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Review Article

Therapeutic alternatives for the prevention of intra peritoneal adhesions

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ABSTRACT

Intestinal adhesions are bands of fibrous tissue created by the intimate contact of two injured surface tissues; these appear in 93% of the patient undergoing intra-abdominal or gastrointestinal surgery. The comorbidities associated with the formation of adhesions have an impact on quality care offered to patients, leading to an increase in healthcare. Goals of this study was to perform a review that includes different therapeutic alternatives in basic and clinical research to prevent the formation of postoperative abdominal peritoneal adhesions. A bibliographic search was conducted in different databases including Pub med, Medline, Cochrane, science direct, from the years 2000 to 2018 using the keywords: gastrointestinal adhesions, small bowel obstruction, prophylaxis, treatment. Only experimental and clinical articles were selected. The development of peritoneal adhesions in most of the experimental studies occurred with cecal abrasion, studying the effect of biodegradable materials, drugs and gels such as mXG Hydrogel. Nanofiber membranes, agents created with recombinant technology such as periostin antisense oligonucleotide and aerosol applications such as polysaccharide 4DryField PH, are positioned to replace in the future the actual limited mechanical barriers application commonly used in abdominal surgery such as seprafilm and interceed. There are several anti-adhesion agents in experimental phase with different mechanism of action that could be used in the short term to prevent the formation of post-surgical intestinal adhesions. The inclusion of gastrointestinal surgeons in basic research is increasing and necessary with multidisciplinary collaboration. It is expected in short term the study and development of a greater number of materials to minimize tissue trauma and decrease the formation of post-surgical adhesions.

Keywords: Gastrointestinal surgery, Intra peritoneal adhesions, Therapeutic alternatives

INTRODUCTION

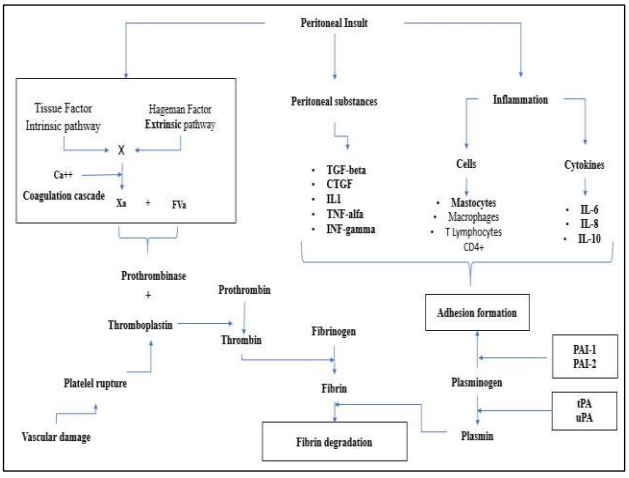
Intestinal adhesions are bands of fibrous tissue created by the intimate contact of two injured surface tissues, mostly created after a surgical procedure. In this case, the peritoneum reacts to the mechanical and inflammatory lesion, creating an adhesion with the visceral or parietal layer, creating bridges of peritoneal tissue.[1] These usually appear in 93% of the population that undergoes a surgical procedure.[2]

Co-morbidities associated are chronic abdominal pain (20% a 50%), infertility (15% to 20%), small bowel obstruction (49% to 74%) and mortality varies between 5% - 20%, attributed to the complications created by the formation of the adhesions.[3-5]

Medical costs per patient treated for complications related to intra-bdominal adhesions during the first 5 years after surgery have been calculated around s $2350 USD after an open procedure and $970 USD after laparoscopic procedure.[6]

Pathophysiology in the formation of peritoneal adhesions

The formation of intra-abdominal adhesions is related with scar formation in the healing process, inflammation, and irritation caused by foreign bodies, activation of the fibrinolytic system, cytokines, proteases and fibroblast growth factors [7] (Figure 1).



tPA: tissue plasminogen activator; uPA: activated urokinase-type plasminogen; PAI-1: Plasminogen-1 activating inhibitor; PAI-2: Plasminogen activator-2 inhibitor. After the peritoneal insult, different metabolic responses arise, such as the coagulation cascade, which purpose is to repair the damage by depositing fibrin. If this fibrin is not degraded due to, an overexpression of PAI-1 and PAI-2 or due to a deficit of tPA and uPA, the fibrin will go on to form scarred bridges of organized tissue difficult to eliminate. In addition, peritoneal damage increases the presence of proinflammatory cytokines in the area of injury and next to the subsequent inflammation the formation of adhesions is stimulated.

Figure 1: Adhesions formation.

The role of cytokines is essential in the formation of adhesions, such as transforming growth factor beta (TGF-B) and interleukin 1, which decreases the fibrinolytic capacity of the peritoneum.[8] Fibrinolysis allows mesothelial cells to proliferate and peritoneal defect is restored within 4 to 5 days, preventing permanent fixation of adjacent surfaces.[9] If this does not occur within 5 to 7 days of the peritoneal injury, or if the local fibrinolytic activity is reduced, the fibrin matrix persists. This causes the temporary fibrin matrix to gradually become more organized as the collagen-secreting fibroblasts and other repair cells infiltrate the matrix. The organization over time of the fibrin bands and their transformation into mature fibrous adhesions is what allows them to persist.[10]

METHODS

A bibliographic search was conducted in different databases including Pub med, Medline, Cochrane, Science Direct, from the years 2000 to 2018 using the keywords: gastrointestinal adhesions, small bowel obstruction, prophylaxis, treatment. Only experimental and clinical articles were selected.

RESULTS

Hydrogels have been used as anti-adhesion agents which are polymers with hydrophilic characteristic that allow them to increase in size while maintaining a physicochemical equilibrium in their application site until they adhere and separate the injured areas. In addition to its properties and biocompatibility, its practical application makes them interesting options to develop.[11-15] In 2017 Zhang E et al, used a biodegradable and thermosensitive gel of modified galactose and xyloglucan (mXG) which was evaluated as a physical barrier device for the prevention of post-operative adhesions. For the group with hydrogel (n = 16), 1ml at 4% (w/v) of mXG solution was applied to the injured areas and the gelation of this occurred in situ in 3 minutes. For the mXG hydrogel group, most of the rats did not suffer adhesions and the damaged caecum and the injured abdominal wall were partially recovered ($P<0.001$, Fisher's exact test) showing a significant difference compared to the control group ($p<0.001$, test U of Mann-Whitney). It was concluded that the mXG hydrogel, besides being effective in the prevention of adhesions, is useful since it does not require any chemical reaction to gel, it is completely degraded at 14 days and is used at 4%, compared to other gels.[11] On the other hand, in 2015, Poehnert D, et al, used the 4DryField gel in his experimental study.[13]

In the experimental group, 300 mg of 4DryField PH gel (5grams of 4DryField in 20 ml of 0.9% sodium chloride solution) were applied to the injured areas. After 7 days the animals were sacrificed, and a second laparotomy was performed to evaluate the results. The results of adhesion formation were submitted to the Lauder scoring systems.

Only 2 of the 9 animals in the experimental group treated with 4DryField PH had detectable adhesions with lauder 1 and 3 scores. The remaining 7 animals treated with 4DryField PH were free of adhesions, resulting in an overall mean Lauder score of 0,4.[13]

Electrospinning is a technique widely used in tissue engineering, to manufacture membranes or scaffolds with nanometric fibers for biomedical application. Currently biocompatible membranes are being developed using these techniques.[16-18] These membranes are more flexible and easier to manipulate in addition they can adhere to the wound without the need for suturing. Dr. Li and his team in 2017 manufactured a membrane using electrospinning of polylactic acid-co-glycolic acid (PLGA) and poly ethylene glycol (PEG).[19,20] Among all the PEG/PLGA membranes, the membranes used in the P1 group showed the best anti-adhesion efficiency.

In 2017 Torii H et al, used sheets of two sheets of gelatin, extracted from porcine skin which were reticulated with ultraviolet light for 2minutes and were frozen for 30 minutes at-80 degrees centigrade afterwards, allowed to thaw for 24hours until the gelatin solution became sponge above the gelatin sheet.[18] As a result, a two-layer gelatin sheet composed of gelatin (10µm thickness) and a sponge layer (1mm thickness) is the result. The objective of the study was to evaluate the prevention of post-operative adhesions of the two-sheet gelatin sheet and to compare the results with those obtained with seprafilm and interceed, which are currently marketed. The score of the group treated with the gelatin sheet was significantly lower ($p<0.05$) than those of the untreated group. The groups treated with seprafilm and interceed showed no significant difference compared to the control group.

The antifibrotic activity of different agents has been evaluated, in 2017, Takai S et al, evaluated the anti-fibrotic effect of the periostine antisense oligonucleotide (PAO) in rats.[21-25] periostin is secreted by fibroblasts during bone remodeling and in inflammatory processes to increase collagen deposition and activate the formation of TGF-beta which, induces the expression of periostin. This cycle can cause an excessive production of fibrinogen. The adhesion score presented in the groups treated with PAO was significantly lower than those presented in the groups with saline and NSO at 14 days after surgery ($p<0.05$). The levels of periostin, TGF-b and collagen I were also significantly attenuated by the treatment with PAO compared with the saline solution and NSO ($p<0.05$). These results showed that the level of periostin increased in the injured cecum and PAO prevented the formation of adhesions together with the attenuation of the level of periostin.

Also, in 2017 Ozbilgin K et al, and his team investigated the immunoregulatory activity of the anti-fibrotic agent pirfenidone (PFD) and evaluated its effect on the function of T-helper type 1 (Th1), Th2 and regulatory T cells (Treg). Th2 cells are responsible for indirectly activating the production of TGF-beta.[22] In this experiment, the agent was given intra peritoneal and orally. The adhesions were minimal in both groups to which PFD was administered, orally and by intra peritoneal administration ($p<0.05$). In addition, it was observed that Th2 cells were the ones that decreased the most compared to the control group.

The role of the inflammatory process secondary to endothelial damage, through cellular chemotaxis and cytokine production in the formation of abdominal adhesions is known. For this reason, anti-inflammatory agents have been experimented to attenuate this response. Bianchi E et al, conducted a study in 2016, in which they injected intraperitoneally ghrelin, a hormone synthesized mainly by the stomach that was defined as the natural ligand of the secretagogues receptor growth hormone (GHS-R).[26-28] Ghrelin has been shown to have an anti-inflammatory and anti-fibrotic effect in murine models with induced pulmonary fibrosis. A reduction of fibrosis and inflammatory cells was detected in the treated group with ghrelin in relation to the group treated with saline. It was concluded that ghrelin significantly reduced adhesion formation compared to the control group ($p<0.001$).

Breviscapine is the active component of the flavonoids extracted from Erigeron breviscapus, a common plant in Asia, has demonstrated the ability to attenuate the inflammatory response. Zhang H et al, in 2015 conducted an experiment using breviscapin versus dexamethasone. On day 11 the rats were sacrificed.[28]

The levels of interleukin (IL) 18, IL-6, tumor necrosis factor (TNF-alpha) in blood serum and transforming growth factor beta (TGF-beta), tissue plasminogen activator (tPA) were determined by immunoassay and of plasminogen activator inhibitor 1 (PAI-1) in the peritoneal fluid, finding that all of them were decreased in the treated group except for the level of PAI-1, concluding that breviscapin has important anti-inflammatory effects.

Table 1: Incidence of adhesions in adults after different types of abdominal surgery.

Surgical intervention	Year	Percentage of adhesions
Open cholecystectomy	2001	100
Laparoscopic cholecystectomy	2001	55
Upper abdominal surgery	2004	70.7
Lower abdominal surgery	2005	3.8
Gynecological surgery	2000	9
Open appendectomy	2012	10.7
Laparoscopic appendectomy	2012	0.2

Table 2: Anti adhesion agents.

Agent	Year	Authors	Study type	Application	Procedure	Decreased adhesion formation
Hydrogels						
mXG hydrogel	2017	Zhang E et al[11]	Experimental with rats	Instillation in damaged area	Cecal abrasion and abdominal wall	Yes (p<0.001)
NOCC-AHA hydrogel	2016	Song L et al[12]	Experimental with rats	Instillation in damaged area	Cecal abrasion	Yes (p<0.01)
Gel 4DryField® PH	2015	Poehnert D et al[13]	Experimental with rats	Instillation in damaged area	Peritoneal and muscular abrasion	Yes (p <0.0001)
Auto-cross linked gel hyaluronic acid	2015	Xiao S et al[14]	Clinical study 120 patients	Gel application in cavity with Foley catheter	After adhesiolysis	Yes (p=0.0009)
Polyethylene glycol (PECE Hydrogel)	2012	Yang B et al[15]	Experimental with rats	Instillation in damaged area	Cecal abrasion and peritoneal	Yes (p<0.001)
Laminar membranas						
Nanofiber membrane PLGA/PEG	2017	Li J et al[16]	Experimental with rats	Instillation in damaged area	Cecal abrasion	Yes (p<0.05)
Autolog peritoneal impant	2017	Bresson L et al[17]	Experimental with rats	Cellular barrier	Peritoneal cauterization	No (p=0.18)
Gel lamina	2017	Torii H et al[18]	Experimental with rats	Instillation in damaged area	Uterine cauterization	Yes (p<0.05)
Oxidase cellulose (Interceed) with IUD	2017	Cai H et al [19]	Clinical study 76 patient	Mechanical barrier.	Barrier application after adhesiolysis	Yes (p<0.001)
Hyaluronic acid and carboxymethylcellulose (Seprafilm)	1996	Diamond MP et al[20]	Multicenter study with 127 patients.	Mechanical barrier	Uterine myyomectomy	Yes (P <0.0001)
Antifibrotic						
Periostine antisense Oligonucleotide (PAO)	2017	Takai S, et al[21]	Experimental with rats	Intraperitoneal	Cecal abrasion	Yes (p<0.05)
Pirfenidone	2017	Ozbilgin K, et al[22]	Experimental with rats	Intraperitoneal and Oral	Abdominal wall	Yes (p<0.05)
Simvastatine	2016	Javaherzadeh M et al[23]	Experimental with rats	Intraperitoneal	Peritoneal abrasion	Yes (p<0.001).
Neurokinin receptor1 antagonist (NK-R1A)	2010	Gónzalez-Torres C et al[24]	Experimental with rats	Peritoneal irrigation	Serosa abrasion in cecum, small intestine and parietal peritoneum	Yes (P=0.001)
Mytomicin-C (MM-C)	2001	Cubukçu A et al[25]	Experimental with rats	Intraperitoneal inyection	Cecal abrasion	Yes (P=0.001).
Anti inflammatory-agents						
NaHS (donor of hydrogen sulfide)	2017	Xia Y et al[26]	Experimental with rats	Subcutaneous	Parietal peritoneum	Yes (p<0.01)
Ghrelin	2016	Bianchi E et al[27]	Experimental with rats	Intraperitoneal	Cecal abrasion	Yes (p<0.001)
Breviscapine	2015	Zhang H et al [28]	Experimental with rats	Intraperitoneal	Cecal abrasion	Yes (p<0.05)
Others						
Lubricine	2017	Oh J et al[29]	Experimental with rats	Intraperitoneal	Cecal abrasion and enterotomy	Yes (p=0.001)
Cetuximab	2016	Kurt A et al[30]	Experimental with rats	Intraperitoneal	Transverse colectomy and anastomosis	Yes (p<0.001)
Oxychloride solution with ClO_2	2014	Zavala-Rodriguez JM et al[31]	Experimental with rats	Intraperitoneal	Peritoneal abrasion.	Yes (p<0.05)
Icodextrina 4% (Adept)	2012	Catena F et al[32]	Clinical study 1 center 181 patients	Intraperitoneal	Adhesyolsis for small bowel obstruction	Yes (p<0.05)
Vitamine E	2009	Yetkin G et al[33]	Experimental with rats	Intraperitoneal	Cecal abrasion	Yes (p=0.001)
Amniotic membrane	2009	Yetkin G et al[33]	Experimental with rats	Intraperitoneal	Cecal abrasion	Yes (p=0.001)
Honey	2009	Yuzbasioglu MF et al[34]	Experimental with rats	Intraperitoneal	Cecal puncture	Yes (p<0.05)

Among the diverse alternatives to prevent the formation of post-operative adhesions.[29-34] Zavala-Rodriguez JM, et al, used chlorine dioxide (ClO_2) and demonstrated that concentrations of 40 to 110ppm significantly reduced the formation of adhesions ($p<0.05$), while solutions of oxychloride containing ClO_2 at 120 or 150ppm did not significantly reduce adhesions compared to the control group.[31]

Even in the presence of fecal peritonitis, the oxychloride solution (containing ClO_2 at 110ppm) significantly reduced adhesions ($p<0.05$). The oxychloride solutions containing ClO_2 at 40 or 70ppm did not modify the adhesion score obtained in the control group with contaminated peritoneal cavities. The results of the comparative study showed no difference between ISS, interceed, guardix and seprafilm, while the oxychloride solution significantly reduced the adhesion score ($p<0.05$). It was concluded that the solution of oxychloride with ClO_2 is effective in the reduction of post-operative adhesions, with the additional advantage that it has anti-septic properties against other commercialized agents which did not significantly reduce post-operative adhesions.

DISCUSSION

The presence of symptoms attributable to the presence of adhesions in the abdominal cavity (i.e. small bowel obstruction), may lead the surgeon to re intervene (lysis of adhesions, bowel resections), the percentage of incidence varies according to the surgical procedure performed (Table 1). And this reintervention will bring surgical risks and eventually, the formation of more adhesions. This motivates the development of new materials and more important, evaluation of this agents in the clinical arena, since most of these agents are only experimental. Currently there is only one chemical approved by the food and drug administration (FDA) to prevent the formation of adhesions: icodextrin 4% (adept), and two mechanical barriers that are similarly approved by the FDA: oxidized regenerated cellulose (Interceed, Ethicon, Somerville, NJ) and carboxymethylcellulose hyaluronate (Seprafilm, Sanofi, Paris, France).

Polyethylene glycol (PEG) (Sprayshield, Integra LifeSciences, Plainsboro, NJ), formerly known as Spraygel and Auto-Cross-Linked gel polysaccharide (ACP) (Hyalobarrier, Nordic group, Paris, France) are also available in the European market.[10]

CONCLUSION

Authors are facing multiple new agents and an increase number of researches focused on the creation of different anti-adhesion agents, many of them in the experimental phase. The formation of peritoneal adhesions is not fully understood, since there are multiple theories and multiple agents with different results, suggesting also, that this process may also be different in every patient, demanding newer techniques to individualize the treatments, since some people are more prone to develop more adhesions than others. The creation of an anti-adherent material, which would decrease or abolish the creation of adhesions in the clinical, will revolutionize the treatment for small bowel obstruction and various gastrointestinal pathologies.

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