in irrigation fluids administered intra-abdominally have caused the formation of adhesions and are therefore not recommended for use as single agents in the prevention of adhesions [47]. Separation of serous surfaces by the application of barriers during the early phases of wound closure. The anti-adhesion barriers fall into two main categories: Macromolecular solutions-barrier/Mechanical Barriers; Solutions barrier/Crystalloid. The absorption of water and electrolytes from the peritoneal cavity is rapid, and up to a quantity of about 500 ml of sodium chloride can be absorbed in less than 24 h [72]. Since 5-8 days are needed for the reconstruction of mesothelial surfaces, a crystalloid solution should be well absorbed before the completion of fibrin deposition and the formation of adhesions. From a theoretical point of view, it is not expected that the intraperitoneal instillation may prevent the formation of adhesions; this is because studies have shown that a reformation of adhesions occur in approximately 80% of patients who received crystalloid instillation [24, 32, 33]. If used in

surgery, laparotomy or laparoscopy, the risk of leaving a large volume of fluid in the abdomen can substantially reduce the ability of the host to eliminate the infections. The increase in the intraperitoneal volume facilitates the accumulation of *E. coli* and contributes to their delayed clearance from the peritoneal cavity. Studies on animals have shown that the increase in the release of contaminated fluid from 1 to 10 ml in the peritoneum of rats increases mortality by 20 to 60%. Since the post-surgical peritoneal cavity is an acid environment, priority should be given to the choice of irrigation solutions used in surgery [37]. The Ringer's lactate is safer, inexpensive, easy to use, and has a buffer capacity greater than the normal saline solution. The instillation of Ringer's lactate solution in animal models reduces the formation and recurrence of adherence [48]. Although the mechanism of action is unclear, but it seems that the Ringer's lactate keeps separate the rough peritoneal surfaces. It is also possible that the Ringer's lactate cleans up the fibrinous exudate which acts as a matrix attachment for fibroblasts and the formation of capillaries, but the solution is rapidly absorbed, and its effectiveness has not been proven clinically. Dextran 70 is a solution commonly used for the prevention of adhesions. Through the hydro-floatation of intra-abdominal structures with dextran solution, you get a physiological separation between the peritoneal surfaces [49]. By dilution, dextran reduces the local concentration of fibrin, preserves local plasminogen activators, and interferes with the expression of adhesion molecules of polymorphonuclear neutrophils. The dextran solution is slowly absorbed, draws liquid into peritoneal cavity, and also reduces the formation of blood clots [42-44]. However, the follow-up studies did not demonstrate any reduction in adhesion formation. Also, there were noticeable important side effects, such as the ascites, weight gain, the pleural effusion, lips oedema, sores, liver changes, and, although rare, disseminated intravascular coagulation, and anaphylaxis. Despite the popular use of high molecular weight dextran (dextran 3270), the results have been largely inconsistent. Hyaluronic acid (HA) HA is a glycosaminoglycan present in nature and is one of the major components of the extracellular matrix, including the connective tissue, skin, cartilage, the vitreous humor and the synovial fluid. HA is biocompatible, non-immunogenic, non-toxic, and is naturally absorbed. As a carboxymethylcellulose, it forms negative charges at acidic pH and is readily soluble<sup>47</sup>. HA covers the serosal surface and it gives protection by drying other types of damage. However, it is used after tissue damage combined with saline phosphate buffer solution (HA-PBS)—HA is combined with PBS in a macromolecular solution to prevent

the formation of adhesions, call Sepracoat®. The HA-PBS is applied intraoperatively, previously to the dissection, to protect the peritoneal surfaces from surgical trauma indirectly, rather than after surgery to separate the surfaces after the trauma. In animal models, this solution has actually reduced the damage, resulting from peritoneal inflammation, and post-surgical adhesion. In human studies HA-PBS definitely and significantly reduces the incidence, extent, and severity of new adhesions in different sites indirectly in traumatized patients undergoing complex and multiple gynaecological laparotomy procedures [50]. Carboxymethyl cellulose is a cellulose derivative, negatively charged at physiological pH and is readily soluble. The systemic clearance is less than that of HA, but it is rapidly metabolized. Its mechanism of action lies in the separation of damaged surfaces allowing the independent healing of the traumatized surface. Autologous peritoneal transplant: Experimental studies have shown that the coverage of the lesions of the parietal peritoneum with microsurgical applications of autologous peritoneum can completely prevent the formation of severe adhesions. Most importantly, was the reduction of adhesions to the visceral serosa with the use of autologous transplantation. The visceral peritoneum damage should generally be covered at the end of an intervention, or with autologous peritoneum or with a synthetic barrier. The advantage of a synthetic barrier is that the material must not be achieved surgically, and can be cut to fit out from the abdomen and then applied without sutures. Synthetic mechanical barriers—A large number of natural and synthetic grafts have been employed in order to reduce adhesion formation on traumatized surfaces. These natural materials include the peritoneum, omentum, HA, fat, amnion, and even the chorion [51]. Among the synthetic materials used in the past include polyvinyl alcohol film and sheets of tantalum. Recently, interest has been focused on the mechanical barriers placed on the injured tissue at the end of the intervention, in order to separate the surfaces. Some barriers include synthetic Gelfilm®, Gelfoam®, Silastic®, Gore-Tex®, Interceed (TC7)®, Sefrafilm®. Gore-Tex The expanded PTFE (polytetrafluoroethylene) is a non-reactive, non-toxic, anti-thrombogenic, with small pores that prevent the transmigration of cellular tissue and adhesions. The use of PTFE is strictly limited to non-contaminated surgery. When placed on the traumatized tissue, it has proven to reduce the formation of adhesions [52]. A PTFE barrier prevents the formation of adhesions and the reforming of them regardless of the type of tissue involved even when haemostasis has occurred. In randomized trials, it has been shown that the PTFE reduces post-myomectomy adhesions and latero-parietal adhesions of the

pelvis; and was also found that PTFE is more effective than Interceed in reducing adhesions to the side wall. The use of PTFE in laparoscopy is cumbersome and not easy also needs to be fixed in place and is non-absorbable, if left in place permanently, it must be surgically removed. PTFE is one of the less reactive polymers and determines small or morphological alterations of the adjacent peritoneum, and resists the chemical or biological degradation even after several years “in vivo” and causes the formation of pseudocapsule. It has also been successfully used in cardiovascular surgery, such as pericardial patches with minimal formation of adhesions and foreign body reaction [54]. The removal of PTFE involves different types of peritoneal trauma that can lead to the formation of adhesions; the removal of laparoscopy should minimize these surgical traumas. Membrane fragments do remain attached to the parietal peritoneum after removal, but they do not involve the formation of adhesions in animal models. While a little bleeding from the sutures may occur in the removal of the barrier, the incomplete haemostasis does not alter the effectiveness of PTFE. Interceed the ORC (-oxidized regenerated cellulose) is the only approved in order to prevent the formation of adhesions. The ORC has been demonstrated in animal studies and in humans, to reduce the formation of adhesions through the formation of a barrier and the physical separation of injured peritoneal surfaces, thereby preventing the development of adhesions between them. The ORC appears to reduce the formation-reformation of adhesions more than a meticulous surgical technique. When applied to a damaged peritoneal surface, it turns into a gel within 8 hours [55]. Clinical observations indicate that minor bleeding at the time of the application of the ORC permeates the material of which it is composed. The fibroblasts grow along the branches of coagulation with subsequent collagen deposition and vascular proliferation [47]. This explains the appearance of adhesions despite the application of the barrier. The most important steps to improve the effectiveness of the ORC are: to carefully remove irritating factors, to inspect the operative field to ensure that an adequate haemostasis has been made, and to use a piece of ORC that is wide enough. If haemostasis is not complete, the ORC turns black or brown-black. In this case, you must remove it, complete haemostasis, and reposition a new piece of ORC barrier. Seprafilm—The HA- CMC (carboxymethylcellulose) is a non-toxic and non-immunogenic material, effective in reducing the incidence and extension of serious post-surgical adhesions. It turns into a hydrophilic gel approximately 24 hours after its positioning and creates a protection around the traumatized tissues for more than 7 days during the reconstruction of

the mesothelium. The component of HA is completely eliminated from the organism in 28 days; less clearance compared to the removal of CMC. The HA- CMC can be used in the presence of blood. The HA- CMC reduces the incidence of adhesions along the incision of over 50 %, and the average percentage of adhesions is 400% less when compared with the controls that underwent laparotomy. Patients receiving HA- CMC also show less severe adhesions when compared to controls. The incidence of adhesions from the incision to omentum, stomach, small intestine, abdominal wall, and bladder is significantly reduced in patients who have undergone an incision along the midline and in which it was placed HA- CMC. It was reported that there is a higher incidence of pulmonary embolism and peritoneal abscess in patients treated with HA- CMC, but these results do not seem statistically significant. The mechanism of these complications is unknown. Probably the differences between HA and CMC clearance could lead to fragmentation of the film and an increase of embolism and abscesses [56]. Minimally Invasive Surgery: The application of laparoscopic surgery and minimally invasive techniques has shown an advantageous benefit also in the treatment of adhesions; the reduction of incidence obtained compared to the same interventions conducted by laparotomy was approximately 50%, with better results for adhesions less than fibrous. After laparoscopic adhesiolysis, it is proved also that, while the recurrence of pre-existing adhesions remains rather frequent, it has significantly limited the incidence of new lesions. The direct demonstration of the presence of sensory nerve fibers in human peritoneal adhesions, suggests that these structures may be capable of conducting pain after appropriate stimulation [57-60]. Sensory peptides were directly detected in several abdominal and pelvic clinical conditions [61-63]

## 4 Conclusions

Postoperative peritoneal adhesions are commonly observed sequelae of several types of surgery which include abdominal, pelvic and vascular surgery. Acute as well as chronic complications, including bowel obstruction, abdominal pain and infertility can arise from adhesion formation. So far, the only reliable treatment is surgical adhesiolysis, which in turn is accompanied by an increased risk of adhesion recurrence. Despite significant progress in modern perioperative medicine, only limited prophylactic approaches are available and atraumatic surgery is still the most important factor. Overall, research

investigations have focused on two major anti-adhesion strategies: firstly, the intraoperative placement of mechanical barriers and secondly novel immunomodulation concepts. Clinical data about the use of anti-adhesive barriers show a heterogeneous outcome. Promising data have arisen from the immunomodulatory approaches and now require a step-up development from experimental to clinical trial level. Recent observation suggests that adhesions themselves are capable of generating pain stimuli via several mechanisms.

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