A REVIEW ON ADHESIONS AND THEIR PREVENTION

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ABSTRACT
Adhesion formation is a physiological consequence of peritoneal tissue repair. Surgical trauma of the peritoneal surfaces induces a sequence of events that effectuates wound healing, therefore can also ultimately leads to adhesion formation. Surgery induces an inflammatory reaction that is characterized by migration of neutrophils, macrophages and other leucocytes to the site of the inflammation during the first 48 to 72hrs. Chemoattractants ( IL-8, MCP-1 ), cytokines ( TNF – alpha, IL-1 beta and IL-6 ), growth factors ( TGF-beta, IGF-1 and PDGF ) and reactive oxygen species produced and released by resident and invading inflammatory cells and subsequent damaged mesothelial cells are the key mediators of this inflammatory reaction. The magnitude of the problem, however, has tended to be overlooked, largely due to a lack of awareness regarding the clinical significance and the true incidence of adhesions. The adoption of effective adhesion prevention strategies will help to minimise the risk of adhesions following abdominal surgery and reduce complications, surgical workload and ultimately healthcare costs. Prevention strategies should include the adherence to good surgical practice alongside safe and effective anti-adhesion adjuvants.

Key words: fibrinous, Etiology

INTRODUCTION:
Adhesions: Adhesions have been defined as abnormal fibrous connections that may contain vascular channels, which join tissue surfaces in abnormal locations. These are fibrous bands of scar tissue that form between internal organs and tissues, joining them together abnormally.

Types of adhesions:
Fibrinous adhesions: An adhesion that consists of fine threads of fibrin resulting from an exudate of plasma or lymph, or an extravasation of blood. These are causes of early postoperative obstruction which settles down within 3–5 days. The majority of fibrinous adhesions will disappear in due course of time.

Fibrous adhesions: If the infection is continuous the fibrinous material is converted into fibrous material.

General Introduction:
Surgical procedures are the most common cause of adhesions [1]. Adhesions are scar tissues that often cause internal organs and or tissues to stick together after surgery. Adhesions can twist and pull organs out of their normal place and are a primary cause of bowel obstruction, infertility (following gynecologic surgery), and chronic pelvic pain. Adhesions can also complicate subsequent abdominal or pelvic operations [2,3]. Adhesion formation is a physiological consequence of peritoneal tissue repair. Surgical trauma of the peritoneal surfaces induces a sequence of events that effectuates wound healing, therefore, can also ultimately lead to adhesion formation [4]. Adhesions are an almost inevitable consequence of peritoneal surgery and their management and prevention should be of great concern to surgeons and gynaecologists alike. The truth is that adhesions are extremely common and occur after almost every abdominal surgical procedure. The increase in the number of gynaecological and surgical procedures in recent years has seen a corresponding rise in the incidence of adhesion-related complications. Adhesions are extremely common and occur after almost every abdominal surgical procedure [5]. Although many adhesions have little or no detrimental effects for patients, a sizeable proportion of cases can lead to serious short- and long-term complications, including small bowel obstruction, fertility-related complications in women and chronic pelvic pain, requiring readmission to hospital and often additional surgery [6]. Adhesion-related

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complications place a significant burden on patients, surgeons and the NHS, in terms of increased complications, additional and often more complicated and time-consuming surgical procedures and increased pressure on already limited healthcare resources. Adhesion formation is a physiological consequence of peritoneal tissue repair. Surgical trauma of the peritoneal surfaces induces a sequence of events that effectuates wound healing, therefore can also ultimately lead to adhesion formation. Surgery induces an inflammatory reaction that is characterized by migration of neutrophils, macrophages and other leucocytes to the site of the inflammation during the first 48 to 72hrs. Chemoattractants (IL-8, MCP-1), cytokines (TNF-α, IL-1 beta and IL-6), growth factors (TGF-beta, IGF-1 and PDGF) and reactive oxygen species produced and released by resident and invading inflammatory cells and subsequent damaged mesothelial cells are the key mediators of this inflammatory reaction. The magnitude of the problem, however, has tended to be overlooked, largely due to a lack of awareness regarding the clinical significance and the true incidence of adhesions. The adoption of effective adhesion prevention strategies will help to minimise the risk of adhesions following abdominal surgery and reduce complications, surgical workload and ultimately healthcare costs. Prevention strategies should include the adherence to good surgical practice alongside safe and effective anti-adhesion adjuvants. Any agent proven to be safe and effective should be used in procedures shown to have a high risk of subsequent adhesion-related complications.

Adhesions can cause complications, such as:

- Small bowel obstruction, the disruption of normal bowel flow, which can result when adhesions twist or pull the small bowel.
- Infertility, which may result when adhesions twist the tissues of the ovaries and tubes, blocking the normal passage of the egg (ovum) from the ovary to the uterus.
- Chronic pelvic pain, which may result when adhesions are present in the pelvis.

Intra-abdominal adhesion formation and reformation after surgery is a cause of significant morbidity, resulting in infertility and pain. The understanding of the pathogenesis of adhesion formation and reformation especially at the cellular and molecular level can help to further develop more effective treatments for the prevention of adhesion formation and reformation. Following an injury to the peritoneum, fibrinolytic activity over the peritoneal surface decreases, leading to changes in the expression and synthesis of various cellular mediators and in the remodelling of the connective tissue. The cellular response to peritoneal injury and adhesion formation and reformation are reviewed. Analysis of the available literature data on the cellular mediators in the peritoneal fluid showed variation in results from different investigators. The potential sources of variability and error are examined. It is still unclear if there is significant individual variation in the peritoneal response to injury. A better understanding of the pathogenesis of adhesion formation/reformation at the cellular and molecular level would undoubtedly help to develop more effective treatment strategies.

**The impact of adhesions:**

Postoperative adhesions occur after almost all abdominal and pelvic surgery. Indeed after laparotomy, almost 93% of patients have been shown to have adhesions at subsequent surgery. They are an everyday problem in clinical and surgical practice, a major cause of morbidity and expense, an occasional cause of mortality and a leading and debilitating cause of chronic pain for patients—estimated as the most common pathology associated with chronic pain. 74% of small bowel obstructions are adhesion-related and it is estimated that between 20 and 40% of secondary infertility in women is as a result of adhesions. Adhesions also pose an important complicating factor for surgeons and patients undergoing future surgery. Adhesions from previous surgery significantly increases subsequent operating time by a median 18 min and even in the hands of experienced surgeons there is a 19% risk of inadvertent enterotomy at reoperative laparotomy and a risk of bowel injury of 10–25% has been reported in laparoscopic adhesiolysis. Indeed, tissue damage to underlying structures is the most common cause of successful surgical negligence suits.

**Etiology and Risk Factors:**

Adhesions may occur in response to injury of various kinds. Non-surgical insults such as endometriosis, infections, chemotherapy, radiation and malignancy may damage tissues and initiate adhesions. However, surgical insults are the most common cause. It is estimated that 55–94% of patients having open surgery have the chance to develop adhesions. Surgical procedures with the highest risk of adhesion formation include cholecystectomy, appendectomy, hernia repair, cancer surgery, liver surgery, and reproductive pelvic surgery. The ovaries, due to their close proximity to other peritoneal surfaces are the most common site for adhesion formation. In fact, the definite etiology of pelvic adhesions is unknown, but the following risk factors have been incriminated:

- Rough manipulation of tissues during surgical procedures.
oxidative stress and post-surgical adhesions:

surgery.

factors but these are largely no longer used during

and suturing. Fibres and glove-dusting powder are also

contents, abrasion, desiccation, heat, light, electrocautery

include ischaemia, exposure to infection or intestinal

that influence adhesion formation during surgery. These

response to trauma to the peritoneum, either as a result

congenital or acquired) [8]. Acquired adhesions develop in

bowel, bladder and urethras.

complications such as internal bleeding and damage to

bowel, bladder and urethras.

Clinical presentation and complications:

Although any major surgery is strongly associated with

adhesion formation, only a few patients will suffer from

clinical symptoms called adhesion related disorders

(ARD). Patients symptoms will vary according to the tissue

or organ involved. In abdominal adhesions, bowel

obstruction may occur. Symptoms may include pains,

intermittent cramps, vomiting, difficulty with bowel

movements and swelling of the abdomen. In pelvic

adhesions, ectopic pregnancy, inability to conceive,

chronic pelvic pains and dyspareunia may occur. In recent

years, ARD have been the subject of increasing

medicolegal litigation [8]. Large retrospective studies

[9,10] have discovered that more than 50% of hospital re-

admissions after surgery are due to ARD. Moreover, the

presence of prior adhesions during surgery may result in

long operative time with increased intra-operative

complications such as internal bleeding and damage to

bowl, bladder and urethras.

Consequences of adhesions:

Adhesions may be defined as abnormal attachments

between tissues and organs (They can be either

congenital or acquired) [8]. Acquired adhesions develop in

response to trauma to the peritoneum, either as a result

of surgery or inflammation. There are a number of factors

that influence adhesion formation during surgery. These

include ischaemia, exposure to infection or intestinal

contents, abrasion, desiccation, heat, light, electrocautery

and suturing. Fibres and glove-dusting powder are also

factors but these are largely no longer used during

surgery.

Oxidative stress and Post surgical Adhesions:

Abdominal surgery is generally known to induce an acute

inflammatory response and oxidative stress in the

peritoneum during the post operative period. Oxidative

stress is caused by an imbalance between the production

of reactive oxygen and a biological system's ability to

readily detoxify the reactive intermediates or easily repair

the resulting damage. All forms of life maintain a

reducing environment within their cells. This reducing

environment is preserved by enzymes that maintain the

reduced state through a constant input of metabolic

energy. Disturbances in this normal redox state can cause

toxic effects through the production of peroxides and

free radicals that damage all components of the cell,

including proteins, lipids, and DNA.

reactive oxygen species (ROS) are produced in a

hyperoxic environment and during the ischaemic/

reperfusion process. The ROS activity is delterious for the

cells. During laparotomy, the partial pressure of oxygen

(150mmHg) is higher than the intracellular pO2 (5-40mm

Hg) and this explains the increase in ROS. ROS scavengers

such as antioxidant enzymes and antioxidant molecules

can help balance the ROS activity and toxicity [15]. The

use of these ROS scavengers was shown to reduce the

adhesion formation following open surgery in animal

studies. Vitamin E, an antioxidant molecule has been

shown to exhibit additional anti inflammatory effects. It

also has the ability to inhibit fibroblast and platelet

adhesion and release. In an experimental model in rats,

intraperitoneal administration of vitamin E reduced 30-

90% of adhesions.

Prevention of Adhesion:

Prevention of the oxidative stress:

The generation of ROS after open and laparoscopic

surgery is well reported. Laparoscopic surgery increases

ROS availability by increasing ROS production or by

decreasing ROS scavengers. ROS scavengers reduce

adhesion formation following open surgery in different

animal models. Indeed, Catalase (CAT),
superoxidismutase (SOD) and trimetazidine reduce

adhesion formation in rats [16]. CAT and SOD also reduce

adhesion formation in an endometriosis rabbits model. In

addition, intraperitoneal administration of methylene

blue reduces adhesion formation in rats; intraperitoneal

administration of melatonin also prevents adhesion

formation in rats. The administration of vitamin E

produced contradictory results in rats [17]. Moreover,

ROS had a direct cytotoxic effect on human mesothelial

cells and, in addition, mesothelial cells apoptosis was

induced by ROS in vitro [16]. These mechanisms create a

further damage of the mesothelial lining extending

beyond the damage created during surgery and

enhancing the possibility to create postoperative

adhesions.

Prevention and Treatment:

Prevention of adhesion formation during surgery entails

reducing surgical trauma and avoiding contamination of

the abdominal cavity with foreign materials. One

common approach to prevent postoperative adhesions is

to place a biocompatible absorbable material between

the viscera and peritoneum. This barrier works as an

isolator between the damaged surfaces in the critical
process of adhesion formation. Biodegradable physical barriers have been successfully used to prevent adhesion formation by mechanically limiting tissue apposition during the critical period of mesothelial repair and healing. By minimizing the development of a fibrin matrix between serosal tissue surfaces, such membranes may prevent adhesion formation [18]. Various polymers are currently used as implants in various orthopedic, neurosurgical, and maxillofacial surgical procedures [19]. Abdominal adhesions refer to scarring or tissue repair that occurs anywhere in the abdomen. They form as the first step in the healing process after any surgery, trauma, infection, or inflammation. Wherever they form, adhesions join structures with strong glue-like bonds that can last a lifetime. Until recently, lysis of adhesions was the only choice medical science offered to treat abdominal adhesions. This involves cutting or burning the abdominal adhesions under general anesthesia, via laparoscopy or laparotomy (open surgery). While lysis of adhesions under general anesthesia, via laparoscopy or laparotomy (open surgery). While lysis of adhesions is used to remove them.

A study in Digestive Surgery showed that more than 90% of patients develop adhesions following open abdominal surgery and 55% to 100% of women develop adhesions following pelvic surgery [20]. Another study reported that 35% of all open abdominal or pelvic surgery patients were readmitted to the hospital more than twice to treat post-surgical adhesions during the 10 years after their original surgery [21].

Pharmacological Adjuvant Therapy:
A number of agents have been investigated, including antibiotics, NSAIDs, corticosteroids and fibrinolytics. To date, no clinical studies have shown adhesion reduction benefits using pharmacological regimens and there are safety concerns with some agents. Theoretically, drugs may be limited by their inability to reach the site and to stay there long enough to be effective, since surgical sites are often poorly vascularised, as are most injury sites. Pharmacological agents can be directed against various causes and components of the inflammatory process (e.g., infection, endotoxin, exudation) and/or of adhesion formation (e.g., coagulation, fibrin deposition, and fibroblastic activity and proliferation). A number of obstacles must be surmounted before agents can be used in adhesion prevention. First, ischemic sites are vulnerable to adhesion formation, but are cut off from the bloodstream and, therefore, from systemic drug delivery. Second, the peritoneal membrane has an extremely rapid absorption mechanism, limiting the half-life and efficacy of many intraperitoneally administered agents. Third, any anti-adhesion agent needs to act specifically against adhesion formation and not normal wound healing processes; these processes of adhesion formation and remesothelialization use the same cascade (exudation, coagulation, fibrin deposition, and fibroblastic activity and proliferation).

Fibrinolytic agents:
Intra-peritoneal thrombokinas, fibrinolysin, streptokinase, urokinase, hyaluronidase, chymotrypsin, trypsin, papain and pepsin act directly by breakdown of the fibrinous mass and indirectly by stimulating plasminogen activator activity (PAA). The use of these agents is still waiting for appropriate human clinical trials. The effectiveness of tissue plasminogen activator (t-PA) and recombinant t-PA [22] has been investigated in animal studies with promising results. The thromboxane synthetase inhibitors (imidazole and ridogrel), as well as thromboxane-A2 receptor blockers, demonstrated a remarkable efficacy in reducing adhesion in a rabbit model. Researchers investigated the ability of thrombin inhibitor (rec-Hirudin1) in reducing postoperative adhesions. Recently, anti-proliferative drugs such as paclitaxel [23] and Camptothecin were shown to inhibit the adhesion formation in the rat cecal sidewall model [24]. Polypeptides such as lysozyme, polylysine, and polyglutamate have drastically decreased abdominal adhesion formation [25].

Anticoagulants:
Since heparin is an effective anticoagulant and clotting is a major contributor to fibrin deposition, local intra-peritoneal instillation of heparin [26] or low molecular weight heparin (Enoxaparin-Na) may result in adhesion free healing [27]. Addition of heparin to the amniotic membrane used to cover injured rabbit uterine horns. Such combinations seem to be more effective in reducing adhesion formation rather than heparin alone.

Anti-inflammatory agents:
These agents are used to decrease the initial inflammatory response to tissue injury. Low-dose aspirin could be effective in reducing adhesion formation by its selective inhibition of thromboxane-A2 over prostacyclin. A study verified the effect of various anti-inflammatory agents as retinoic acid, quinacrine, and dipyridamole in reducing adhesions in animals. Antihistaminics with corticosteroids inhibit fibroblast proliferation. The potential side effects of these agents include immunosuppression with subsequent wound infection, and delayed wound healing with subsequent wound dehiscence or incisional hernia. Non-steroidal anti-inflammatory drugs [22] have an anti prostaglandin...
Mechanical separation:
Separation of raw peritoneal surfaces during early days of healing process is the ideal method to prevent postoperative adhesions.

Peritoneal instillates:
Crystallloid solutions were the most commonly used instillate in the abdominal cavity after surgery. In addition to its mechanical action in separation of raw peritoneal surfaces it dilutes fibrin and fibrinous exudate released from traumatized tissue. Ringer’s lactate has a better buffering capacity than normal saline. Intra-peritoneal instillation of lactated Ringer’s solution in animals decreases adhesion formation and reformation [28]. Unfortunately, these fluids are absorbed from the peritoneal cavity at an estimated rate of 35 ml/h. So, a volume of 500 ml will be absorbed within 14 h, and at least 5 l of fluid are needed to cover the first 6 postoperative days. Its other drawbacks include possible risks of infection, fluid overload with pulmonary oedema, and leaking at puncture sites. In an attempt to prolong the period of instillate persistence inside the peritoneal cavity, more viscous solutions have been tried, such as 32% Dextran-70 (Hyskon1). It acts as a siliconizing agent coating the raw surfaces and as an osmotic fluid causing hydroflotation of viscera. Its recorded complications are vulvar and leg edema, right pleural effusion, and elevation of liver transaminases. However, these complications are transient and resolve within days.

Although carboxymethylcellulose (CMC) was found to be more effective than Hyskon1 [29]. Yet, combination of t-PA and CMC has the best results [30]. Hyaluronic acid (HA) is a naturally occurring bio-compatible agent. HA combined with phosphate-buffered-saline (Sepracoat1) should be applied prior to tissue dissection. It considered a prophylactic anti-adhesiogenic agent for patients undergoing abdominal mesh repair for hernia. HA cross-linked with a trivalent iron 0.5% ferric hyaluronate gel (Lubricoat1) was effective in reducing adhesions at operative sites. Auto-crosslinked hyaluronan (ACP-gel) is used to prevent adhesions with inadequate hemostasis. The ACP-gel holds promise as a novel resorbable biomaterial for reducing adhesions after laparoscopic myomectomy. N,O-carboxymethyl chitosan (NOCC) is a non-toxic absorbable agent that is also used to prevent postoperative adhesion formation [31].

Barriers:
The ideal mechanical barrier, besides being safe and effective, should be non-inflammatory, non-immunogenic, persist during the critical healing phase, be fixed in place without the need for sutures or staples, remain active in the presence of blood, and be completely biodegradable without the need for removal. While the use of endogenous barriers such as amniotic membrane grafts and autologous peritoneal transplants were effective in the prevention of severe adhesions, exogenous barriers such as 0.5% ferric hyaluronate gel (Intergel1) appeared to be more effective for reducing adhesions in general. However, Gynecare T.M, the manufacturing company, withdrew Intergel1 from the market on March 28th 2003 after it received reports of late onset postoperative pain, foreign body reactions and tissue adherence. Seprafilm1 is composed of hyaluronic acid with carboxymethylcellulose. It turns into a hydrophilic gel 24 h after placement and provides a protective coat for traumatized tissue for up to 7 days. Adhibit T.M is a gel used to reduce adhesion formation following cardiac surgery. Adept1 is a clear fluid for intra-peritoneal instillation. It should not be used in patients with a known allergy to starch or with maltose intolerance [31]. SprayGel1 is an adhesion barrier system which consists of two polyethylene glycol-based liquids that when mixed together rapidly cross-link to form absorbable hydrogel in situ. It is safe and well-tolerated, and has demonstrated efficacy in patients at risk for adhesion formation [32]. Poloxamer 407 (Flowgel1) is an effective anti-adhesiogenic agent that converts from a liquid state at room temperature into a gel at body temperature. Polytetrafluoroethylene (Gore-Tex1) is an anti-thrombogenic synthetic fabric that inhibits tissue adherence. However, its use in the laparoscopy is difficult. Fibrin glue and oxidized-regenerated cellulose (Surgicel1) [33] are used more frequently to assist in the control of surgical bleeding. Interceed1 is a commonly employed absorbable fabric patch in open surgery for reducing postoperative adhesions after meticulous hemostasis. A modified version called neutralized Interceed (nTC7) is characterized by being blood insensitive.

New agents:
Polyethylene oxide with carboxymethylcellulose film (Oxiplex1) has been tested for strength and tissue adherence in a rat model with good results. A pilot study has proved the efficacy and safety of another new non-
absorbable barrier called Shelhigh Dome pericardial patch No-react in reducing adhesion after myomectomy. Pluronic F127/F68 alginate ibuprofen mixture (Sol–Gel1) was highly effective and showed a low inflammatory response. Aloe Vera gel has considerably decreased postoperative adhesions.

REFERENCES:


