Adhesion prevention in reabsorbable polyethylene glycol hydrogel (Coseal®) coated polypropylene mesh in rabbits[1]

Reynaldo Martins e Quinino[I], Irami Araújo-Filho[II], Francisco Piganataro Lima[III], André Luís Costa Barbosa[IV], Tatiana de Carvalho Maia[V], Alberto Goldenberg[VI]

[I]Fellow Master degree, Postgraduate Program in Interdisciplinary Surgical Science. Assistant Professor, Integrated Medicine Department, Rio Grande do Norte Federal University (UFRN), Brazil. Conception and design of the study, surgical procedures, interpretation of data, manuscript writing, critical revision.
[II]PhD, Associate Professor, Department of Surgery, UFRN. Rio Grande do Norte, Brazil. Interpretation of data.
[III]PhD, Associate Professor, Department of Pathology, UFRN, Rio Grande do Norte, Brazil. Interpretation of data.
[IV]Attending Physician, Onofre Lopes University Hospital, UFRN. Rio Grande do Norte, Brazil. Manuscript writing.
[V]Attending Physician, Onofre Lopes University Hospital, UFRN, Rio Grande do Norte, Brazil. Technical procedures.
[VI]PhD, Associate Professor, Surgical Gastroenterology Division, Department of Surgery, Sao Paulo Federal University (UNIFESP), Brazil. Interpretation of data, critical revision.

ABSTRACT

PURPOSE: To evaluate of postoperative adhesion prevention and inflammatory response to polypropylene mesh, coated with reabsorbable hydrogel of polyethylene glycol (Coseal®) in contact with small bowel in an experimental model in rabbits.

METHODS: Twenty female rabbits underwent laparotomy to implant two polypropylene meshes, 2x1cm, in the right and left flanks. The right mesh was protected with Coseal® spray (Group 1) and the left mesh received no treatment after implantation (Group 2). Thirty days after implantation, the rabbits underwent laparoscopy for adhesion analysis; the prosthesis were removed en bloc with the adjacent tissue for microscopic analysis of inflammation. Statistical analysis used the Mann-Whitney test.

RESULTS: There was adhesion formation in five meshes (36%) from Group 1 and in 14 meshes (100%) from Group 2, with statistical significance ($p<0.01$). There were no differences in the inflammatory response, fibrosis, foreign body reaction, presence of collagen and type of inflammatory cells between the two groups.

CONCLUSION: Polypropylene mesh coated with Coseal® showed a significantly lower rate of adhesion formation when compared with uncoated meshes, without interfering with inflammatory response.

Key words: Tissue Adhesions. Polyethylene Glycols. Polypropylenes. Rabbits.

Introduction

Surgical treatment of abdominal wall hernias are amongst the most commonly performed procedures by general surgeons. In the United States there are more than a million surgeries per year, with an approximate annual cost of $ 2.5 billion. Technical aspects of abdominal hernia repair have had great advances in the last hundred years, along three lines: suturing, use of autologous grafts and prosthesis use[1].

The first descriptions of the use of polypropylene mesh are from the last century. As time passed, due to the low hernia recurrence rate, the flexibility and ease to be placed in any kind of defect, it became the most commonly used material for hernia repair[2]. However, the intraperitoneal placement of prosthetic polypropylene can lead to adhesion formation, with serious consequences such as bowel obstruction, infertility, pelvic pain and increased need of new abdominal operations. The risk of adhesion formation occurs specially in situations where the mesh needs to be placed in contact to intra-abdominal viscera[3].

Many authors evaluated different prosthetic materials and coating products for meshes in order to prevent adhesion formation, such as oxidized collagen, polytetrafluoroethylene (PTFE), absorbable barrier of hyaluronate sodium, among others. However, the results were conflicting[4].

With the purpose of developing a mesh able to maintain the polpropylene properties with a lower adhesion formation rate and appropriate tissue integration, we reviewed literature looking for agents studied in the prevention of peritoneal adhesions.

The adhesion formation process is triggered by a serosal lesion and deposition of a fibrin matrix over the traumatized tissue. Strategies to prevent this event are based on the development of substances that act toward fibrin degradation, impair the clotting process, inhibit collagen synthesis or create a barrier between the wound surfaces. The barrier method showed the best results[5].

Coseal® is a reabsorbable hydrogel formed by mixing two synthetic polymer polyethylene glycol solutions in a co-extrusion process using an activating solution. At first, it was approved as a sealant in vascular reconstructions but, since 2002, it has been used in Europe for reducing postoperative adhesions in patients undergoing cardiac surgery[6]. More recently, Mettler *et al*.[7] in a prospective, randomized, double-blind study evaluated the safety and efficacy of Coseal® in reducing adhesion formation after myomectomy surgery performed by laparotomy or laparoscopy, presenting the first clinical evidence for the use of Coseal® in reducing peritoneal adhesions.

In the absence of publications using Coseal® coated prosthesis in hernia treatment, its use as a coating product for polypropylene mesh to prevent peritoneal adhesion in an experimental model in rabbits was investigated. It was also evaluated the inflammatory response to the mesh in the surround tissue.

Methods

The research project was approved by the Research Ethics Committee of Sao Paulo Federal University, protocol number 1893/11.

Twenty New Zealand lineage albino rabbits (*Oryctolagus cuniculus*), three-month-old, female, weighing between 2000g and 2500g were used. The animals were from Training Center for Surgery and Experimentation of the Albert Einstein Israelite Institute of Education and Research. All procedures met the standard criteria, the technical standards and international right standard for animal research, as well as the standards of the Ethics Committee of the Brazilian College of Animal Experimentation. The animals were housed under conditions of constant light and temperature and received complete diet *ad libitum* through the research. The rabbits were assisted by the veterinarian in charge.

The prosthesis used was the Prolene® Mesh (Ethicon – Johnson & Johnson) which was supplied by the manufacturer in its original size of 30x30cm, and it was cut into identical sterile fragments 2x1 cm for use. As coating product, the Coseal® (Baxter Healthcare Corporation) was used, and also supplied by the manufacturer. The product kit included two syringes and an applicator. It was mixed and packaged in a sterile environment for use.

The rabbits were numbered from 1 to 20 and the weight, anesthetic medication, complications of implanted mesh and intraoperative and postoperative complications were recorded. After 12h fasting, the animals received pre-anesthetic medication: a combination of 25mg/Kg of ketamine, 5mg of xylazine and 0.05mg of atropine through deep intramuscular route. The abdomen was shaved and povidone iodine antiseptic solution was applied. The procedure was performed with aseptic technique. Maintenance anesthesia was made with an additional dose of 25mg/Kg of ketamine and, if necessary, 2mg/kg intravenous midazolam was injected through the puncture of the peripheral vein of the ear. Venous access was maintained with 0.9% saline solution and monitoring was performed with a pulse oximeter. A 5cm median laparotomy incision was made, the meshes were positioned in the right and left flanks and they were fixed to the peritoneum by two 4-0 polypropylene sutures. On the right side,

the meshes were protected by Coseal® spraying (Group 1). A Spray set device provided by the manufacturer was used to apply Coseal® at a distance of 5cm from the prosthesis, the average amount of 0.3mL was applied until a uniform layer was obtained on the mesh surface (Figure 1). After application, the time interval for complete polymerization of the product – 60s – was achieved. On the left side, the meshes received no specific treatment (Group 2). The meshes were left in contact with the small bowel. Abdominal wall was sewn with polyprolene 3-0 and skin was closed with nylon 3-0.

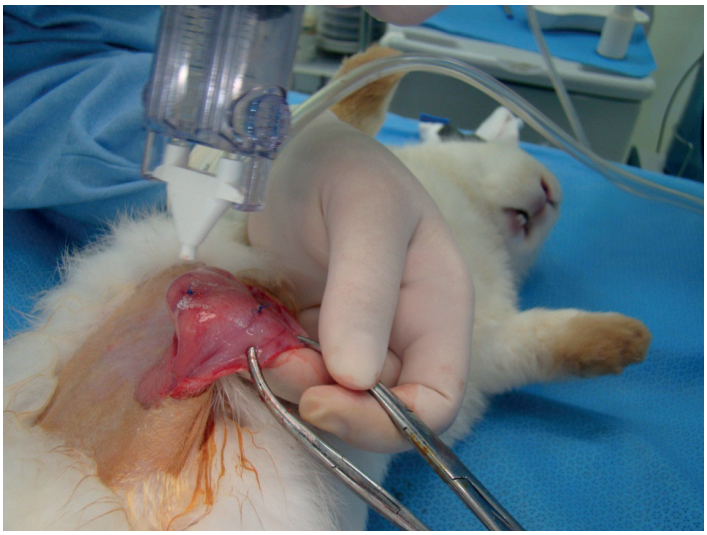

FIGURE 1 - Spraying Coseal® on polypropylene mesh.

After the end of procedure, the animals received one dose of 1.200UI intramuscular benzathine penicillin and 1mL dipyrone subcutaneously. The rabbits were sent to the vivarium, where they were observed for 30 days. The animals were assessed daily and data recorded. After the post-surgical period, the animals underwent laparoscopic approach, using the same anesthesia, antiseptic techniques used in the first surgery. The pneumoperitoneum was performed with carbon dioxide through an insuflator maintaining the maximum pressure of 8mmHg. For visualization, a 5mm optical laparoscopic device was connected to a micro camera and to a light source were used.

Access to the peritoneal cavity was obtained through two punctures: Median line, above the pubic symphysis of 5mm, where the pneumoperitoneum and the optics were placed and right hypocondrium, with the introduction of 5mm trocar for manipulation of probable adhesions with laparoscopic forceps.

The peritoneal surfaces in the middle line and in the prosthesis implantation sites were evaluated. The findings were recorded on DVD for later analysis. The prostheses were removed en bloc with the peritoneum, aponeurosis and adjacent muscles through a median laparotomy. The material was immersed in a solution of 10% formaldehyde and sent for microscopic evaluation by a pathologist. At the end of the procedure, the rabbits were euthanized by a lethal dose of intravenous anesthetic.

The fixing intraperitoneal structure found in some of the implantation sites of the prosthesis were considered adhesions. The video analysis was performed by an independent surgeon who was unaware of the meshes with protection on one side only. Adhesions were classified according to the qualitative grading scale proposed by Shimanuki[8]:

Grade 0 - No adhesions.

Grade I – Vascular adhesion easily lysed without bleeding.

Grade II - Vascular, easily lysed, bleeding at the time of lysis.

Grade III - Thick, requires intense sharp dissection.

Fragments were placed in a 10% formaldehyde solution and processed according to the routine technique of paraffin inclusion. Blocks were cut with a microtome with thickness of 4 micrometers. The sections were glued onto glass slides, stained with hematoxylin-eosin and examined under an optical microscope. The presence and intensity of inflammatory reaction, fibrosis degree, the presence of a foreign bodies and the collagen amount were evaluated by the same pathologist. The classification of the inflammatory reaction was based on a semi quantitative analogic visual scale.

For the statistical analysis, the nonparametric Mann-Whitney test was used to evaluate the different adhesion formation rates among the two groups. The significance level (α) set for all tests was 5%.

Results

There were no complications during surgery. Three rabbits died due to anesthetic complications. On the first postoperative day, three rabbits were euthanized due to eviscerations. The remaining 14 rabbits showed good clinical evolution during the observation period.

Laparoscopic evaluation

Of the 28 analyzed prostheses, five (36%) of the protected meshes and 14 (100%) of the meshes without protection presented adhesion. In Group 1, nine meshes (64%) had no adhesions, two (14%) had Grade I adhesions, three (22%) grade II adhesions and none had Grade III adhesion. In Group 2, all meshes had

adhesions (100%): one Grade I adhesion (8%), seven (50%) Grade II adhesions and six (42%) Grade III adhesions (Table 1). The difference in the rate of adhesion formation was statistically significant (p<0.001). The degree of adhesion in Groups 1 and 2 are shown in Figure 2 (Boxplot).

TABLE 1 - Frequency of adhesions in groups according to the Shimanuki scale.

			DEGREE				Total
			0	I	II	III	
GROUPS	Group 1	N	9	2	3	0	14
		%	64%	14%	22%	0%	100%
	Group 2	N	0	1	7	6	14
		%	0%	8%	50%	42%	100%
Total		N	9	3	10	6	28
		%	32%	11%	36%	21%	100%

p<0.001* (Mann-Whitney)

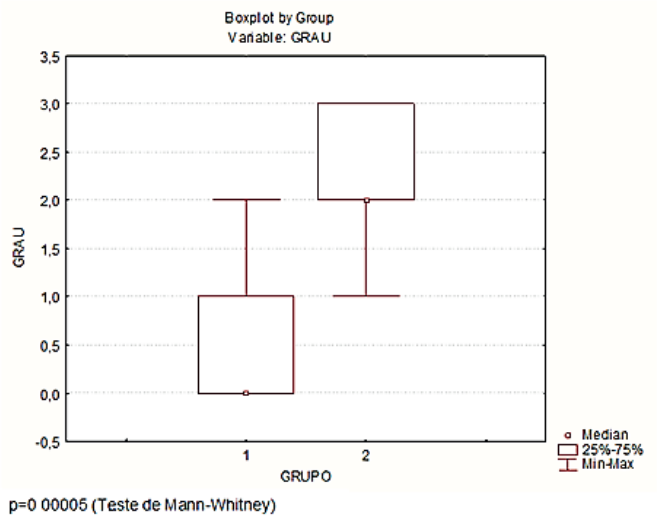

FIGURE 2 - Boxplot: adhesion degree in Groups 1 and 2.

Histological study

Inflammation was predominantly mild in both groups: 57% in Group 1 and 64% in Group 2 (Table 2). There was no statistical significance between the two groups (p = 0.782).

TABLE 2 - Inflammation intensity Groups 1 and 2.

			Inflammation				Total
			Absent	Mild	Moderate	Intense	
Groups	Group 1	N	1	8	4	1	14
		%	7%	57%	29%	7%	100%
	Group 2	N	1	9	3	1	14
		%	7%	64%	21%	7%	100%
Total		N	2	17	7	2	28
		%	7%	61%	25%	7%	100%

p=0.782 (Mann-Whitney)

Fibrosis was predominantly mild and moderate in both groups, 36% and 21% respectively in Group 1 and 14% and 71% in Group 2 (Table 3 – Figure 2). There was no statistical significance between the two groups (p = 0.747).

TABLE 3 - Fibrosis intensity in Groups 1 and 2.

			Fibrosis				Total
			Absent	Mild	Moderate	Intense	
Groups	Group 1	N	1	5	3	5	14
		%	7%	36%	21%	36%	100%
	Group 2	N	0	2	10	2	14
		%	0%	14%	71%	14%	100%
Total		N	1	7	13	7	28
		%	4%	25%	46%	25%	100%

p=0.747 (Mann-Whitney)

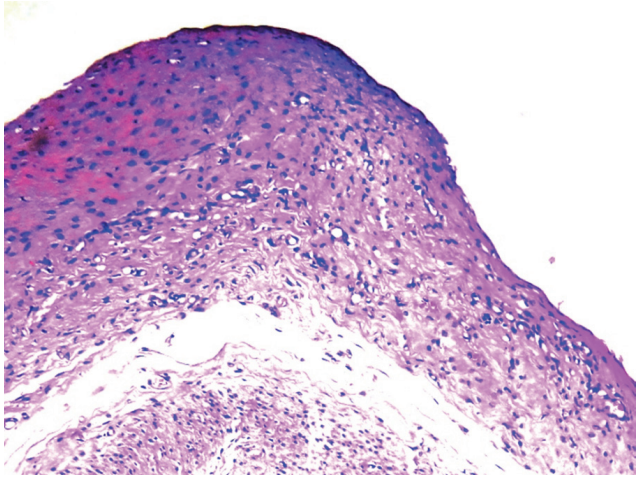

FIGURE 3 - Mild fibrosis, HE, enlarged 20 times. Animal 3 - Group 1.

The foreign body reaction was absent in most animals, 64% in Group 1 and 57% in Group 2 (Table 4). There was no statistical significance between the two groups (p = 0.782).

TABLE 4 - Foreign body reaction intensity in Groups 1 and 2.

			Foreign Body Reaction				Total
			Absent	Mild	Moderate	Intense	
Groups	Group 1	N	9	3	1	1	14
		%	64%	21%	7%	7%	100%
	Group 2	N	8	4	1	1	14
		%	57%	29%	7%	7%	100%
Total		N	17	7	2	2	28
		%	61%	25%	7%	7%	100%

p= 0.782 (Mann-Whitney)

Regarding collagen deposition, there was prevalence of mild collagen deposition in both groups, 79% in Group 1 and 64% in Group 2 (Table 5). There was no statistically significant difference between the two groups (p = 0.520).

TABLE 5 - Collagen deposition in Groups 1 and 2.

			Collagen Deposition				Total
			Absent	Mild	Moderate	Intense	
Groups	Group 1	N	1	11	2	0	14
		%	7%	79%	14%	0%	100%
	Group 2	N	1	9	3	1	14
		%	7%	64%	21%	7%	100%
Total		N	2	20	5	1	28
		%	7%	71%	18%	4%	100%

p=0.520 (Mann-Whitney)

Discussion

Peritoneal adhesions are a major clinical challenge in gastrointestinal surgery. The occurrence of this complication after major abdominal procedures has been estimated to be 63 to 97%. Adhesions result in increased need of resources and increased costs to the health care system. In 1994, 1% of all hospital admissions in the United States were associated to treatment of peritoneal adhesions, resulting in a cost of 1.33 billion dollars[9]. The main complications of peritoneal adhesions are small bowel obstructions, chronic abdominal or pelvic pain and infertility. Additionally, It prolongs the time needed to access the abdominal cavity and results the increased risk of intestinal injury in a reoperation[10].

In order to prevent the occurrence of adhesion it is essential to understand how it is formed. The serous surfaces, such as the peritoneum, are constituted of mesothelial cells that produce surfactant phospholipid compounds that have fibrinolytic activity and protect against adhesion and thrombosis, besides producing cytokines that participate in tissue repair and in the renewal of the extracellular matrix. When the peritoneal surface is damaged, the coagulation cascade leads to the formation of fibrin deposits. Polymerized fibrin monomers form a network that serves as a model for wound healing or as a bridge to the development of tissue adhesions[11]. Prevention strategies can be divided in four categories: general surgical principles, surgical technique, chemical agents and mechanical barriers[5].

Some general principles must be observed during surgery, such as avoiding unnecessary peritoneal dissection, preventing soiling of intestinal secretion and using powder-free gloves. Another important factor is the choice of the access route: the laparoscopic approach is associated with less adhesion formation; however, some authors did not mention this information[12].

Chemical agents may prevent the formation of the persisting fibrin by inhibiting the proliferation of fibroblasts. The most commonly used agents are: Anti-inflammatory non-steroids, corticosteroids, calcium channel blockers, histamine antagonists, antibiotics, fibrinolytic agents, anticoagulants, antioxidants, hormones, vitamins, colchicine and selective immunosuppressive drugs[12].

Liquid or solid mechanical barriers may prevent the formation of adhesions by keeping apart the serous surfaces damaged during a period of 5-7 days (enough time for a peritoneal reepithelialization to take place). An ideal barrier method should be biodegradable, safe, non-inflammatory, non-immunogenic, stand until the end of the remesothelization process, remain in place without suturing or stapling, maintain activity in the presence of blood and should be allowed to be quickly and easily applied. Mechanical barrier methods are often considered the most useful ones for the prevention of peritoneal adhesions. Liquids such as crystalloids, dextran, hyaluronic acid and icodextrin have been used to prevent adhesions. However, it's effect remains controversial. The most solid barriers used are the oxidized regenerated cellulose, polytetrafluoroethylene, acid carboximetilcelulose hyaluronic acid and polyethylene glycol[13].

Coseal® is a surgical sealant, activated by a solution of hydrogen chloride and carbonate sodium phosphate. It was described in 2001 as a completely synthetic material, easy to apply,

quickly drying and favorably adherent to collagen membranes, PTFE grafts and biological tissues. It's similarity with other formulations are low initial viscosity, such as fibrin sealants and cyanoacrylate preparations, requiring a suitable applicator. Several studies have assessed it's efficacy in vascular reconstructions. Subsequently, it's use as way of preventing adhesions was tested experimentally and in clinical trials[14]. In 2008, as previously mentioned, a multicenter clinical trial was published, it was a randomized, double-blind study evaluating the safety and efficacy of Coseal® in reducing postoperative adhesions[7]. Thus, the use of Coseal® as a barrier method to prevent adhesions and coating polypropylene meshes seemed promising.

Albino rabbits of New Zealand strain were used in this study because these animals are easy to use, can be obtained at a low cost, and their use has already been validated in literature and in the research field. The rabbits used in the experiment were similar in age, sex and weight, thus making a homogeneous sample.

Polypropylene mesh, the most commonly used in clinical practice, was used. It is associated to a high rate of peritoneal adhesions when placed directly in contact with the bowel, as it was observed in the present study[15].

In the present study, it was observed a significantly less adhesion formation in Group 1 when compared to Group 2. In the group with the protected mesh (Group 1), nine animals (64%) had no adhesion formation and none of meshes had Shimanuki Grade III adhesions. In Group 2, there was adhesion formation in 100% of the prostheses, and in 13 of them (98%) the adhesions were Shimanuki Grade II and III. The difference among the studied groups was statistically significant ($p<0.001$). These findings are consistent with other studies showing a high incidence of peritoneal adhesions, when non-protected polypropylene meshes are placed in contact with the viscera. This incidence can occur in 100% of the prostheses. Coseal®, like other materials used as barrier methods to avoid adhesions, was effective in the prevention of adhesion, as experimentally demonstrated in cardiac surgery and in a randomized double-blind study[7,16].

The histological analysis showed in both groups a prevalence of mild inflammatory response, corresponding to 57% in Group 1 and 64% in Group 2, with no significant difference between them ($p=0.782$). This is consistent with the healing period at the time of removal for analysis (30 days) and similar to what can be found in the literature[17].

Assessment of fibrosis degree showed the predominant presence of moderate to severe fibrosis, representing, respectively, 21% and 36% in Group 1, and 71% and 14% in Group 2, with no statistical significance ($p = 0.747$). These results indirectly demonstrate that a proper integration of the mesh to the adjacent tissues occurred, in a compatible way to an early and fast inflammatory response[18].

The foreign body reaction was absent or mild in most of the studied material, accounting for 64% and 21% in Group 1 and 57% and 29% in Group 2, respectively. There was no statistically significant difference among groups ($p = 0.782$). This fact, coupled with the fact that no residues were found in the microscopic material analysis, shows that total degradation of Coseal® occurred as expected, within 30 days. The absence of material, after four weeks, avoids the perpetuation of an exacerbated inflammation and excessive foreign body reaction, as evidenced Park *et al*.[19] in an experimental model of laparoscopic nephrectomy in pigs. The conclusion was that there was no evidence of humoral or cellular immune response to the sealant after two weeks thus proving that Coseal® has one extra advantage over other barrier methods.

Collagen deposition, assessed by optical microscopy, proved to be more often mild, corresponding to 79% in Group 1 and 64% in Group 2, with no significant difference among the groups ($p = 0.520$). Other studies also demonstrated an early deposition of total collagen, decreasing after the twenty-first day[20].

In summary, when evaluating the microscopic changes as a whole, there was no difference among groups, showing that the material used does not interfere significantly in the inflammatory reaction and in the integration of the mesh to the tissue. This makes Coseal® promising for clinical use, as a form of protection from peritoneal adhesions, particularly in those that appear in prosthesis. As an advantage, It may be mentioned the ease of application by spraying, both in conventional and laparoscopic surgery. It must also be emphasized it's almost instantly drying, which does not prolong the operative time, and the possibility of being used to complement peritoneum closure in a procedure which was not initially expected to require a protected mesh. However, additional studies are needed to confirm the effectiveness of Coseal® as a barrier method in the prevention of peritoneal adhesions of prosthesis in other experimental models and in clinical trials.

Conclusions

The absorbable polyethylene glycol hydrogel (Coseal®) coated polypropylene mesh presented significantly lower rates of adhesion formation compared with the unprotected meshes.

There were no differences related to inflammatory response, after 30 days, among the absorbable polyethylene glycol hydrogel (Coseal®) coated polypropylene mesh and the

unprotected mesh.

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Correspondence:
Reynaldo Martins e Quinino
Avenida Nilo Peçanha 301/701
59012-300 Natal – RN Brasil
Tel.: (5584)9149-2526
reynaldoquinino@yahoo.com.br

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