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Postoperative Abdominal Adhesions: Pathogenesis and Current Preventive Techniques

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Abstract

Postoperative Abdominal Adhesions (PAA) are a condition that occurs in more than 90% of patients undergoing abdomen surgery, they can cause chronic abdominal pain, female infertility and repeated bowel obstruction, requiring repetitive surgical interventions causing morbidity and mortality, as well as high costs. The formation of the PAA is due to an imbalance between the fibrinogénesis and fibrinolysis in favor of the first, associated with tissue hypoxia secondary to aggression of the peritoneum, also due to the own inflammatory response and the increase in the population of adhesion fibroblasts which inhibit the degradation of the extracellular matrix and facilitate mature collagen and supporting connective tissue. The prevention of adhesions will decrease secondary complications, as well as hospitalizations, unnecessary surgeries and consequently, cost containment.

Keywords: Postoperative adhesions; Abdominal surgery; Peritoneum

Introduction

Abdominal adhesions are vascularized and innervated connective tissue bridges formed randomly between the peritoneum, the intestinal bowels and the abdominal wall [1]. Reports indicate that after surgery intra-abdominal adhesions can lead to surgical re-intervention, chronic abdominal pain, intestinal obstruction and infertility in women [2-4]. It has also been reported, that up to 93% of patients who have had one or more previous surgeries develop abdominal adhesions [5], while up to 15% to 20% of female infertility occurs as result of post-surgical adhesions [4]. The importance of understanding the pathogenesis of the Postoperative Abdominal Adhesions (PAA) is to found possible prevention methods in its formation by intervening in the different moments during the formation of adhesions, as well as recognize the proteins that will be useful as markers in the monitoring of formation of adhesions during experimental studies on different models.

PAA are the result of tissue injury, likely to occur by the injury of an incision, electrocoagulation trauma and sutures, or by foreign bodies damaging the parietal and visceral peritoneum, which reacts forming abundant aberrant peritoneal healing and scars [6,7]. After injury of the mesothelial cells, a release of vasoactive substances and kinins occurs mainly by the mast cells acting at the site of the injury, leading to vasodilation and increase of vascular permeability, which forms a fibrin-rich exudates [6,8-10]. During the normal repair of peritoneum, the initial morphological reaction of the serosa occurs within the first 12 hours, appearing as a dense layer of fibrin, densely infiltrated with polymorphonuclear leukocytes; between 24-36 hours, the major cellular component is that of macrophages that are observed laying over a fibrin layer; additionally, mesothelial cells can be seen buried within the deep regions of the lesion. During the 5th day, when the process of repair is partially completed, it shows a simple layer of mesothelial cells. However, it is up to the 8th day when injured segments appeared covered by one characteristic monolayer of mesothelial cells, firmly attached to the basal membrane [7,8,10]. These would be the morphological changes of the damaged peritoneum, and are given by the activation or inhibition of repair complex proteins.

The Fibrin, present in this first reparation "soup" then is the end-result of the coagulation cascade process that forms deposits, while there is a concomitant proliferation of fibroblasts responsible for the formation of an Extracellular Matrix (ECM) and collagen, which favours the formation of scar tissue translating into true adhesions. Subsequently, an increase of the expression of the Vascular Endothelial Growth Factor (VEGF) occurs, leading to endothelial cell proliferation and late formation of vascular structures within adhesions [8,10]. The Extracellular Matrix (ECM) is the forerunner of connective tissue repair, consisting mainly of fusiform fibroblasts, mature

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Table 1: Main factors of growth (GF) involved in the repair of the peritoneum.

FC	Name	Origin	Action
EGF	Epidermal GF	Macrophages, epithelial cells and platelets	Stimulate production of epithelial and endothelial cells and activate inflammatory cells and fibroblasts
TGF-α	Transforming GF-alfa	Macrophages, neutrophils and platelets	Activate fibroblasts and promote angiogenesis (proliferation, synthesis of collagen and collagenase)
FGF	Fibroblastic	Macrophages and epithelial cells	Fibroblasts migration (Chemotaxis)
TGF-β	Transforming GF-beta	Macrophages and platelets	Stimulate angiogenesis and migration of neutrophils, macrophages and fibroblasts to Extracellular Matrix (ECM)
PDGF	Platelets Derived GF	Platelets, macrophages, fibroblasts and endothelial cells	Stimulate fibroblasts proliferation and its chemotaxis toExtracellular Matrix (ECM)
SP	Tachykinin Substance P	Macrophages, platelets and neutrophils	Vasodilation, chemotaxis, fibroblasts activation and production of pro-inflammatory interleukins

collagen synthesized by fibroblasts, fibrin and fibronectin (supporting tissue). The activation of fibroblasts to synthesize collagen and fibronectin, as well as their migration to the MEC is given by growth factors synthesized by platelets, polymorphonuclear cells, damaged endothelial cells and macrophages (Table 1).

It has been demonstrated that fibroblasts originating from tissue adhesions have a different phenotype when compared to normal fibroblasts found within the peritoneal tissue [4]; such transformation of phenotype has been related to tissular hypoxia, while fibroblasts adhesion determine an increase in the mRNA expression of collagen I, fibronectin, metalloproteinase-1, Tissue Inhibitors of Metalloproteinases (TIMP-1), Tissue Growth Factor TGF-beta1, Cyclooxygenase-2 (COX-2) and IL-10, all these proteins are in favor to formation of adhesions acting at different times (Figure 1).

COX-2 is an enzyme that regulates the inflammatory processes of angiogenesis on the formation of post-surgical adhesions. In the presence of tissular hypoxia and/or fibroblasts adhesion, the expression of COX-2 increases [8]. During the formation of dense postoperative adhesions, the fibrinolytic system plays a pivotal role to degrade fibrin formed at the site of injury by conversion of the plasminogen into plasmin, ultimately responsible to degrade fibrin. The conversion of plasminogen into plasmin is determined by the tissue Plasminogen Activator (tPA) and activator type urokinase (uPA) [1,6,8-11]; both are expressed by the complex of the endothelial and mesothelial cells, macrophages and fibroblasts.

It has been observed that the peritoneal cavity tPA has been shown to be responsible for up to 95% of the plasminogen activation and fibrin degradation [1,6], whereas uPA plays a more important role during tissue remodeling, because it acts degrading pericellular matrix components. Further, plasminogen activation is inhibited by the inhibitory factor of plasminogen activator 1 and 2 (PAI-1 and 2), although the PAI-1 glycoprotein elicits a superior inhibitory activity. Both, PAI-1 and PAI-2, are produced by the endothelial, and mesothelial cells, monocytes, fibroblasts and macrophages. PAI-1 is considered an important factor associated to the pathophysiology of adhesions, finding its high maximum concentrations in patients suffering peritoneal adhesions [1].

On the other hand, in normal fibroblasts the common radius of tPA/PAI-1 is 80% higher than in adhesion fibroblasts, esteeming fibrinolysis. During a hypoxic event the tPA/PAI-1 radius decreases up to 90% in normal fibroblasts, while a critical decrease is observed by the presence of fibroblasts adhesion (98%) [8]. Thus, tissue hypoxia favors the conversion of adhesion fibroblasts, inducing the release of markers of inflammation that culminates in the development of postoperative adhesions.

Considering how complex are the mechanisms that trigger the formation of postoperative abdominal adhesions, its genesis can be summarized as the end-result of an imbalance between the process of fibrogenesis and fibrinolysis, enhanced in this case by the first response associated to tissular hypoxia, secondary to mesothelial damage, inflammatory responses of the injured tissue, and an increase of the population of adhesion fibroblasts, inhibiting the degradation of extracellular matrix.

In this phenomenon of adhesion formation, experimental studies must focus on the different steps of the coagulation cascade to try to reduce the formation of fibrin and its organization as well as the maturation of collagen and its degradation, can also take part in the steps involved in the process of inflammation: vasodilation and increased permeability decreasing concentrations of fibrin and their precursors or through the inhibition of COX-2, in encourage the action of plasminogen activators, as well as prevent the formation or action of inhibitors of plasminogen activation factors.

Prevention

Numerous strategies have been devised in the search of methods aimed to decrease the formation of Postoperative Peritoneal Adhesions (PPA), mostly based on specific data related to the pathophysiologic origin of adhesions. Among various approaches are [3,12]:

The surgical technique

Atraumatic handling of delicate tissue is critical during surgery to avoid damage to serous membranes and decrease the fibrinolytic activity and local hypoxia [2]. There are two basic principles aimed to prevent the formation of adhesions: avoid incisions on highly vascularized tissues (e.g. muscle) and minimize the extent of the surgical trauma, including the abuse of electrocoagulation [13].

The specialists of microsurgery have agree that handling soft tissues using surgical gloves is less traumatic than the contact with surgical instruments; however, electron microscopy reports indicate that both can induce significant damage to serous membranes [2]. In animal models, it has been recorded that the duration of surgery and the perioperative bleeding increases their predisposition of form PAA, concluding the existence of a direct effect over tissular damage induced by careless tissue maneuvers and mishandling, but related also to the duration of surgery [14]. Most studies concur that laparoscopy drastically reduces post-operative adhesion formation when compared to laparotomy [3,15-17].

Pharmacologic prophylaxis

NSAIDs drogas inhibit COX-1 and COX-2, preventing thus the síntesis of prostaglandins and thromboxanes [2]. Most animal studies have agreed that the use of NSAIDs decreases the formation of surgical adhesions. In rats for example, a selective COX-2 inhibitor

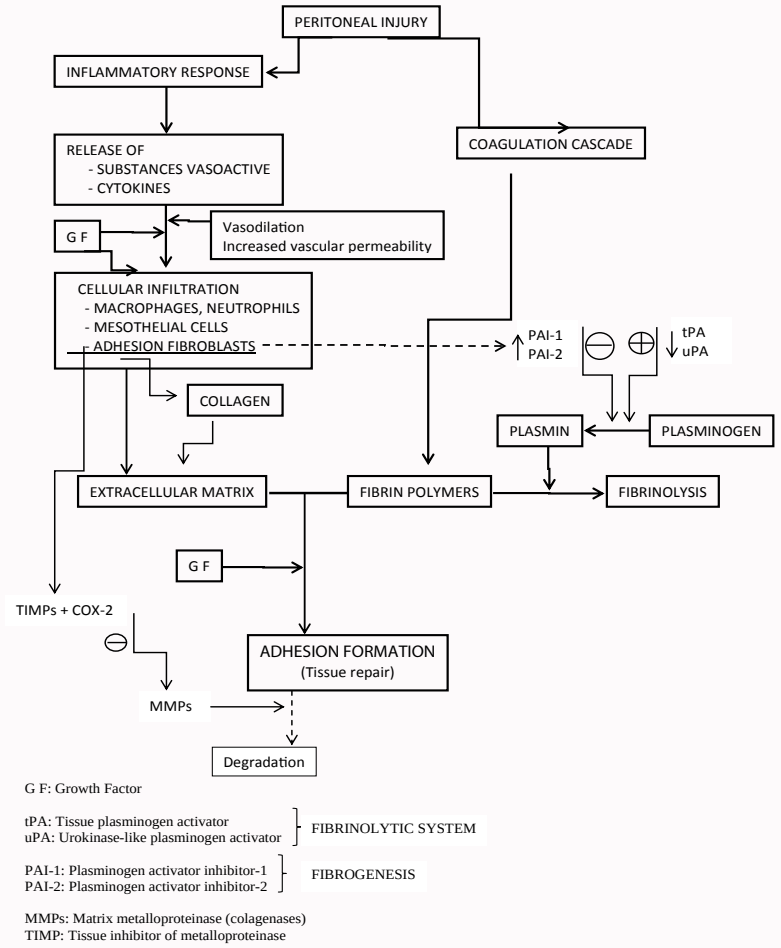

Figure 1: Postoperative abdominal adhesion formation start with the peritoneum injury followed by an inflammatory response associated with the activation of the coagulation cascade favoring the excessive formation of fibrin deposits that will be support of fibrous tissue repair.

administered IP reduced peritoneal adhesion formation [18-20].

Furthermore, when comparing selective COX-2 inhibitors (Nimesulide, celecoxib and parecoxib) and their respective effects under intraperitoneal or intramuscular injection, they showed a reduction in the formation of surgical adhesions [21-23]; although no significant difference related to their site of administration was reported. Pharmacological agents such as NSAIDs have shown to prevent the appearance of postsurgical adhesions in various animal models; however, there is no significant evidence nor publications recommending its use for human beings [13,21].

The heparin is a glycosaminoglycan acid-anionic acid that binds to anti thrombin-III (AT-III) to form the complex heparin-AT-III, inhibiting the activation of factors of coagulation IX, X, XI and XII preventing the formation of fibrin. A study in laboratory rats, demonstrated that the administration of heparin combined with carboxymethylcellulose at different doses resulted effective and safe (62.5 IU, 125 IU and 250 IU), obtaining the best results when the highest dose of heparin was applied [16].

Furthermore, the optimal dose needed to limit the formation of adhesions still poorly understood and therefore it becomes necessary to identify an effective dose for the prevention and formation of adhesions, without increasing the risk of bleeding. Experiments in murine models subjected to surgical manipulation and subsequent peritoneal lavage with heparin, concluded that heparin decreased the peritoneal inflammatory reaction and the formation of adhesions [24,25]. In addition, Low Molecular Weight Heparin (LMWH) showed to decrease adhesion formation in animal models when applied intraperitoneal and subcutaneously [2,26].

Other therapies

Alternative therapies have been tested to avoid adhesion to a mechanical barrier, that in terms of an ideal response should be non-reactive, bio absorbable, easy to use and endure complex recovery phases [18]. Among the liquid mechanical barriers, the most commonly used is dextran 70 (hypertonic solution). Nevertheless, its use has been abandoned because it does not show sufficient clinical efficacy [1,12], while among the solid mechanical barriers the most representative include the polyethylene glycol (SparyGel®), the sheet of oxidized regenerated cellulose (Interceed®) and carboxymethylcellulose associated with Sodium hyaluronate (Seprafilm®); both drugs approved by the FDA in the US.

These barriers have been primarily employed for gynecological and pelvic surgery, and although they have shown some efficacy to decrease the degree, severity or extension of PAA between the bowel and abdominal wall loops, they have not prevented their formation in all cases [2,27]. In addition, it has been seen that it can inflict significant damage to the anastomosis and therefore its use is not recommended in such cases [1,28]. A reduced degree of efficiency has been found using liquid barriers and gel [12].

Discussion

Glucocorticoids have been also studied alone or in conjunction with antihistamines; it is known that the former decreases the inflammatory response, while antihistamines inhibit the proliferation of fibroblasts [2,9]. No significant benefit has been found with the use of glucocorticoids (intravenous, enteric or intraperitoneal) to avoid the formation of real adhesions [9], which in addition have elicited adverse effects such as immunosuppression and delayed wound repair [2].

The prophylactic use of antibiotics against infection and in turn diminishing postoperative adhesions is common, under the principle that by decreasing intraperitoneal infection and inflammation it can lead to less adhesion formation. According to Sortini et al. [22] the intraperitoneal instillation of antibiotics promoted the formation of adhesions.

Recombinant tissue Plasminogen Activator (tPA), an agent directly promoting fibrinolysis has been used among other attempts to prevent adhesions, given that when applied locally reduces the formation of adhesions in rabbits. However, the concentration of the fibrinolytic system required to prevent adhesions increases the risk of postoperative hemorrhage, while delaying wound repair; consequently, its use is considered unsafe and ineffective [2,9].

Conclusion

Recent studies have suggested the use of methylene blue, an inhibitor of oxygen free radicals and therefore inflammatory response aimed to decrease adhesion formation. Unfortunately, its tendency and capacity to cause damage at the site of pressure of an anastomosis during the early repair phases has been reported [2].

There are studies in which substances apparently unrelated to the genesis of adhesions have effects on prevention in their formation, such as the studies at the surgical research laboratory of Boston University School of medicine, MA [27,28], who found that antiemetic medications that contain receptor antagonists of Neurokinin-1 (aprepitant, Emend®, and others still in research) have proven to be effective in the reduction of abdominal adhesion formation, mainly when they are applied directly in peritoneum [29,30]. The Neurokinin-1(NK-1RA) stimulates emesis in the central nervous system in synergy with the substance P which is a potent vasodilator, also implicated as a mediator in inflammation to the favor chemotaxis, lymphocyte proliferation and production of pro-inflammatory interleukins (IL-1, IL-6, IL-10 and TNF-α) and increase in peritoneal exudate that contains fibrin and also stimulating to TGF-β growth factor; so, Neurokinin-1 receptor antagonists have some effect on the formation of adhesions.

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