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Non-barrier agents for postoperative adhesion prevention: clinical and preclinical aspects

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Abstract
Purpose The purpose of this document is to review the non-barrier methods to prevent postoperative adhesion formation in humans.
Methods A MEDLINE computer search was performed to identify relevant articles using the keywords "postoperative adhesion prevention" "abdominal" and "humans". Subsequent searches were performed using the keyword "non-barrier" to further supplement the information obtained. After careful review of the abstracts, 15 articles were selected for inclusion in the manuscript.
Results Many methods, drugs and materials have been demonstrated effective for reducing postoperative adhesion in animal models. Among them, four types of drugs have been clinically used in attempts to reduce postoperative adhesions: gonadotropin-releasing hormone agonists, anti-inflammatory drugs, humidified CO_2 and hydroflotation. Many clinical and meta-analyses revealed that hydroflotation materials do not increase adhesion-free outcome. GnRHa pretreatment using a standard clinical dose (3.75 mg monthly) before myomectomy do not decrease adhesion formation. The role of CO_2 on the reduction and/or prevention of postoperative adhesions have been reported only in cardiac surgery. None of them have been adopted for clinical standard therapy, despite positive reports in animals or preclinical applications.
Conclusion In contrast to the results from animal studies, there is no substantial evidence that the use of non-barrier materials reduces postoperative abdominal adhesions in humans.

Keywords Postoperative adhesion prevention · Non-barrier agents to prevent postoperative adhesion · Gonadotropin-releasing hormone analog · Hydroflotation · Anti-inflammatory drugs · Humidified CO_2

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Introduction

Postoperative adhesions are a natural consequence of surgical tissue trauma and healing [1–4]. Peritoneal adhesions may result in small bowel obstruction, chronic abdominal pain or infertility and may increase the technical difficulty of subsequent abdominal or pelvic surgery [1–4]. A number of different approaches for the reduction and/or prevention of postoperative pelvic adhesions have been reported. Current research has focused on the anti-adhesion potential of various barrier membranes and materials [5–8]. With the barrier technique, surgically traumatized surfaces are kept covered during peritoneal regeneration, thus preventing adherence of adjacent structures and reducing adhesion formation. Although several of the barriers developed to date have proven more efficacious than no intervention, adhesion formation is still reported to occur in a high percentage of treated patients [1–3, 6, 8]. There is no substantial evidence that their use improves fertility, decreases pain or reduces the incidence of postoperative bowel obstruction [3]. Most of the adhesions in the barrier-treated patients

Table 1 Non-barrier agents for postoperative adhesion prevention in animal models and humans

Agent	Administration route	Dose	Complications	References
Humidified CO_2	Intraperitoneal	Fumidified 100% CO_2 (local)	CO_2 emboli (much better tolerated)	[40] [42]
Hydroflotation	Intraperitoneal	Icodextrin 4% at laparotomy	Edema of the labia, vulva and vagina	[6, 17–19, 21–25]
Anti-inflammatory drugs	Intramuscular (ibuprofen) or intraperitoneal (dexamethasone)	100 mg (ibuprofen) 5 mg (dexamethasone)	No specific complication	[3, 26, 27]
GnRHa	Subcutaneous	3.75 mg monthly	Estrogen-deficient syndromes	[39]

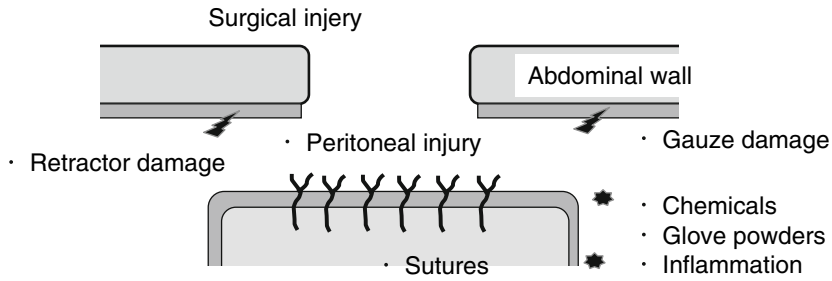

Fig. 1 Surgical trauma. Tissue trauma may result from (sharp, mechanical or thermal) injury, infection, ischemia, abrasion or foreign body (powders or chemicals) reaction

developed in uncovered areas appear in the abdomen. As of yet, no strategy is capable of complete prevention. In addition, a number of limitations have been associated with their use; e.g. difficulty in laparoscopic deployment [9]. These facts underline the necessity of using liquid anti-adhesive agents to cover all potential peritoneal lesions. This article reviews the current non-barrier choices, as summarized in Table 1, to prevent postoperative adhesion formation in humans (in contrast to the results from animal studies [7]).

Methods

An exhaustive literature review was performed in MEDLINE using the keywords "postoperative adhesion prevention" "abdominal" and "humans". The results were filtered by limiting the search to English manuscripts that discussed studies of human subjects. This initial search produced 160 associated articles. Subsequent searches were performed using the keyword "non-barrier" to further supplement the information obtained. After careful review of the abstracts, 15 articles were selected for inclusion in the manuscript.

Pathogenesis

Surgical trauma to the peritoneum is the main cause of postoperative adhesion formation. The trauma may be inflammatory or mechanical, may include exposure to infection or intestinal contents, ischemia, irritation from foreign materials (such as sutures, gauze particles or, historically, glove powder), desiccation or overheating by lamps or irritation fluid (Fig. 1) [10].

The peritoneum is the most extensive serous membrane in the body, serving to minimize friction and facilitate free movement of abdominal viscera, to resist and localize infections and to store fat [2, 11]. This mesothelial monolayer is extremely delicate and hence susceptible to damage (Fig. 2), although it also has excellent healing properties provided that there is no ongoing inflammation that reduces fibrinolytic activity or deprives tissues of oxygen. In general, abrasion and other trauma during surgery lead to the disruption of the peritoneal mesothelium and fibrin is then released along with a cascade of other elements, including leukocytes and peritoneal cells [2, 11]. Unlike skin wounds, which heal from the edges, the repair of peritoneal defects occurs from the underlying mesenchyme [3]. The fibrin is deposited at the damaged surface as a result of bleeding and posttraumatic inflammation (Fig. 3). Diminished fibrinolytic activity transforms the fibrin deposit into an adhesion (Fig. 3).

The peritoneal damage induces an inflammatory response that ultimately leads to the upregulation of the expression of tissue factor by macrophage and mesothelial cells [1–3]. This causes activation of the extrinsic pathway of the coagulation cascade, eventually leading to the formation of fibrinous exudate. The fibrinogenesis is in balance with fibrinolysis under normal circumstance (Fig. 4). Decreased peritoneal fibrinolytic capacity due to an imbalance of tissue-type plasminogen activator (t-PA) and plasminogen activator inhibitor type 1 (PAI-1) has been shown to play a pivotal role in the formation of postoperative adhesions [12]. Intraabdominal surgery disturbs the balance

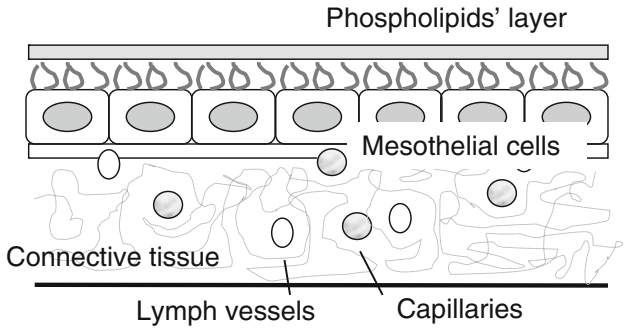

Fig. 2 Anatomy of the peritoneum. Peritoneum comprises a single-cell monolayer of mesothelium lying on a sub-mesothelial connective tissue matrix which contains numerous capillaries and lymphatic channels. The vessels open into the mesothelial cell monolayer. The surface of the mesothelium is coated in phospholipids

between tPA and PAI-1 resulting in a decreased fibrinolytic activity and an increase in fibrin exudate, eventually leading to an increase in adhesion formation [13]. When the peritoneum is slightly damaged and mesothelial cells are mostly intact, there will be a dynamic balance between fibrinolysis and fibrinogenesis and adhesion-free healing may then take place; reepithelialization is complete 5–7 days after the initial trauma [8]. When more severe trauma is caused during an operation, loss of mesothelial integrity will occur, exposing the underlying connective tissue and extracellular matrix. Normal fibrinolytic activity will be lost for at least 48 h post-trauma, although individual differences are present in patients. The fibrinous adhesions will organize into fibrous adhesion due to ingrowth of fibroblasts and endothelial cells that is followed by capillary formation and incorporation of collagen, all stimulated by cytokines and growth factors up to day 7 [8].

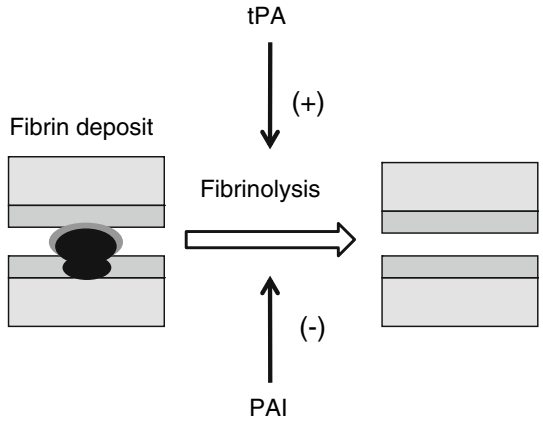

Fig. 4 Fibrinolytic capacity. The fibrinogenesis is in balance with fibrinolysis under normal circumstance. The process of fibrinolysis is driven by the enzyme plasmin, which is derived from its inactive substrate plasminogen by tissue-type plasminogen activator (tPA). On its turn, tPA is inhibited in its reaction by plasminogen activator inhibitor (PAI), to maintain a balance

Reduction in adhesion formation

Fibrinous exudates from within 3 h after injury and result from decreased fibrinolytic activity. If not quickly removed absorption or fibrinolysis, the invasion of fibroblasts and blood vessel soon follows. Most fibrinous exudates are transient and break down within a few days, but trauma-induced local suppression of peritoneal fibrinolysis predisposes to their organization into adhesion [3]. No new adhesion formation occurs after postoperative day 7 [14–16]. Theoretically, optimal prevention of adhesion formation requires intervention throughout the critical 7-day period of peritoneal healing.

The role of different activators and factors in the adhesion formation process is a matter of considerable research,

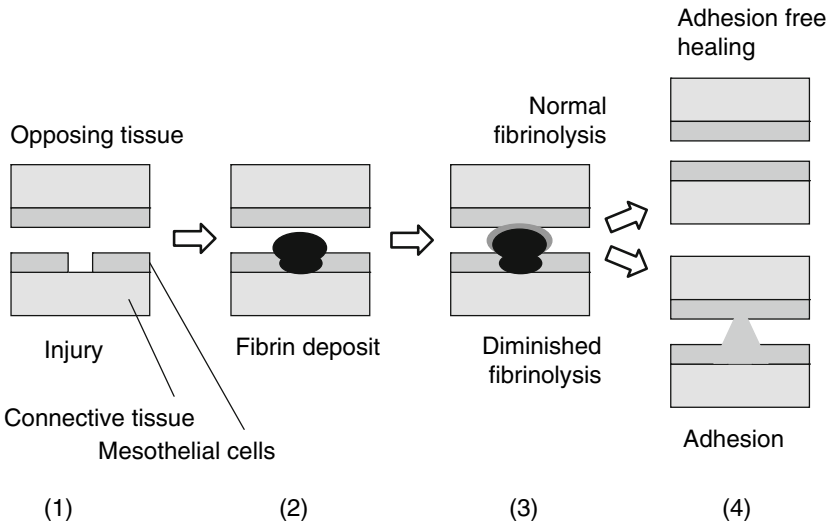

Fig. 3 Normal tissue repair and adhesion formation. On peritoneal injury (*1*), fibrin deposits from damaged mesothelium enlarge to form a bridge between opposing tissue surfaces (*2*). Locally generated fibrinolytic factors are released which may degrade all or part of this fibrin bridge (*3*). When the peritoneum is slightly damaged and mesothelial cells are mostly intact, there will be a dynamic balance between fibrinolysis and fibrinogenesis and adhesion-free healing may then take place. Diminished fibrinolytic activity transforms the fibrin deposit into an adhesion (*4*)

aimed at not only improving our understanding of the development of adhesions, but also, most importantly, finding optimal strategies for adhesion prevention. The most promising avenues of research are strategies to separate damaged peritoneal surfaces, the fostering of the process of fibrinolysis and the regulation of hypoxia and prevention of angiogenesis. Research in adhesion prevention has focused on non-barrier materials.

Hydroflotation

The use of crystalloid solutions is known as hydroflotation; some crystalloid is left in the pelvis at the end of surgery to allow the tissues to float apart from one another and thereby decrease the risk of adhesion formation [6]. The results from multiple studies looking at the use of hydroflotation with crystalloids have been discouraging [17]. Some investigators add heparin to the crystalloid solutions used for irrigation. The rationale behind the use of heparin includes the prevention of blood clotting and fibrin deposition, which are involved in adhesion formation. Unfortunately, the largest randomized, placebo-controlled clinical trial addressing this approach showed no benefit in terms of adhesion formation between the study and control groups [18, 19]. It has been suggested that fluid absorption is too rapid for sufficient fluid to be present for activity, if indeed hydroflotation is the mechanism of action [20].

Owing to its high viscosity and long half-life in the peritoneal cavity, high-molecular weight dextran has been used for hydroflotation. However, none has been demonstrated effective for reducing adhesion formation [18, 21]. Icodextrin 4% solution has been recently added to the armamentarium of adhesion prevention as an adjunct used intraperitoneally in patients undergoing gynecologic laparoscopic adhesiolysis [22–24], that is, a water soluble, high-molecular weight, alpha 1,4)-linked glucose polymer in an electrolyte solution. Although a preliminary randomized, controlled pilot study observed the icodextrin 4% reduced adhesion formation [25], a systematic review concluded that there is insufficient evidence for its use as an adhesion-preventing agent [21]. Wiseman et al. [17] searched clinical reports of 30-year period containing details of rates of adhesion development after abdominopelvic surgery. Adhesion-free outcome (sites) was lowest for reformed (26.3% laparotomy; 14.3% laparoscopy), higher for de novo (direct trauma) (45.2% laparotomy, 37.2% laparoscopy) and highest for de novo (indirect trauma) adhesions (82.4% laparoscopy). Crystalloid solution instillates reduced adhesion-free outcome at sites (45.2 vs. 20% de novo adhesions in laparotomy) and in patients (43.5 vs. 19.9% reformed, laparotomy; 71.7 vs. 25% de novo, laparoscopy). It was lower in laparoscopy than in laparotomy for de novo and reformed adhesions. Crystalloid instillates did not increase adhesion-free outcome. Similar analyses [21, 25] demonstrate that there is no evidence on any benefit for improving adhesion development when pharmacological and fluid agents are used as an adjunct during pelvic surgery. There is insufficient evidence for the use of the following agents: steroids, icodextrin 4%, spray gel and dextran in improving adhesions following surgery. In the same trial, a number of treatment-related complications were identified, including excessive edema of the labia, vulva and vagina [6].

Anti-inflammatory drugs

Anti-inflammation agents, such as non-steroid anti-inflammatory drugs or dexamethasone has been also recommended to prevent postoperative pelvic adhesions by blocking the production of thromboxanes and prostaglandins, known to be involved in biochemical pathways leading to adhesion formation [3, 26, 27]. However, lack of adequate studies evaluating their safety and efficacy has limited their clinical application [3].

Gonadotropin-releasing hormone agonists

Gonadotropin-releasing hormone agonists have beneficial effects on the size and symptoms of endometriosis and uterine myomas by suppressing ovarian steroidogenesis [28, 29]. GnRHas are also the preferred drugs for postoperative adhesion prevention. Experimental and clinical studies have demonstrated various mechanisms of action to be involved in adhesion prevention when GnRHas are used for treatment [30]. In studies involving uterine surgery in animal models, postoperative uteroomental adhesions were reduced with preoperative therapy using GnRHa [7, 31]. The hypoestrogenism induced by GnRHa might alter balance of fibrinolysis-fibrin formation and extracellular matrix remodeling that thereby played a role in the mechanism of GnRH-reduced adhesion formation [32]. This is consistent with a prior report that has demonstrated the presence of sex steroid receptors in pelvic adhesions [33, 34]. Estrogen-dependent growth factors appear to play an important role in adhesion formation, such as transforming growth factor-β, insulin-like growth factor-1, epidermal growth factor, platelet-derived growth factor, angiogenic growth factors, vascular endothelial growth factor, basic fibroblast growth factor and also some pro-mitogenic cytokines, such as interleukin (IL)-1β and IL-8 have the same effect [35, 36]. GnRHa antagonizes these estrogen-dependent growth factors to develop adhesion formation.

In the past several years, numerous studies have shown that GnRH and its analogs can exert direct effects on extra pituitary peripheral tissues by binding to its specific receptor [29, 30, 37], including peritoneal cells [34]. GnRHa

might increase the fibrinolytic activity in peritoneal cells. The in vitro study demonstrates that GnRHa in millimolar concentration caused a significant increase in fibrinolytic capacity of human peritoneal cells [32, 34]. Peritoneal GnRH level must be less than nanomolar concentration in patients treated with a GnRHa, although no previous reports have measured. It is unlikely that the usual clinical dose of GnRHa (1.88–3.75 mg monthly) ever reaches concentrations in the peritoneal cavity that are necessary to stimulate peritoneal cell GnRH receptors. A higher dose of GnRHa administered intraperitoneally would be required for preventive action against postoperative adhesion. In addition to such direct action of GnRHa, decreases in the serum estrogen level, which may theoretically favor the limitation of permanent adhesion formation, have been associated with the coagulatory and fibrinolytic responses [38], through downregulation of the estrogen-dependent growth factors. More recently, Coddington et al. [39] found that GnRHa pretreatment using a standard clinical dose (3.75 mg monthly) before myomectomy did not decrease adhesion formation as predicted. Twenty patients underwent an initial abdominal myomectomy followed by a second-look laparoscopy for evaluating uterine adhesions after random allocation to groups receiving either GnRH analog or placebo for 3 months before the initial surgery. Presurgical GnRH-a treatment did not decrease adhesion formation when compared with placebo. For every additional centimeter of incision length, the total adhesion area over the uterine serosal surface increased by 0.55 cm^2. The number of myomas removed and the number of incisions were positively correlated with total adhesion area. Preoperative treatment with GnRH-a for 3 months before open abdominal myomectomy did not decrease postoperative uterine adhesions. Following the standards of good surgical technique, adhesions are minimized with fewer and smaller incisions. Differences between the lack of clinical effect on adhesion prevention by GnRHa in the human trial and the effectiveness on adhesion formation in rat models [31] may suggest that other effecting factors or the experimental process were more influential in developing adhesion. For example, as mentioned before, a higher dose of GnRHa administered intraperitoneally would be required for preventive action against postoperative adhesion. Further studies are necessary with these pharmacological drugs on human subjects and comparative studies with other preventive agents that have been widely applied and found effective in the prevention of adhesion.

Humidified CO_2

The formation of adhesions after open surgery is partly due to the perioperative exposure of the wound cavity to ambient air, which initiates various local processes that cause inflammation and cellular damage in mesothelial layers. These adhesiogenic processes, include superficial desiccation, airborne bacterial contamination and subsequent wound infection and exposure to atmospheric oxygen with ensuing hyperoxia and oxidative stress [40]. Matsuzaki et al. [41] investigated whether supplemental perioperative oxygen could reduce postoperative adhesion formation through increasing the peritoneal tissue oxygen tension in a mouse model. There was no significant difference in the incidence of abdominal wound adhesions; however, the severity of adhesions was significantly reduced in group (on day 0, over the course of the 90 min procedure including the 60 min of laparotomy) as compared to another group (fraction of Inspired oxygen). It has recently become possible to establish a local atmosphere of 100% carbon dioxide (CO_2) in an open surgical wound cavity by flooding it with the gas.

Persson and Linden [40] put forth the hypothesis that intraoperative field flooding with warm humidified CO_2 can decrease the occurrence of adhesions after open surgery through preventions of desiccation, surgical site infection and oxidative stress. Support for the present method is provided by the results from related research in laparoscopic surgery, after which adhesions are also common and where CO_2 is insufflated into the closed surgical wound cavity to facilitate endoscopy [40]. CO_2 is 25 times more soluble in blood and tissue than air and CO_2 emboli are, therefore, much better tolerated than air emboli. Moreover, the density of CO_2 (50% heavier than air) facilitates air displacement in a cavity [42].

Surgical technique

The formation of adhesions might be reduced by minimizing peritoneal injury during surgery, by preventing the introduction of reactive foreign bodies, by reducing the local inflammatory response and by inhibiting the coagulation cascade and promoting fibrinolysis [3, 43, 44]. Peritoneal closure has been performed to reduce postoperative complications including adhesions. The review of the literature does not support the closure of peritoneum to prevent adhesions [45, 46]. However, parietal peritoneal closure at primary cesarean delivery has been observed to yield significantly fewer dense and filmy adhesions [47, 48]. The adhesion-related symptoms rarely occurs after laparoscopic supracervical hysterectomy [49] and perhaps after transvaginal hysterectomy.

Regardless of the surgical approach selected, procedures, such as myomectomy often result in adhesions. The prevalence of adhesions after open abdominal myomectomy is greater than 90%, but is still at least 7% after laparoscopic myomectomy [1, 3].

Conclusion

Several drugs and substances are used locally or systematically for postsurgical adhesion formation, including mechanical barriers and physical, chemical and pharmacological agents [1–3, 5, 6, 8]. Research in adhesion prevention has focused strongly on barrier films. Current adhesion barriers include expanded polytetrafluoroethylene (Gore-Tex®), oxidized regenerated cellulose (Interceed®) and sodium hyaluronate and carboxymethylcellulose (Seprafilm®). Although they may reduce postoperative adhesions, the therapeutic and physiological effects of barriers may be limited to the site of application. The fact that the membrane is thin, crisp and filmy may make it difficult to use. This may be particularly true during difficult abdominal wound closures or cases involving a small incision.

The search for an effective non-barrier device has been continuing for decades. Many methods, drugs and materials have been evaluated to prevent postsurgical adhesion formation in animal models (see [7]). Despite positive reports using GnRHa, anti-inflammatory drugs and hydroflotation, none of theses have been adopted for clinical standard therapy. More detailed studies are needed on this topic, and future studies on the efficacy of a material in decreasing adhesion formation should include a comparison of several control materials including barrier materials.

Conflict of interest statement None.

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