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THE MAIN DIRECTIONS OF PREVENTION OF ADHESIONS IN ABDOMINAL AND THORACIC SURGERY

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ABSTRACT

The article presents a review of the literature on the main areas of prevention of the most common complication of abdominal and thoracic surgery - the adhesions. It is noted that adhesion processes have different clinical significance in the chest and abdominal cavities. At *the same time, the experience of studying the causes of adhesion in the abdominal cavity can serve as a foundation for further research on pleural adhesions. The key factor determining the pathogenesis of adhesion formation and its prevention is fibrinolysis. There have been several studies on this issue. Their results are promising, but most of them are contradictory and have been carried out in experimental models.*

KEYWORDS: *Abdominal And Thoracic Surgery, Postoperative Adhesion, Anti-Adhesion Coatings.*

INTRODUCTION

Postoperative adhesions are a pathological condition that occurs in more than 90% of patients who underwent abdominal surgery and in 45-70% after thoracic surgery, and remains one of the most difficult problems in general surgical practice [5, 26]. Indirectly, the frequency of lesions of the pleural sheets by the adhesive process can be judged by the detection of pleural adhesions at autopsy, which, according to different authors, range from 48 to 80.5%. In a significant proportion of cases, pleural adhesions found at autopsy are an accidental finding and are asymptomatic [7].

Consideration of the influence of the adhesion process on the further course of the disease, and, therefore, the issue of management tactics (prevention and dissection of adhesions or stimulation of their formation) is reduced to solving the following main tactical points: the pathological process that led to adhesion formation; topography of adhesions; massive adhesions and the associated respiratory dysfunction.

According to most authors, the adhesive process in the pleural cavity is fundamentally different from that in the abdominal cavity and is of a compensatory and adaptive nature [2, 8]. In this connection, the attitude to adhesion formation in the pleural cavity cannot be considered unequivocally as a negative phenomenon, since in some cases (chest trauma, residual pleural cavity, spontaneous pneumothorax, etc.), adhesion stimulation may be a necessary component of treatment.

The available literature data indicate a high level of incidence of postoperative adhesive disease, while the mechanisms of adhesion formation are not fully understood [13]. The frequency of relaparotomy, according to various literature data, is estimated at 63% -97%. Repeated surgical interventions are more time-consuming and technically difficult, which, in turn, creates a potential risk of damage to vital structures. Approximately 1/3 of patients who undergo abdominal surgery are re-admitted within 10 years after surgery to address a problem directly caused by adhesions or complicated by adhesions, leading to serious clinical problems such as chronic pain, infertility and intestinal obstruction. More than 20% of all readmissions are noted within the first year after primary surgery [9].

Until now, a number of methods and anti-adhesive coatings have been developed, which have been successfully used in experimental studies. Their role is to activate fibrinolysis, hinder coagulation, reduce the inflammatory response, inhibit collagen synthesis, or create a barrier between adjacent wound surfaces. These prevention strategies can be divided into four categories: general principles, surgical techniques, mechanical barriers and chemicals [1, 23, 26].

As you know, some basic surgical principles must be followed in all abdominal surgeries. These principles are close to the Halsted Principles (W.S. Halsted 1852-1922), the first surgeon to recognize the importance of these measures. Injury to the peritoneum should be avoided through careful tissue handling, careful hemostasis, continuous irrigation and avoidance of unnecessary drying out, ineffective use of foreign bodies, and suturing or clamping of tissue. The use of thin and biocompatible sutures, atraumatic instruments and starch-free gloves is also recommended. Starchy gloves are a significant risk factor for postoperative adhesions. Several experimental studies have shown that the use of gloves with powdered starch during laparotomy is associated with an increased risk of extensive postoperative peritoneal adhesions [23, 26]. However, recent evidence suggests that, in the absence of additional peritoneal trauma, foreign bodies are an infrequent cause of adhesion induction [16].

Certain intraoperative techniques should be employed, such as avoiding unnecessary pleural dissection or avoiding peritoneal closure. Many experimental studies have shown that non-closure of the peritoneum is associated with a decrease in the formation of peritoneal adhesion [18].

W.J. Brokelman et al. (2006) showed in a prospective study that there is no difference in the concentration of tPA antigen, tPA activity, uPA antigen or PAI-1 in abdominal biopsies taken at the beginning compared to the end of the laparoscopic procedure, regardless of whether high intra-abdominal pressure is created or light activity. In contrast, some studies have not reported a difference between both surgical approaches [10].

The role of CO2-pneumoperitoneum in adhesion formation after laparoscopic surgery has been reported [4]. It is known that, during laparoscopic surgery, CO2-pneumoperitoneum itself has a real effect on the peritoneum. It has been demonstrated that adhesion formation increases with the duration of the CO2-pneumoperitoneum and the insufflation pressure. Indeed, long-term laparoscopic surgery requires long-term and large volumetric gas insufflation, raising concerns about the adverse consequences of long-term gas insufflation. The standard CO2 used in modern laparoscopic practice is cold dry CO2, which is not physiologic to normal abdominal conditions.

C.R. Molinas et al. (2001) demonstrated that CO2-pneumoperitoneum increases postoperative peritoneal adhesions depending on time and pressure, and that this increase decreases with the addition of 2-4% oxygen, which indicates peritoneal hypoxia as a driving mechanism. It is assumed that with a decrease in fibrinolytic activity, the process of adhesion formation no longer depends on the surgical approach, but develops on its own [27].

A multicenter, randomized, blind, controlled trial (2017) analyzed the short-term results of using an auto-linked polysaccharide (ACL) gel - a gel with hyaluronic acid. The use of ACL-hyaluronic acid gel showed a significant reduction in the frequency of intra-abdominal adhesions (13% versus 30.6% in the control group).

In a study by E. Aysan et al. (2020) prevention of postoperative adhesions was carried out using glycerol [6]. Previously, S. Mortier et al. (2005) reported that glycerol increases the efficiency of peritoneal dialysis and provides a protective effect on the peritoneal surface [28].

Glycerin is a viscous liquid alcohol with a molecular weight of 92.09 daltons [6]. It is soluble in water and alcohols, but not in liquid hydrocarbons. Glycerin is one of the most abundant molecules in living organisms and is also a central component of lipids. Adipose tissue is composed of one glycerol molecule combined with three fatty acid molecules.

In their early publications, E. Aysan et al. noted that 1% glycerol solution used in the process of mechanical separation of the healing surfaces of the peritoneum from the surrounding tissues is effective for the prevention of adhesions [6].

Aysan E, et al. (2020) increased the viscosity (3%) of glycerin in order to extend the absorption time and reveal a longer mechanical separation effect [6]. The authors studied the effect of a new composition of a solution of 3% glycerin and 3% sodium pentaborate on the prevention of adhesions, creating a synergistic effect; as a result, the frequency of postoperative adhesions was statistically reduced. According to the macromolecular structure, when injected into tissues or spaces in the body, absorption of glycerol through capillaries is difficult. Thus, glycerol remains in the injection site for a long period of time [29]. Consistent with the anti-inflammatory activity of sodium pentaborate in accelerating wound healing, there was less inflammation and fewer adhesive molecules were obtained with faster wound healing. Meanwhile, 3% glycerin provides effective mechanical separation around the wound healing environment. This synergistic activity revealed less PPA formation.

The positive effect of various boron compounds on the wound healing process has been demonstrated earlier [20]. In in-vitro and in-vivo studies, sodium pentaborate has been shown to have anti-inflammatory effects through cell proliferation and migration, and growth factor expression pathways, accelerate healing in various wound models [12].

Liquids such as crystalloids, dextran, hyaluronic acid, and icodextrin have been used to prevent adhesion. They separate damaged surfaces using "hydroflating", but their effectiveness is controversial. Crystalloids such as saline and Ringer's lactate are used in large quantities, but are rapidly absorbed. The most commonly used hypertonic solution was 32% dextran-70, but it was abandoned due to serious complications [Watson 2000]. Other liquid barriers that have the advantage of a longer residence time in the abdominal cavity such as hyaluronic acid (Sepracoat®, Genzyme Corporation, Cambridge, MA, USA), cross-linked hyaluronic acid (Intergel® Hyalobarrier gel; Baxter, Pisa), Italy) and Icodextrin (Adept®, Baxter Healthcare Corporation, Deerfield, Illinois, USA) has shown promising results in experimental and clinical studies. Brown et al. (2007) demonstrated that Adept is a safe and effective means of reducing adhesion in laparoscopy [11].

There are non-absorbable and bio-absorbent films, gels, or hard anti-adhesion membranes. The most commonly used mechanical barriers are oxidized regenerated cellulose (Interceed®; Johnson & Johnson Medical, Arlington, TX, USA), expanded polytetrafluoroethylene (Preclude Peritoneal Membrane®; WL Gore and Associates Inc., Flagstaff, Arizona, USA), hyaluronic acid- carboxymethyl cellulose (Seprafilm®; Genzyme Biosurgery, Cambridge, MA, United States) and polyethylene glycol (SprayGel®; Confluent Surgical Inc., Waltham, MA, United States).

The most widely studied bioabsorbable films are Seprafilm and Interceed. Seprafilm is absorbed within 7 days and excreted from the body within 28 days. Prospective randomized controlled trials have shown that Seprafilm is effective in reducing the incidence and severity of postoperative adhesions. However, Seprafilm can cause significant disruption of anastomoses and should not be used in cases of anastomosis [15, 24]. Other experimental studies have shown that covering lesions of the parietal peritoneum with microsurgical autologous peritoneal grafts can completely prevent the formation of severe peritoneal adhesion. However, the advantage of the synthetic barrier is that the material does not need to be obtained surgically and can be cut to dimensions outside the abdominal cavity and then applied without sutures [34].

Chemical agents such as non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, calcium channel blockers, histamine antagonists, antibiotics, fibrinolytic agents, anticoagulants, antioxidants, hormones, vitamins, colchicines, and selective immunosuppressants, prevent persistent fibroblastin formation [3] ...

NSAIDs reduce peritoneal adhesion in some animal models by inhibiting the synthesis of prostaglandin and thromboxane. They reduce vascular permeability, plasmin inhibitors, platelet aggregation and coagulation, and improve macrophage function.

In known studies, postoperative administration of anti-inflammatory drugs at the site of injury reduced the formation of postoperative adhesions in two animal models. An experimental rat model was used to investigate the efficacy of nimesulide, a selective cyclooxygenase-2 inhibitor, in preventing adhesion formation. Preoperative intramuscular or postoperative intraperitoneal injection of nimesulide into the injury site reduced the formation of postoperative adhesion [29, 33]. Typically, some anti-inflammatory drugs may be effective in preventing adhesions, but there is no clinically relevant evidence from any published study to recommend their use in humans for this purpose, and some side effects remain to be seen.

Corticosteroid therapy reduces vascular permeability and release of cytokines and chemotactic factors, and decreases peritoneal adhesion formation in some animal models. However, corticosteroids have side effects such as immunosuppression and delayed wound healing.

Kirdak et al. (2008) investigated the effectiveness of different doses of methylprednisolone in the prevention of experimentally induced peritoneal adhesions in rats. They found that there was no difference in the effectiveness of different doses of topically administered methylprednisolone in preventing peritoneal adhesion formation, and, furthermore, steroids did not prevent the development of peritoneal adhesion [22].

The positive effect of progesterone is known in a slight decrease in adhesion, formed after a small injury to the peritoneum. In addition, it was shown that neither estrogen nor gonadotropin-releasing hormone prevented adhesion formation [30].

The use of anticoagulants to prevent abdominal adhesions has been enthusiastically described in the scientific literature. Several studies are known using heparin or dicumarol, which prevent adhesion by increasing fibrinolysis and serinesterase activity [31, 33, 35]. However, their effectiveness in reducing adhesion formation, whether administered alone or in combination with an additional agent, has not been demonstrated in clinical trials.

M. Kement et al. (2011) evaluated low molecular weight heparin at a dose of 66 IU / kg every 12 hours for five days in an experiment undergoing laparotomy of horses, and there was no positive effect on postoperative complications or survival [21]. No favorable results have been obtained in humans. The recommended dose of heparin remains controversial. One recommendation is 20-150 IU / kg every 6-12 hours for two to five days. Although no intraperitoneal studies have been performed, 30,000 IU of heparin diluted in saline is commonly used and is informally called effective.

Fibrinolytic agents, such as recombinant tPA, when applied topically, reduce adhesion in animal models. However, these fibrinolytic agents can cause hemorrhagic complications [36]. Three different drugs, tPA (Actilyse®; Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany), fondaparinux (Arixtra®; GlaxoSmithKline, France) and activated drotrecogin alpha (Xigris®; Ellie Lilly & Co., DSM Pharmaceuticals, Inc. Greenville , North Carolina, USA), which affect the coagulation process at different stages, were studied for their effectiveness in preventing the formation of intraperitoneal adhesion in rats. All three agents were effective in preventing adhesions when compared with the control group. However, activated Drotrecogin-alpha appeared to be most effective except where clinical applicability was considered, in which case fondaparinux appeared to have the greatest benefit. However, further studies have shown that all of these approaches can have only limited success, prevent the lack of safety, efficacy and many adverse effects without eliminating the problem of postoperative formation of peritoneal adhesion [30].

Vitamin E is the most studied vitamin in adhesion prevention. In vitro studies have shown that vitamin E has antioxidant, anti-inflammatory, anticoagulant and anti-fibroblastic effects and reduces collagen production. It has been found to be effective in reducing the formation of adhesion by some authors [36]. Research has shown that intraperitoneal vitamin E is as effective as the carboxymethylcellulose membrane in preventing postoperative adhesions. In contrast, the same effect was not achieved after intramuscular administration. A significant difference was found between intraperitoneal and intramuscular administration of vitamin E [36].

Today, prophylactic agents that have a certain value are viscous solutions of high molecular weight polymers, such as solutions of 1% carboxymethyl cellulose (CMC), hyaluronate and CMC bioabsorbable membranes, heparin and peritoneal lavage [19].

Viscous CMC solutions have lubricating properties, reduce trauma during processing and serve as barriers to serous surfaces. CMC demonstrates variable efficiency in rats and rabbits [19]. Despite low efficacy, intraperitoneal use of 1% CMC does not appear to affect anastomosis or surgical incision healing and doubles survival [29]. The use of a CMC solution is recommended at the beginning of the operation and whenever it is necessary to lubricate the serous surfaces, reducing tissue damage from surgical trauma [29].Oxidative stress plays an important role in the mechanism of adhesion formation, mainly due to suppression of the fibrinolytic activity of mesothelial cells. Antioxidants used intraperitoneally reduce oxidative stress and increase fibrinolytic activity. N-acetyl-cysteine (NAC) is an antioxidant that acts on the synthesis of intracellular glutathione and is believed to inhibit adhesion through active cellular mechanisms of inflammation and angiogenesis. Seeking an evaluation of clinical use, S. MacKinnon et al. [25] used fucoidan in 33 colic underwent laparotomy. Fucoidan (PERIDAN concentrate) (50 ml) was mixed in 5 L of Ringer's lactate solution (LRS) or plasmolyte solution and 500 ml LRS or 1 L of plasmolyte. The solution was mixed and administered until the abdominal cavity was closed.In recent studies, a new hydrogel, poly-ε-caprolactone-poly-ethylene glycol (PCEC), has demonstrated the potential to prevent postoperative adhesions in rats [17]. PCEC is thermosensitive and at body temperature the solution containing the micelles turns into a hydrogel. PCEC is biodegradable and has low toxicity in vitro and in vivo [17].Much more interest has been directed to the use of drugs such as angiotensin II receptor blockers (ARA-II) and HMG-CoA reductase inhibitors (statins) [14]. ARA-II decreases the levels of TGF-β, and atorvastatin increases the profibrinolytic environment in the peritoneum, which leads to inhibition of adhesions.P. Dinarvand et al. (2013) compared the use of losartan (1.5 and 10 mg / kg), atorvastatin (1.20 and 30 mg / kg), losartan (10 mg / kg) and atorvastatin (20 mg / kg) and sodium hyaluronate / carboxymethylcellulose (HA / CMC) intraperitoneally to 90 male mice. After 7 days, the degree of adhesions was assessed, and the simultaneous intraperitoneal administration of losartan and atorvastatin resulted in a much greater reduction in adhesions compared to that in the HA / CMC group [14].

The results of a study by Z. Song et al. (2019) on the use of Xanthan gum XG polymer anti-adhesion coating with different concentrations (from 0.5% to 2%) and molecular weight (Mw) 2.5 × 106 Da - 6.9 × 106 Da showed that XG has an anti-adhesive effect in the abdominal rat cavities. The 1% high Mw XG gel (6.9 x 106 Da) was more effective in preventing adhesions compared to the commercially available gel (1.2% sodium hyaluronate). Histological and cytotoxic evaluation demonstrated that the XG gel showed no side effects during wound healing and had no in vitro cytotoxicity for L929 cells [30].

L.X. Lin et al. (2017) synthesized a gelatin hydrogel - cross-linking carbodiimide-modified chitosan hydrogel (cd-CS-gelatin). The results of an experimental study showed that the hydrogel solidified within 3 minutes after mixing the reagents. Caecum-abdominal adhesion was observed in all rats without anti-adhesion treatment. The use of cd-CS-gelatin significantly reduced the adhesion level from 100% to 50%, compared to liquid chitosan (only up to 88%). The decrease in adhesion tensile strength also showed that cd-CS gelatin was more effective than chitosan fluid in reducing postoperative intra-abdominal adhesion formation [23].

Summarizing the conducted literature review, the following conclusions can be drawn:Postoperative adhesion formation is the most common complication of abdominal and thoracic surgery. The adhesion process as a complication of the effect on the mesothelium is most fully studied, both clinically and experimentally, in relation to the abdominal cavity. Relatively recently, adhesive complications have become the subject of study of the consequences of injuries and surgical interventions on the organs of the chest. It should be taken into account that although the processes of adhesion have different clinical significance in the chest and abdominal cavities, the experience of studying the causes of adhesion in the abdominal cavity can serve as the foundation for further research on pleural adhesions. Fibrinolysis is a key factor in the pathogenesis of adhesion formation and its prevention. There have been several studies on this issue.

Their results are promising, but most of them are contradictory and have been carried out in experimental models. Despite the long-term existence of the problem, issues related to the prevention of adhesions and the treatment of adhesive disease are among the still unsolved problems of thoracoabdominal surgery. In the current state of scientific knowledge, preclinical or clinical studies are still needed to evaluate the effectiveness of several proposed strategies for the prevention of postoperative adhesions.The literature actively discusses the development of a universal scheme for the classification of adhesions, as well as a predictive assessment system for identifying patients with a high risk of postoperative adhesions, which is necessary to determine the indications for the use of anti-adhesive coatings. In the future, anti-adhesion agents and anti-adhesion measures will become increasingly important.Thus, a review of published studies devoted to the problem of abdominal and pleural adhesions shows the need for further experimental and clinical studies to find and develop new preventive measures, anti-adhesion coatings and a comparative analysis of their effectiveness.

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