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Purified porcine collagen membrane modulates integration of polypropylene mesh implant in a rat model

Luiz Carlos Maciel [1,*], Cássio Luís Zanettine Riccetto [2], Benedicto de Campos Vidal [3] and Paulo César Rodrigues Palma [2]

[1] *Department of Medicine, University of Taubaté, Taubaté, São Paulo, Brazil.*
[2] *Medical Sciences College, University of Campinas, Campinas, São Paulo, Brazil*
[3] *Biology Institute, University of Campinas, Campinas São Paulo, Brazil*

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Abstract

Old women are expected to undergo pelvic organ prolapse (POP) surgery. Distress caused by POP affects women´s quality of life. Although polypropylene mesh (PM) is considered a good material to restore the pelvic floor, there are concerns about infection and vaginal mesh exposure.

This research studies the optic properties of inflammatory reaction and the tissue repair induced by a PM covered by porcine collagen membrane (CM).

Thirty female rats were shared in two groups: (A) exposed to PM covered by CM and (B) exposed to PM alone; five animals each group were euthanized at day 7, 14 and 28 of post-operation day (POD). Collagen anisotropic properties were analyzed.

In the 7○PO group A pushes vascular proliferation on, as lymphocytes and fibroblasts infiltration. Group B evidenced amount of histiocytes and beginning of encapsulating. At the 14○PO group A keeps the characteristics of lymphocytic infiltration and rounding the PM there is a thin layer of fat tissue separating it from the muscles layer; Group B evidenced amount of fibroblasts rounding the PM and multinucleated giant cells crushed by a wrap of collagen and fibroblasts. The 28○PO group A revealed big fibroblasts process with expressive histiocytes presence. Group B shows much multinucleated giant cells trying to wrap up the polypropylene, a considerate decreased infiltration, and the striated muscles layer infiltrated the implanted area.

PM covered with a highly purified porcine collagen membrane showed earlier resolution of inflammatory reaction, better neoangiogenesis and more organized host collagen deposition than in pure PM.

Keywords: Pelvic organ prolapse; Polypropylene meshes; Collagen; Distress; Quality of life

1. Introduction

Pelvic organ prolapses (POP) is a multifactorial connective tissue disorder caused by damage to the supportive structures of the pelvic floor and he POP symptoms not only seriously disrupt social and daily activities but also influence the mental health of middle-aged and old women. The prevalence in women over 60 years old is 25%, and the risk of hospitalization due to symptomatic prolapse is 2/1000 per year. The risk of developing POP increases 10% every decade of life, and the risk of a woman to need surgical treatment for such a disease in her lifetime is 11.1%. Of them,

* Corresponding author: Luiz Carlos Maciel

30% would need a second surgical procedure because of a failure in the first attempt of correction[1,2,3, 4]. Most of the procedures are based on correction techniques by sutures exclusively. Studies have shown that such techniques present high recurrence rates in a midterm follow up[4].

Currently there are no suture-based techniques that have proved to be efficacious enough to promote total and everlasting cure of POP[5,6]. Thus, the use of meshes in the reconstruction of the pelvic organ support has increased with promising anatomical results before its abandon[6,7].

From the many materials tested, polypropylene is the most often used as it is an inert synthetic non-absorbable material[8,9]. The use of polypropylene for POP is highly efficacious, reducing the duration of surgery without the risk of transmitting disease from biological grafts, besides showing far better anatomical results[5,6,10,11]. However, its use may cause potential problems in the female perineum[6,7,12,13]. Besides the perineum and the vagina, there are reports of complications related to inflammatory reaction caused by the polypropylene mesh when it is implanted in other anatomical sites[14,15].

As integration defects of polypropylene meshes are relatively frequent and may determine the need for its removal[6,7,10,12,13], the research of strategies which enable to reduce such events on the vaginal wall is justifiable.

The aim of this study is to verify the effect of the lining with porcine collagen biomembrane in the integration of monofilament polypropylene mesh implanted in the subcutaneous tissue of adult female rats.

2. Material and methods

The study was approved by the Committee on Animal Research and Ethics (CEEA-IB-University of Campinas, Brazil, protocol 1336-1). Thirty-three-month-old female Wistar rats, weighing from 290 grams to 430 grams, were submitted to the implant of pure and collagen biomembrane-coated polypropylene mesh fragments (Prolene® Mesh Ethicon©, Inc; lot number: RME077), 15mm x 15mm, in the subcutaneous abdominal tissue.

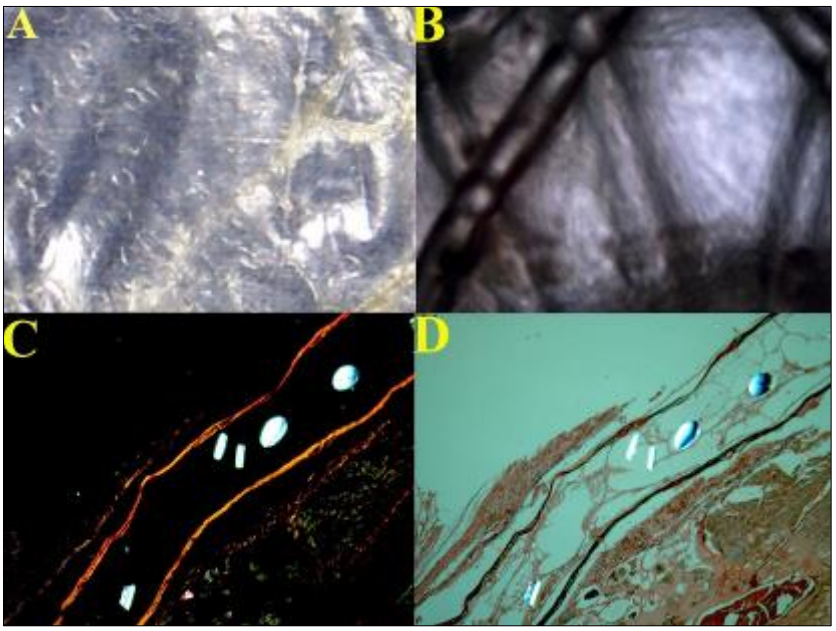

Figure 1 A) A sheet of biomembrane purified from porcine small intestinal submucosa in an optic microscopy view; B) Polypropylene mesh wrapped by BMSS before implantation (10X0.65); C) Polypropylene mesh wrapped by BMSS, HE (4X0.65); non-compensated birefringence showing collagen, after seven days post implantation. Polypropylene polymers are in white; D) Polypropylene mesh wrapped by BMSS, HE (4X0.65); compensated birefringence showing of collagen. Polypropylene polymers are in white. No extensive acute inflammation was observed

Biomembrane was prepared from porcine small intestinal submucosa by enzymatic and decellularization processes, leaving only the components of the extracellular matrix (ECM), where collagenic proteins are the most abundant constituents. The biomembrane of porcine small intestinal submucosa (BMSS) obtained was prepared in the shape of a

sheet, which was 20 μm thick, and fitted to both sides of the polypropylene mesh with a collagen gel obtained according to Vidal (1995)[14] (Figure 1).

In each animal, a transversal incision in the hypogastrium, and desiccation of subcutaneous cellular tissue were performed, preserving the conjunctive tissue membrane of the mean line, resulting in two isolated compartments. The mesh coated by BMSS on both sides was implanted on the right side and the pure polypropylene mesh was implanted on the left side (controls).

The thirty animals were divided into four groups, each containing 10 animals that were euthanized after 7, 14 and 28 postoperative days. After the euthanasia, in block exeresis of the abdominal wall was performed and the areas containing the meshes were identified, separated and kept in separate containers.

Histological slices, 7-micrometer-thick each, were made perpendicular to the skin, aiming for appropriate assessment of the collagen anisotropic properties. Four specimens were placed on each slide, each consisting of skin, subcutaneous tissue with the polypropylene mesh, abdominal fascia, abdominal musculature, and parietal peritoneum. Two slides were prepared for each animal, one of which was stained with Hematoxiline-Eosine, and the other was left unstained, for the analysis of tissue birefringence.

Histological assessments were carried out by using an Olympus BX51 Polarizing Microscope (Olympus, Tokyo-Japan), connected to a computer with Image Pro-Plus 6.0 Software (Mediacybernetics, Inc; Bethesda, MD-USA) for the analysis of the shape birefringence.

3. Results

There were neither deaths nor extrusions of meshes implanted in the animals' subcutaneous tissues in the observation period. No behaviors or reactions that might have suggested systemic action of the mesh or the BMSS were noticed.

In the samples analyzed on the 7th day after implant, the polypropylene mesh coated by the BMSS presented intense vascular proliferation, vessel dilatation, and significant infiltration of monocytes with lymphocytary aspect. Nuclear remains of neutrophils were also observed next to the biomembrane, as well as on the threads of the polypropylene mesh. The birefringence analysis demonstrated high fibroblastic proliferation accompanied by the production of fine fibers of birefringent collagen (Figure 1).

In the control, 7 days after implant, one observed smaller monocytary infiltration next to polypropylene filaments. These monocytes could be histiocytes diagnosed by the reniform aspect of the nucleus. Cells with fusiform nuclei, characterized as fibroblasts, were placed on the surface of the mesh wrapping it (Figure 2).

In the meshes coated by the BMSS assessed after the 14th day of implant, one presented right under the dermis a layer of relatively thin adipose tissue that separated the implant region, and under it, the muscular layer in adherence to the polypropylene. In one sample also was noticed the lymphocytary infiltrate.

The control meshes were covered with fibroblasts. However, the accumulation of nuclei was frequently observed, which suggests the presence of giant cells with a flat aspect covered by fibroblastic collagen (Figure 2). One observed remains of erythrocytes, new collagen fibers covering the polypropylene filaments, fibrocytes and mononuclears (histiocytes). No significant lymphocytary infiltrations were noticed. Wrapping the polypropylene mesh, one also observed a loose tissue (myxomatosis-like) with starred cells, confirming that there was no predominance of newly elaborated fibers.

In the assessments carried out on the 28th postoperative day one observed that the polypropylene mesh initially covered by BMSS presented a predominance of exuberant fibroblastic proliferative process, mainly wrapping the remains of the biomembrane interweaving them (Figure 2). One noticed the expressive presence of mononuclears with histiocytary aspect. Such cellular type penetrated the polypropylene mesh filaments, which might originate foreign body giant cells in the site. The presence of giant cells is associated with the presence of polypropylene polymers.

In the isolated polypropylene meshes, one observed, under the dermis and adipose tissue, a layer of striated muscular tissue, which appeases in the implant site, separated from that by a thin layer of fibrous tissue. The musculature seems to be firmly adhered to the implant.

Outstanding reduction on inflammatory infiltrate was detected, with persistence of mononuclear cells (histiocytes) around the polypropylene filaments. Some of these cell nuclei get together forming giant cells around the polymer. Typical giant cells were observed in this phase, associated with the polypropylene filaments. On the opposite side of the musculature there was a relatively thin strip of neoformed collagen fibers colonized with typical fibrocytes.

These results are summarized at the table one in qualitative way.

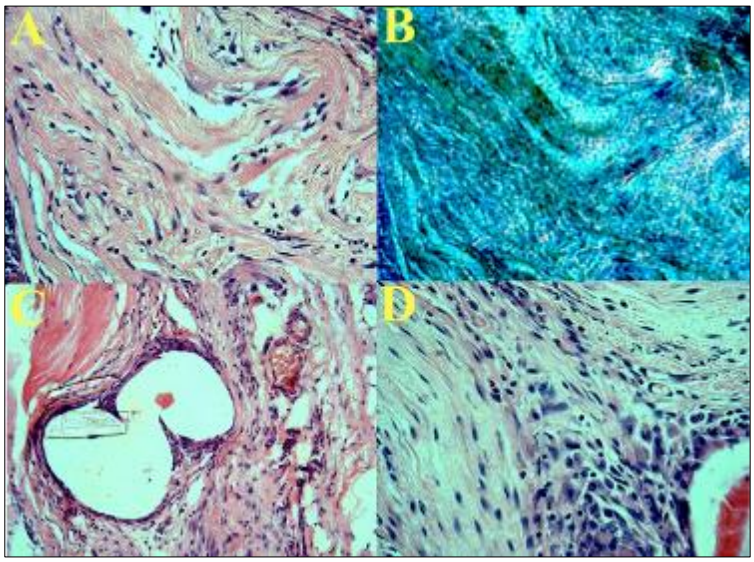

Figure 2 Histological sections stained by HE showing the morphological aspects and polarized microscopy anisotropy; A) Image from polarized microscopy after polarizer moved by small angles enough to diminish collagen brightness in order to show fibroblasts nuclear and the absence of acute inflammatory reaction; Collagen fibbers are showing molecular order and integrity (yellow arrow); (40x0,65); B) Same image as (A) showing the compensate "fibbers" birefringence in dark (yellow arrow); (40x0,65); C) Polypropylene filaments surrounding by giants cell agglomeration fated on its surface (green arrow); Monocitary infiltrate and collagen fibbers are observed; (20x0,65); D) The same region as (C) showing details of inflammatory infiltrate (green arrow); (40x0,65)

4. Discussion

Previous studies demonstrated that the quantity of collagen present in the supporting tissue of pelvic organs in females with POP is smaller than in females who do not have the disease[4,17,18]. Also, it has already been shown the relation between changes in quantity and quality of collagen in females with the Ehlers-Danlos syndrome and Marfan's syndrome, who have a greater incidence of POP[19,20].

Conventional treatment for POP has been based on the anterior colporrhaphy, which presents high rates of recurrence. Recurrence rates for this disease after non-implant surgery varies from 30% to 40% in the first two years, and from 62.5% to 70% after 5 postoperative years[5,6,7]. Such considerations make it clear that a successful surgical repair of the vaginal wall in patients with POP is still a challenge. The mechanisms and principles of surgical correction to this disease are like those described in the treatment of abdominal hernias. That has stimulated the use of biological implants and synthetic meshes to reduce postoperative recurrences[5,6,7,10,11,12].

Nevertheless, the uses of biological or synthetic implants are not exempt from complications[6,7,10,11,12,13,21].

Recurrence rates of POP when using synthetic material implant are quite reduced, thus achieving expected success. However, complications do occur, such as the frequent mesh exposition/erosion, which may vary from 3.8% to 25% in patients undergoing surgical correction of POP[5,6,7,10,11,12,13]. Other complications related to the use of vaginal implants are dyspareunia, hyperactive bladder, and painful buttocks, among others. Thus, it is reasonable to infer those defects related to the integration of these biological and/or synthetic materials might have occurred[4,5,10,12,21].

Tissue repair has different phases, which are sequential and sub entrant, classified as precocious or hemostatic and inflammatory; intermediary or proliferative; final or collagen maturation. Integration process of polypropylene meshes follow similar steps, independent of the type of implant, each step duration depends on several factors, such as

conditions of host immune system, levels of local bacterial contamination, biocompatibility of implant materials and amount of devitalized tissue. Complete resolution of inflammatory response, that is, the reconstitution of the native tissue will not be possible in the long run, as the continuation of aggressive factors related to the physical and chemical properties of the implant material will not allow that[8,14,21]. The integration is defined as the final product of the interaction between the implant and the host, represented by distinct fibrosis levels[8,9].

Collagen and elastic fibers, as well as the viscoelastic matrix of proteoglycans are the elements that make up the conjunctive tissue. The physical properties present in this tissue are determined by the relation between the fibers and the components of its ECM. Type I and III collagen fibers are important elements in the composing of force and tension of the pelvic floor[4,8,9]. Type I collagen is the main component in the fibrosis developed around the polypropylene meshes[22].

Collagenous proteins are the most abundant constituents of ECM in most tissues of animal origin. Several forms of intact ECM are commercially used like biological moulds, which have been successfully applied in surgery of ligament and tendon reconstruction, facial esthetics, genitourinary tract reconstruction, meninges and peripheral nerves[23,24,25,26,27]. The ECM that originates biological moulds can be obtained from the bladder, skin, liver, and other tissues[23,24,25].

The biomembrane processed from porcine small intestinal submucosa (BMSS) is one of the most studied and traded biological moulds, as they have great malleability, which permits their fitting to lesioned tissues. Also, they are receptive to host cells, non-carcinogenic, easily sterilized, and resistant to different mechanical forces. The regenerative process in the implant site generates a tissue structurally and functionally like the original tissue, which is more organized than the cicatricial tissue[21,24,25,26,27].

Tests to adjust BMSS to clinical use showed, in experimental implants, that membranes of up to 10 μm thick are absorbed without inducing inadequate inflammatory process in host tissues[21,23]. BMSS does not cause rejection reactions when implanted in rats, but the existence of immune response was noticed, activating T-helper 2 cells, as well as cytokines, tumor necrosis factor and interleukin (IL) I and IV. This fact may have been caused by the presence of glycosaminoglycans, which may activate cytokines and several other growth factors that participate in cicatricial and revascularization processes[21,28]. An important characteristic of the BMSS is the capacity to be quickly and totally degraded after being implanted[23].

Based on what has been reported in literature, the hypothesis of coating the polypropylene mesh with BMSS in order to enhance the first cell and tissue responses enabling better incorporation of meshes to surrounding tissues in the implant site proves to be an evolution in the implantable materials. The search for hybrid materials, that is, implants that have absorbable or temporary components and non-absorbable or definite components comes up in medical literature as an alternative that may minimize complications associated with implants and isolated materials[21,29,30,31,].

The results obtained in this experiment model showed that coating the polypropylene mesh with BMSS improved the quality of tissue repair with positive increase in the integration of polypropylene mesh, and that was also observed in other tissues. Synthesized collagen in the interface with the polypropylene mesh showed an organizational structure superior to the control group, according to the anisotropic properties' analysis.

5. Conclusion

The biological characteristic of the ECM wrapping the polypropylene implants allows us to conclude that the mesh coated by BMSS induced better integration of the polypropylene mesh in comparison to the one isolated implanted in the rats' subcutaneous tissue. These properties could represent an advantage in clinical setting.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

No conflict of interest.

Statement of ethical approval

The study was approved by the Committee on Animal Research and Ethics (CEEA-IB-University of Campinas, Brazil, protocol 1336-1).

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