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Original articles

The concept of protected mesh to minimize adhesion formation in intraperitoneal abdominal wall reinforcement. Preclinical evaluation of a new composite mesh

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Summary: The repair of inguinal or incisional hernias may occasionally require the placement of an intraabdominal mesh to reinforce parietal wall defects or weaknesses. An original composite mesh, consisting of a conventional polyester mesh combined with a coated hydrophilic and absorbable membrane designed to prevent intraperitoneal adhesions was evaluated. The efficacy of the product was tested through three experiments. The first carefully examined the absorption properties of the hydrophilic film as well as the biocompatibility of the patch after subcutaneous implantation. The second experiment was designed to evaluate adhesion formation in an animal model, comparing the mesh to two other commercially available membranes and to a control. In the third experiment, the product was tested in a porcine model. This was done in order to better evaluate the performance of the mesh in a model closer to human dimensions. These three experimental procedures demonstrated the biocompatibility of the membrane, the dramatically superior performance of the patch compared to other commercially available ones and to controls, and the validity of the concept in large animals. The composite mesh made of polyester and coated hydrogel fulfils the conditions for human evaluation.

Key words: Hernia – Mesh – Adhesion – Polyester – Collagen

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It is well-known that the presence of a peritoneal defect or foreign body in the abdominal cavity creates adhesions. These in turn may result in major complications, including intestinal obstruction and migration of the foreign body into the bowel. Complications resulting from intraperitoneal adhesions account for 1% of all emergency surgical admissions and 3% of emergency abdomiinal surgery [Luijendijk 1996]. The surgical repair of hernia defects often requires the placement of a reinforcement mesh in cases of parietal wall defects. The mesh's major function is to make up for the loss of abdominal wall substance and to re-establish the interplay of the abdominal musculature. In certain circumstances, it is necessary to place the mesh in an intraperitoneal position. In

these cases, the biomaterial used to reinforce the parietal wall will be in contact with the bowel and in this context the use of a prosthetic material that results in minimal adhesion formation is ideal. Expanded polytetrafluorethylene (ePTFE) meshes have been used since 1985 in such situations by many, and with excellent result [Wool 1985]. Nevertheless, their use carries specific complications (seromas, infections), hence the necessity to continue research efforts to find a more suitable bioprosthetic material. Over the last few years, new generations of surgical prostheses, combining the strength of conventional meshes with the anti-adhesive action of the original biomaterials, have been evaluated. These composite meshes combine conventional reinforcement mesh (polyester or polypropylene) with less adhesive materials (PTFE, collagen) in order to offer a good mechanical resistance and a low adhesion rate. A polyester hernia mesh coated with a collagen-oxidized film has been developed. This mesh has been shown in previous studies to significantly restrict the tendency of the polyester portion to cause abdominal adhesions [Therin 1998]. The use of an antiadhesive protected mesh for intraperitoneal abdominal wall reinforcement required preclinical evaluation before human application. The purpose of this study was threefold: first, to evaluate the film absorption and its *in vivo* properties; second, to compare the experimental mesh to two other hernia mesh prostheses (which have also been developed to resist adhesion formation in a rat model); and third, to test the product in a large animal i.e. the pig. Using standardized models, the hernia mesh materials were evaluated and compared for incidence and strength of adhesions.

Material and methods

All tested materials were used sterile and quality-assured.

Preparation of the hydrophilic and absorbable film. A hydrophilic and absorbable film was prepared from a solution of oxidized bovine atelocollagen type I, polyethylene glycol and glycerol. The obtained film was elastic, transparent and non-sticky.

Coated **polyester mesh.** A conventional three-dimensional polyester mesh (Parietex®, Sofradim, Trévoux, France) was used for the experimental study. This mesh has been extensively used for the past decade and showed adequate properties for abdominal wall reconstruction [Benchetrit 1998]. A high porosity (97%, mean pore diameter 1.7 mm), conformability, and a moderate weight (75 g/m^2) mainly characterized this mesh. To obtain a coated mesh, the hydrophilic film was molded on the surface of the conventional three-dimensional polyester mesh (Fig. 1). The mesh was fully protected by the film on one side (which overlapped all edges of the mesh by 5 mm), while the open porosity of the mesh was maintained on the other side. The mechanical properties of the mesh (multidirectional elasticity, conformability and strength) were unchanged compared to the uncoated mesh. Samples of different size were used in rats (15 x 25 mm) and pigs (7 x 14 cm).

ePTFE membrane. A standard sterilized ePTFE patch (Goretex Dual Mesh®) was prepared in 15 x 25 mm pieces. One surface of the biomaterial was smooth for minimal tissue attachment while the other surface was slightly textured in order to allow tissue ingrowth. Compared to the other meshes, the ePTFE mesh appeared to be very different in appearance and application from the two other meshes. It was not a woven and macroporous material, but a seemingly homogeneous and microporous, slightly compressible solid, about 1 mm in thickness. Both surfaces looked similar in consistency; however, one surface (the one placed against the abdominal wall defect) had large rounded, slightly raised patterns (like a mattress), and presented 3 µm perforations. The opposite surface presented 22 µm perforations allowing easy cellular ingrowth. The cut edges were very smooth, and

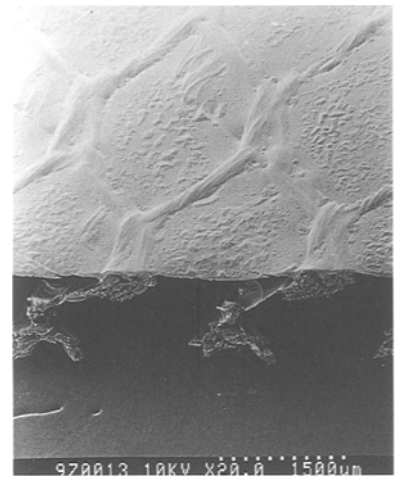

Fig. 1
SEM aspect of the coated polyester mesh (magnification x 20)

appeared similar to the surfaces in consistency. Since there were no woven fibers to loop the sutures through on the underside of the material to secure it to the parietal wall defect, a small bite was taken completely through the material at each corner of the defect.

Polypropylene/PTFE mesh. A composite mesh made of woven macroporous polypropylene fibers bonded on one side to a thin sheet of PTFE (which did not extend over the cut edges of the mesh) was used as a comparative model in the experiment. The pieces were cut into 15 x 25 mm portions and sterilized.

Experimental studies

First experimental procedure

In order to evaluate the absorption of the collagen fleece coated on the polyester/collagen mesh, and the biocompatibility of the entire mesh, subcutaneous placement of the membrane was carried out in 27 animals divided into three groups of nine. Histologic examination and macroscopic evaluation of the film absorption were performed. The reaction of the tissues to the poly-

ester mesh was used as a control, since polyester is approved for human use at the present time.

A subcutaneous normative implantation test (ISO 10993-6) was performed in order to determine the specific influence of the film on the tissue integration of the mesh and to investigate the absorption kinetics of the film. 12 samples were implanted per material and time period. The implanted samples were harvested with the surrounding tissues after 3, 14 and 28 days.

Qualitative and semiquantitative histologic analysis on sections stained by Masson's trichrome after resin embedding (for both meshes) were performed in order to detect the remaining film and to determine the various cell populations around and within the implants.

Second experimental procedure

The procedure was performed on 40 female Sprague-Dawley rats (250-300 g). The animals were randomized into 4 groups and evaluated in numerical order. The experimental model has been previously described [Harris 1995]. The animals were anesthetized with sodium pentobarbital (43 mg/kg intraperitoneally), their abdomens were shaved and prepared for aseptic surgery using iodophor solution rinsed with 70% isopropyl alcohol. A 4 cm incision was made through the peritoneal cavity. The right abdominal wall was reflected and a 2 x 1 cm surgical defect made in each rat on the peritoneal surface of the wall, removing the peritoneum and some associated muscle fibers. The medial edge of this defect was parallel to and 1 cm lateral to the midline incision. A similar sized defect was created on the cecum by rubbing a moistened gauze pad on its surface until the serosal sheath covering the cecum was peeled away. Both the abdominal wall and the cecum were lightly scraped with a scalpel blade to promote petechial bleeding, then exposed and allowed to air dry for 15 min. The non-defect areas of the abdominal wall and cecum were protected from drying by placing a moist gauze over them during the drying period. After 15 min., and for each group, a piece of mesh was centered over the abdominal wall defect and secured to the abdominal wall defect, using 4 sutures of 6/0 polypropylene (Ethicon). The knots were buried under the mesh and secured to the fibers on its underside without penetrating the surface antiadhesive coating if possible. The two injured surfaces were placed in close proximity and the animals were allowed to recover for 21 days before analysis. Ten animals were included for each type of mesh and 10 served as controls, where the abdominal wall was left untreated.

At 21 days post surgery, all the animals were examined for the presence of abdominal adhesions. Eight animals in each group were used to quantify the area and strength of adhesions. The remaining two animal meshes in each group were used unaltered for histology samples. Each histology sample was bisected and preserved with either buffered formalin (for light microscopy) or fresh cacodylate/glutaraldehyde (for scanning electron microscopy).

Third experimental procedure

In order to validate these experimental procedures in a larger animal, closer to the human anatomy, a third experimental procedure was performed. The rat model was adapted and a comparable experimental study was developed in the pig. This study was performed on 4 domestic pigs (25-35 kg). The parietal abdominal wall was reflected and two 4 x 10 cm parietal defects were made in each pig by removal of the peritoneum. The muscles were exposed for mesh application on the right and left sides of the peritoneal surface of the abdominal wall. A similar sized defect was created in two consecutive loops of the spiral colon (left side) and in the right jejunum by carefully excising the serosal sheath of the intestine. In two pigs, two pieces of coated mesh (7 x 14 cm) were secured to both abdominal wall defects using 4/0 polypropylene sutures (Ethicon). Two pigs were left untreated as controls. The two injured surfaces were placed in close proximity and the animals were closed in standard fashion and allowed to recover for 2 weeks before analysis. At the time of sacrifice, analysis of the postoperative adhesions was performed in each animal. The presence of adhesions between the spiral colon and the parietal wall, and between the jejunal loop and the parietal wall were separately assessed. Any extraneous adhesion was noted. Samples were harvested and prepared for histologic and ultrastructural investigations.

Analysis of adhesion formation

The animals were euthanized by anesthetic overload immediately prior to analysis. The skin and muscle layers of the abdomen were incised lateral and distal to the location of the original defects. The resulting U-shaped flap was slowly lifted to reveal the adhesions, if present. Any extraneous adhesions (i.e. retroperitoneal flap, bowel, omentum) were carefully noted and separated. The caudal edge of the U-shaped muscle flap was secured in a pin clamp such that the peritoneal wall was approximately 40-45° from the horizontal. In order to separate the stronger adhesions seen after 3 weeks, a clip was attached to the terminal end of the adherent cecum and attached to a strain-gauge mounted on the lead screw of a constant rate distraction tensiometer. As the lead screw was advanced at 8.8 cm/min., the cecum or abdominal wall were peeled off the hernia mesh. The required force was plotted against time on a calibrated x-y recorder. After the two surfaces were separated, the length and width of the area involved in the adhesion were measured with a caliper. The following values were calculated for every experimental animal: area of adhesion, percent of complete adhesion formation, maximum strength encountered during separation, average strength of separation, work to separate and a normalized work value. The normalized work value was used because the work to separate each adhesion is rela-

Table 1. Incidence of adhesions after 3 weeks in the cecal abrasion model

Hernial mesh	Incidence of 1:1 adhesion	*P* =
Coated polyester mesh	2/10 (20%)	0.001
ePTFE mesh	5/10 (50%)	0.03
Polypropylene/PTFE mesh	7/9 (78%)	NS
Controls	10/10 (100%)	

1: 1 adhesion = direct adhesions / *p* compared to controls

Table 2. 3 week analysis of the different meshes and controls

Hernial mesh	Area of 1:1 adhesion	% of adhesions	Max strength (N)	Mean strength (N)	Work (Ncm)	Work % Adhesion (Ncm)
Coated polyester mesh	0.30 (1 of 10)	15	1.1	0.6	0.4	2.9
ePTFE mesh	0.72	36	1.5	0.8	0.6	3.1
Polypropylene/PTFE mesh	0.49	25	1.8	0.9	0.8	4.7
Controls	1.67	83	3.2	2.14	4.0	4.7

ted to the adhesion area. The work required to detach the adhesion was calculated using the formula W = F.d, where W = work, F = the average force, and d = the measured length of the peritoneal area involved in the adhesion. The normalized work was then calculated as the work, W, divided by the percentage of complete adhesion formation.

Results

First experimental procedure

The non-coated mesh was adherent to its surgical pocket as soon as day 3 but not the coated one. On day 28, both meshes, coated or non-coated with the hydrogel film, were intact and the film was no longer observed. No local toxicity associated with either mesh could be observed. Microscopically, the film was intact at day 3, partially absorbed at day 14, and fully absorbed at day 28. The film partially delayed tissue ingrowth within the mesh only on its anchoring side; on the opposite side, constituted by the woven polyester, the textile fibers were colonized as soon as the third postoperative day. After 28 days, the histologic reaction to the coated mesh was similar to the reaction observed within the uncoated one.

Second experimental procedure

All animals but one in the polypropylene/PTFE group tolerated the procedure without complications and recovered normally. Results are presented in Tables 1 and 2.

Coated polyester mesh

The animals of this group were remarkably free of any type of adhesions, even to the fat, omentum and bowel. The mesh remained flat, smooth and of uniform dimensions. There was no visual evidence of any residual part of the collagen-coated film. The mesh surface was covered by a thin sheet of new mesothelial tissue, forming a neoperitoneal sheet (Fig. 2). Only two of the ten animals developed true 1:1 adhesions from the cecum to the coated surface of the mesh. One of these adhesions was fixed for histology. The second was a very small adhesion to the extreme caudo-medial corner of the mesh. It measured 0.30 cm^2, and had a maximum strength of 1.1 N, with a normalized work value of 2.97 Ncm. In this animal, the cecum was adherent at the midline as well, so it is likely that the midline adhesion held the cecum in place on the edge of the mesh long enough for a serosal attachment to develop.

At histologic analysis, the edges of the meshes were in most cases noted to be smoothly covered by a new layer of mesothelium. At that time period, the film was fully absorbed and complete tissue integration of the mesh was noted. The frequency of adhesions in this group was significantly less than in the group treated with the polypropylene/PTFE coated mesh ($p = 0.02$) or controls ($p = 0.001$).

ePTFE membrane

This group had a significantly lower incidence of adhesions than the control group ($p = 0.03$), but was not significantly different from both other mesh groups. Five of the ten animals of this ePTFE group had developed adhesions. The majority of the adhesions in this group occurred at the caudo-medial corner or an edge of the mesh. Although small suture loops were present on the surface of the mesh, they did not appear to cause the adhesions. Of the 4 animals tested for adhesion strength, a mean area of 0.72 ± 0.81 cm^2 was found, with a mean strength of 1.50 ± 0.59 N, and a mean normalized work value of 3.10 ± 1.79 Ncm. The most notable observation at analysis was that the mesh had shrunk in size by about 40% (to 12 x 18 mm) and the edges were wrinkled or buckled (Fig. 3). Retroperitoneal fat and omentum were invariably adherent to the edges and surface of the mesh, often extending under the lifted edges of the mesh. No significant tissue ingrowth within the material was histologically observed while a thin peripheral encapsulating membrane surrounded the ePTFE sheet.

Polypropylene/PTFE mesh

This experimental group had a significantly higher incidence of adhesions than the coated polyester meshes

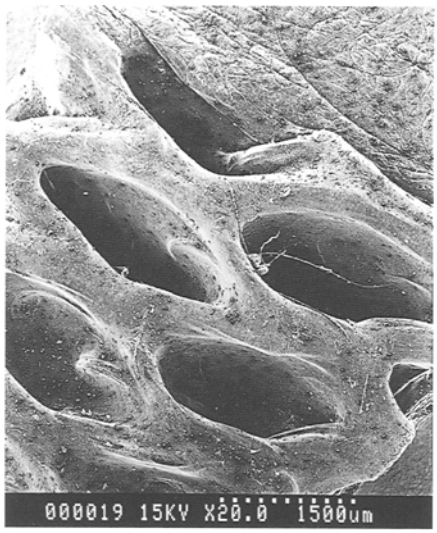

Fig. 2
SEM aspect of the coated polyester mesh after three weeks (magnification x 20)

Fig. 3
SEM aspect of the ePTFE mesh after three weeks (magnification x 20)

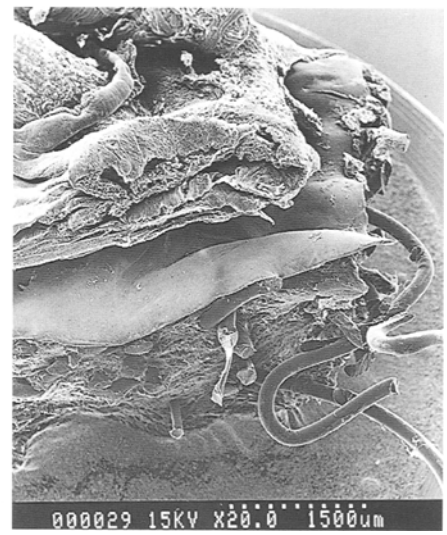

Fig. 4
SEM aspect of the polypropylene – PTFE mesh after three weeks (magnification x 20)

group ($p = 0.02$), and was not significantly different from the controls or ePTFE groups. Only nine animals were evaluated in this group. Seven of the nine animals had developed adhesions. Of the six animals tested for adhesion strength, a mean area of 0.49 ± 0.31 cm^2 was found, with a mean maximum strength of 1.85 ± 0.84 N, and a normalized work value of 4.75 ± 3.57 Ncm. One notable observation at analysis was that the PTFE coating on the mesh had shrunk in size on the surface of the mesh by up to 45%. A significant fibrous membrane surrounding the PTFE film was histologically correlated to this macroscopic shrinkage. The exposed cut edges of the mesh were frequently, as predicted, involved in 1:1 adhesions to the cecal defect. In addition, the retroperitoneal fat and omentum were invariably adherent to the edges and surface of the mesh, often extending under the edges of the mesh (Fig. 4). The mesh edges were raised and not uniformly covered by a new layer of mesothelium as seen in the polyester/collagen group.

Control group

All of the 10 control animals had typical 1:1 adhesions of the cecal defect to the abdominal wall defect. These adhesions involved an average area of 1.67 ± 0.32 cm^2, and required an average maximum force of 3.21 ± 0.78 N to separate them, with a normalized work value calculated at 4.76 ± 0.96 Ncm.

Third experimental procedure

The results obtained in the rat experiment were confirmed in the pig model. In this series, one animal from the sham group died after 9 days due to an occlusive syndrome related to adhesions and was excluded from the study. At autopsy, dense and diffuse adhesions were observed. Results are presented in Table 3. Small bowel adhesions were never observed in the tested groups. Only moderate colon adhesions were focally observed to an exposed edge of the hernia mesh. Histologically, the antiadhesive film was partially absorbed after 2 weeks and an effective cellular covering was already present. The incorporation of the mesh in the abdominal wall was not delayed by the presence of this film. On the other hand, the samples harvested in the sham group exhibited complete fusion of the muscular layer of the intestine to the abdominal wall.

Discussion

The placement of surgical reinforcement meshes directly adjacent to bowel loops results in a significant risk of intestinal adhesions and their attendant complications. Such complications are well established at the present time [Ellis 1982]. Postoperative adhesions are the consequence of scar formation between a defect in the peritoneum and any intra-abdominal organ or the parietal wall of the abdomen. The process involves fibroblast proliferation and collagen type I deposition [Nagler 1998]. The kinetics of peritoneal adhesion have been extensively studied [Harris 1995] and a temporary protection during the early healing phase was demonstrated to be effective in preventing these adhesions [diZerega 1994, Becker 1996]. Numerous biomaterials have been evaluated in hernia repair in an attempt to

Table 3. Intestine abrasion model in pigs

		Incidence	Surface (%)
Jejunum	Sham	4/4	87
	Coated mesh	0/4	0
Colon	Sham	4/4	100
	Coated mesh	1/4	8

prevent the formation of postoperative adhesions. In a first attempt, an absorbable mesh made of polyglycolic acid was placed on the underside of the nonabsorbable one to protect the viscera. However because of the intrinsic inflammatory response to this material and its porosity, the results were disappointing [Amid 1995, Baykal 1997]. The ePTFE mesh is one of the most commonly used mesh products attempting to limit adhesions. It has been employed since 1985 [Wool 1985] in conventional surgery and more recently in laparoscopic surgery by the IPOM (Intraperitoneal Onlay Mesh) technique [Spaw 1991] or for incisional hernias [Tsimoyiannis 1998]. This biomaterial is two-sided, with one side displaying a pore size of < 3 μm, minimizing the possibility of tissue attachment. Nevertheless, this material has been associated with several complications such as seromas and infection. The concept of combining conventionally used biomaterials (polypropylene, polyester) with a less adhesive coating in contact with the peritoneum seems to offer a useful solution. The efficiency of several biomaterials in adhesion prevention has been demonstrated experimentally and clinically [Therin 1998, Becker 1996, Gury 1998]. A collagen-based product was chosen to provide a hydrogelic and temporary barrier during the healing phase without compromising the expected tissue ingrowth into the mesh on the opposite side. This new concept had to be validated by standard biocompatibility studies as performed in the first of our experiments.

Aware that both biomaterials (polyester and collagen) are already in clinical use, the experimental study confirmed the good biocompatibility and lack of inflammatory reaction linked to the combination polyester/collagen coated mesh.

The main goal of a physical barrier is to prevent tissue apposition during the critical stages of mesothelial repair. In this fashion, the cellular cascade leading to adhesion formation may be interrupted. The biomaterial used to create this barrier effect needs to be biologically inert i.e.: it should not cause an inflammatory reaction by its own nature. Such an inflammatory reaction would abolish the barrier effect and promote adhesions [diZerega 1994]. The first and second experiments performed in this study clearly demonstrated the lack of adverse reaction to the collagen-coated mesh. The collagen film thus serves as a passive physical barrier. This barrier effect is probably due to two factors : first, the hydrophilic nature of the membrane, providing an effective protection against the formation of an organized fibrin matrix by day 5 [Milligan 1974], and second, the complete and rapid absorption of the collagen portion of the mesh. This resorption was complete within 3 weeks, when tissue ingrowth was conventionally observed into the non-coated mesh and in all experiments in both the rat and pig models. Theoretically, one can surmise that the barrier effect is no longer useful after this period, with the healing process having resulted in regeneration of a new peritoneal covering over the film [Harris 1995]. Furthermore, we demonstrated that the film allowed complete restoration of a neoperitoneum within several days of its insertion. This phenomenon, combined with complete tissue integration of the permanent mesh, should minimize the risk of further adhesion formation due to persistent foreign body reaction. Our results demonstrate a significant reduction in adhesion formation in the experimental animals and, when adhesions were present, significantly less surface and rupture strength related to these adhesions.

The construction of the biomaterials certainly contributed to their efficacy. The hydrophilic film was 5 mm larger than the mesh on each edge. This allowed the film to completely cover all edges of the mesh. In contrast, as demonstrated in the second experiment, the polypropylene/ PTFE mesh showed poorer results than the ePTFE patch due to the exposure of the polypropylene at the rolled edges of the mesh, leading to adhesion formation. The hydrophobic PTFE material (expanded or not) was correlated with the formation of a peripheral fibrous capsule which seemed responsible for a significant shrinkage of the material. Even if direct visceral adhesions to the PTFE were rarely observed, some were regularly noted to the fibrous capsule surrounding this material.

Conclusion

We feel that this original biomaterial offers the ability to combine the benefits of a synthetic reinforcement mesh used in hernia repair with the antiadhesive effects of an original collagen barrier. It represents a unique alternative to other existing meshes and can be placed in the abdominal cavity for the treatment of abdominal wall defects. The performance of this patch is dramatically superior to the other membranes tested, with markedly reduced adhesion formation.

We feel that these experimental studies have demonstrated the safety and efficacy of this product in animal models. Further testing of this product in human studies in the context of clinical trials is now necessary to validate these results.

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