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Application of Anti-Adhesive Barriers in Abdominal Cavity (Mini-Review of Clinical and Experimental Observations)

Husakouskaya EV*, Shigatov GO and Olizarovich MYu

Grodno State Medical University, Department of Pathological Physiology named after DA Maslakov, Republic of Belarus

ABSTRACT

Objective of the study: To study the literature sources about application of anti-adhesive barriers in abdominal cavity in clinical practice and in experiment.

Materials and Methods: Search, study and analysis of literature data.

Results and Conclusion: Numerous data available in the literature on the use of anti-adhesive barriers in abdominal surgery indicate the need to select the most optimal of them, as well as the importance of developing new combined multilayer hydrogels containing effective medicines with a prolonged release of active drug components. The use of such composite materials in clinical practice can improve the quality of treatment of urgent abdominal pathology.

KEYWORDS: Abdominal cavity; Anti-adhesive barriers; Abdominal surgery

INTRODUCTION

Intra-abdominal application of anti-adhesion barriers is most commonly used to prevent adhesion formation after surgery. However, not only the adhesion prevention is of interest, but also the suppression of an acute inflammatory process with the acceleration of peritoneal mesothelium regeneration using barrier methods. In turn, an acute inflammatory process in the abdominal cavity, peritonitis, is one of the most frequent and life-threatening complications of acute abdominal pathology with high lethality [1,2]. One of the reasons for this is the late medical aid appealability and admission of patients [3]. However, an important role in lethality reduction and the risk of complications in acute abdominal surgical infection belongs to timely and adequate treatment, including a set of measures: surgery, antibacterial treatment, detoxification, immunomodulatory, anti-inflammatory therapy and other methods [4]. In its turn, high lethality indicates the need to search for new methods of treatment. Thus, the topical application of anti-adhesive barriers in abdominal cavity is of interest due to their ability to separate peritoneal sheets and facilitate their sliding preventing additional damage to them [5]. It seems appropriate to use these barriers to disconnect damaged areas of the peritoneum and diminish inflammatory process in abdominal cavity by means of their combination with effective medicines. In this regard, the objective of this study was to analyze literature sources about application of anti-adhesive barriers in abdominal cavity in clinical practice and in experiment, focusing on the use of combined hydrogels containing effective cure components in adhesive commissures and peritoneum inflammation.

MATERIALS AND METHODS

Search, study, and analysis of data from literature sources about application of anti-adhesive barriers in abdominal cavity in clinical practice and in experiment.

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Address for correspondence: Husakouskaya EV, Grodno State Medical University, Department of Pathological Physiology named after DA Maslakov, Republic of Belarus

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RESULTS

Peritonitis occurs in 15-20% of patients admitted in surgical departments, and it's one of the most dangerous complications of urgent abdominal pathology due to high lethality, reaching 20-53% [1,6]. In most cases, peritonitis complicates the course of acute appendicitis, cholecystitis, pancreatitis, perforated gastric and duodenal ulcers, strangulated hernia, and injuries to the abdominal organs [7]. In the treatment of peritonitis, a surgical method is mandatory, that's carried out urgently to minimize the risk of complications and death. In this case, during surgery exudate and the source of peritonitis are removed from the abdominal cavity, then the abdominal cavity is laved with a sterile antiseptic solution and drained [1,4]. At the same time, the patient's treatment includes nonoperative measures, including the use of antibiotics, analgesics, anti-inflammatory and immunomodulatory drugs, and others.

An important approach in the treatment of acute abdominal surgical infection is the separation of injured areas by means of «barrier» to disturb close contact and gluing of the damaged peritoneum sheets that improve the sliding of them and prevent development of ileus and abdominal pain [5,8,9]. Therefore, it is in the treatment of adhesive commissures of the abdominal organs that gel compositions are most widely used [10, 11]. In addition, the topical administration of medicines that possesses microbicidal, anti-inflammatory, immunomodulatory and antioxidant activity as part of the «barrier» can contribute to the soon relief of the inflammatory process. Intraoperative administration of medicines is aimed at solving these problems, for example, intraperitoneal administration of glucocorticoids which impact on all phases of inflammation [12,13, 14,15], or N-acetyl-l-cysteine, upregulating peritoneal fibrinolytic activity and antioxidant defenses without affecting normal healing of damaged tissues [16]. However, the single use of them and the application often in peritoneal commissures that has already developed reduces the effectiveness of the therapy. In addition, the intraperitoneal administration of the cures in the form of solutions limits the time of their expose inside the abdominal cavity. Postoperative prevention of adhesion formation is also based on physiotherapeutic approach (for example, the use of ultrahigh frequency therapy), which requires a significant amount of time to fulfill a set of procedures and is not effective enough [17].

In turn, the application of gels into peritoneal cavity should be devoid of the listed disadvantages, since they have to correspond to certain requirements: to be biodegradable, reliable, non-immunogenic, possesses significant rate and facility of formation (without fixation to the peritoneum with suture material), preservation of barrier properties in the presence of blood and peritoneal exudate, stay at the site of application for at least 5-7 days after surgery, that's necessary to restore the peritoneal mesothelium [18,19]. The technical advantage of these methods is the simplicity of uniform distribution on the peritoneum, including use through the laparoscope, and the duration of exposure in the abdominal cavity and the effectiveness of the «barrier» are sufficient to prevent the adhesions formation [20].

By their structure, barriers can be liquid, gel-like and in the form of solid films or membranes [21]. The application of solid barrier materials represents the most successful clinical strategy to prevent postoperative adhesion. However, a simple physical barrier effect might be insufficient in preventing adhesion satisfactorily [22]. Hydrogels have found wide application in medical practice due to their high biocompatibility, which is directly related to their physicochemical properties and therefore serve as «barriers». Representing a transparent jelly-like mass without color and odor, the gel, when applied to horizontal and inclined surfaces (the angle of inclination changed up to 90°), doesn't spread, it doesn't contain air bubbles or graininess, indicating the homogeneity of its structure [23]. Hydrogels based on polytetrafluoroethylene, carboxymethylcellulose and hyaluronic acid are widely used as barrier methods [20,24]. But insoluble polytetrafluoroethylene films aren't absorbable and need to be fixed with sutures with their following remove. Other listed films are solvable and therefore more appropriate.

Carboxymethyl cellulose is a derivative of cellulose that is the basic component of commonly used and commercially available barriers for adhesion prevention, e. g. Interceed (USA), composed of oxidized regenerated cellulose which degrades within 2 weeks after placement. Barriers using oxidized regenerated cellulose are commonly believed to offer an inertand inactive barrier to cellular adhesions because they don't appear to alter the signaling behaviour of mesothelial cells directly [19].

Of particular interest in this aspect is hyaluronic acid, a nonsulfated glycosaminoglycan found in almost all tissues of the human body (at the highest concentrations in the skin, synovial fluid, vitreous body of the eye and cartilage tissue) in the form of sodium hyaluronate. The unique hygroscopicity, the ability to maintain a sufficient viscosity of the solution necessary to ensure the functions of the vitreous body, synovial fluid and maintain skin turgor, as well as the immunomodulatory effect, participation in wound healing, antioxidant activity, antibacterial and anti-inflammatory properties of hyaluronic acid indicate the validity of its use as an anti-adhesive agent in the treatment of infectious and inflammatory processes, and one of the advantages of compositions based on hyaluronic acid is their relatively low cost [25,26].

This is of great interest to study the effects of combine antiadhesive compositions. Discussed hyaluronic acid and carboxymethyl cellulose can be applied together as it's described in a mouse model of redo laparotomy, where authors have used Hyaluronan-Carboxymethyl cellulose, and it was found to be effective in preventing adhesions mostly when applied onto dense adhesions at the time of the redo surgery [27]. The Seprafilm (USA), one of the most studied «barriers», consist of a solid sheet of biodegradable sodium hyaluronate and carboxymethyl cellulose that physically separates tissue surfaces [28,29]. However, use of combined gel compositions is discussed. For example, thermally cross-linked gelatin film provides better handling than the conventional film from hyaluronic acid and carboxymethylcellulose, due to better physical strength and ductility without any cytotoxicity [30,31], and it's better to use two-layered gelatin sheet [9]. This was confirmed by formation of a single-cell layer of mature mesothelium layer 3 weeks after surgery in the gelatin group, demonstrating early regeneration of the peritoneum and little inflammation, when peritoneum regeneration in the Serafim and intercede groups was delayed and incomplete in the early phase.

Combination of cellulose, chitosan (linear polysaccharide that's yet to be employed in clinical use in humans) and seaweed polysaccharide (CCS composition) also was developed to significantly alleviate the formation of postoperative adhesion in rats with abdominal trauma through inhibition of fibrosis, collagen deposition, inflammation and vascular proliferation [32]. In this model for antifibrosis effect, downregulation of plasminogen activator inhibitor-1 (a key factor for the adhesion formation)

achieved by CCS composition, the activation of tissue plasminogen activator is significantly promoted resulting in generation of plasmin, that's a fibrinolytic factor capable of breaking down fibrin. For implementation of anti-inflammation effect, CCS composition suppress the phosphorylation of classic kinases (e.g., transforming growth factor-activated kinase 1, c-Jun N-terminal kinase and p38) in the mitogen-activated protein kinase inflammation signaling pathway.

In another study the use of carboxymethyl cellulose and chitosan was combined with collagen that formed the composite membrane crosslinked by Transglutaminase possessing satisfactory anti-adhesive effects with high biocompatibility and low antigenicity, which could be used as a preventive barrier for peritoneal adhesion [33].

The complications from surgery associated peritoneal adhesion and inflammation can be alleviated by combination of physical isolation and pharmaceutical treatment [34]. The research of Popov AM on the study of properties of a gel composition based on the alkaloid triptanthrine (courochitin) in connection with the proposal of its use in the acute stage of peritonitis is of interest [3]. The authors noted that this composition containing triptanthrin, chitosan and distilled water has a wide range of biological effects: anti-inflammatory and wound-healing properties, non-toxicity, and high bioavailability of triptanthrin due to its conversion into a bioavailable liquid-gel form. Being a specific inhibitor of COX-2 cyclooxygenase and 5-lipoxygenase, the expression of which rise steeply during inflammation, triptanthrine, administered at a dose of 20mg/kg, has an anti-inflammatory effect comparable to that of indomethacin and has better bioavailability and fewer side effects, compared with other anti-inflammatory drugs. In addition, long-term use of courochitin orally at a dose of 20mg/kg for 15 days doesn't have a toxic effect on experimental animals.

Keratinocyte growth factor has been proven to improve the proliferation of mesothelial cells, which may enhance fibrinolytic activity to suppress postoperative adhesions. The combined administration of keratinocyte growth factor and hyaluronic acid significantly increases the plasminogen activator levels but reduced the levels of interleukin-6, tumor necrosis factor α and transforming growth factor β1 in the peritoneal fluid and prevent postoperative adhesive commissures formation by disconnection of the injured peritoneum and promoting mesothelial cells regeneration [35].

Administration of N,O-Carboxymethyl chitosan can prevent postsurgical intestinal adhesion formation significantly decreasing the levels of leukocytes, TNF-α, IL-1β, IL-2, IL-6 and IL-8 along with significant reduce in collagen and detection of fewer inflammatory cells and fibroblasts [36]. The N,O-carboxymethyl chitosan/oxidized regenerated cellulose composite degradable gauze exhibits excellent antimicrobial functionality against *S. aureus* and *E. coli* bacteria and possesses notable hemostatic efficacy and nontoxic toward normal tissues and can restrain the adhesion of fibroblast cells [8]. The data about application of thermogels is of importance due to their physicochemical properties. The study of aqueous solutions of polymers based on polyethylene glycol/polyether showed the presence of «sol-gel» transitions with an increase in body temperature with the formation of semi-solid hydrogels on the example of an experimental model of intestinal peritoneum injury. At the same time, the effects of the polyethylene glycol/polyether thermogels composition were explained by the viscoelasticity of the matrix, the hydrophilicity of the created surface, and sufficient stability in vivo, which effectively prevented postoperative adhesion formation in experimental peritonitis [37].

Wu et al. [38] proposed the use of a thermosensitive hydrogel composite containing polymer micelles with dexamethasone, which made it possible to implement an anti-adhesive effect in combination with a controlled release of a steroidal anti-inflammatory drug. This hydrogel passed through the "sol-gel-sol" phases depending on temperature changes, while a significant regression of the adhesive process was noted, which was confirmed by the restoration of mesothelial layer integrity with microvilli on their surface after electron microscopy. Use of thermosensitive hydrogel contained poly(N-isopropylacrylamide), chitosan and hyaluronic acid also indicate barrier effect to reduce fibroblasts penetration while induce little cytotoxicity *in vitro* [39]. Thermosensitive hydrogel barrier by combining mitomycin C with modified tempo oxidized nanocellulose through EDC/NHS-chemical conjugation ensuring controlled release of mitomycin C from hydrogel throughout 14 days followed by integration with methyl cellulose did not show *in vitro* fibroblast cells toxicity as well as ensured complete adhesion prevention efficacy, reperitonealization in rat side wall-cecal abrasion model [34]. Naproxen nanoparticles loaded with chitosan hydrogel were used to prevent postoperative adhesions. Prepared hydrogel was thermosensitive and suitable for injection and on day 7 post surgery, the wounds were completely covered by a new epithelial layer, whereas wounds in the negative control group were glued together. The synthesized hydrogel had fewer toxic and side effects on major tissues and organs, including the liver, spleen, heart, lung, and kidney. Drug delivery system based on Chitosan/Naproxen hydrogel has the potential to prevent postoperative abdominal adhesions, relieve pain and contribute to the administration of the hydrophobic drug naproxen [10].

In addition, the use of homeopathic medicines in combination with gel-forming substances for the treatment of peritonitis has recently been discussed. In particular, experiments to study the effects of aloe vera were carried out due to presence in its composition of several biologically active compounds: mannose-6-phosphate, carboxypeptidase, glutathione peroxidase and superoxide dismutase, which possessing antibacterial, anti-inflammatory, immunostimulant and antioxidant properties [7]. According to experimental studies, aloe vera gel has an inhibitory effect on the migration of neutrophils into the abdominal cavity and reduces the total content of leukocytes, the level of IL-1β, IL-6 and PgE2 in the dialysate and peritoneal tissue, the concentration of stable NO metabolites – nitrites/nitrates and the secondary product of lipid peroxidation – malondialdehyde, compared with the values of indicators in the group of animals with peritonitis without its administration [40]. At the same time, the toxic effect of the gel form of aloe vera extract is also reported [41]. Application of the hydrogels in the form of patches was also proposed [42]. Thus, nanostructured fibrin-agarose hydrogel patch didn't result in hematoma, contributed to diminish in adhesions formation and grades of hemorrhage, inflammation and necrosis in histological analysis which identify nanostructured fibrin-agarose hydrogel patch as a promising hemostatic agent likely in a range of surgical procedures.

In efforts to have a barrier that is user friendly, spray-type barrier systems have been developed. The preventive effect of the ligustrazine nanoparticles nano spray for postoperative peritoneal adhesions was reviled in rat models when it was applied in doses 5mg/kg and 10mg/kg [43]. The adhesion score and extent was

lower than in group without its use in macroscopic assessment and significant differences of tumor necrosis factor-α and tissue plasminogen activator level in the peritoneal fluid also were demonstrated. Although the spray delivery systems facilitate easier use and can incorporate various products, none have been consistently effective in preventing post-operative adhesion formation [44,22]. Is of importance to provide the prolonged release of medicines combined with gel composition. The drug release behavior can be controlled by crosslinking lidocaine-loaded alginate/carboxymethyl cellulose/polyethylene oxide nanofiber films prepared by electrospinning [45-47]. Lidocaine is mainly used as an anesthetic and is known to have anti-adhesion effects. Sustained release of oxaliplatin was observed from hydrogels compared that from solutions, which release drugs through diffusion, following the Higuchi and Korsmeyer-Peppas models [11].

The two-layered gels application is useful option as an anti-adhesive agent for deeply injured and hemorrhagic sites [9]. Multilayered structures can be designed with an outer layer as the barrier and an inner layer to respond to relative drug release. The bilayer film composed «barrier» layer and layer to respond to the release of anti-fibrosis drug is the highly effective in postoperative adhesion prevention in terms of both physical barrier effect and anti-fibrosis effect of the poly(l-phenylalanine-co-p-dioxanone) macromolecular prodrug. Besides anti-fibrosis effect, poly(l-phenylalanine-co-p-dioxanone) also suppress excess proliferation of vascular endothelial cells and microvessel caused by long-term stimulation of implantation materials to the surrounding tissues [23]. It should be noted that the available literature data contain information about the application of anti-adhesive barriers in the abdominal cavity to prevent adhesion formation, suppress inflammation and enhance regeneration, however, further study of the effects of hydrogels containing highly active components in their composition is required in experimental and clinical observations.

CONCLUSION

Thus, the available literature data on the topical use of anti-adhesive barriers containing immunomodulatory, anti-infectious and anti-inflammatory cures in abdominal surgical pathology are numerous, indicating the need to select the most optimal of them, as well as the importance of developing new combined multilayer hydrogels containing effective medicines with a prolonged release of active drug components. Taking into account the fact that peritoneum alteration, microcirculation disorders, immunological reactivity and the development of oxidative stress play an important role in the pathogenesis of urgent abdominal surgical pathology, it seems important to use composite materials containing drugs in their composition, the action of which is aimed at correcting these mechanisms. The use of such composite materials in clinical practice can improve the quality of treatment of urgent abdominal pathology.

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