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# Postimplant intraperitoneal behavior of collagen-based meshes followed by laparoscopy

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## Abstract

*Background* When repairing an abdominal wall defect, sometimes a prosthetic mesh needs to be placed directly on the parietal peritoneum. Although the standard mesh for this purpose is the laminar implant expanded polytetrafluoroethylene (PTFE), it is gradually being replaced by the laminar collagen-based meshes. This study was designed to assess the intraperitoneal behavior of three of these biomeshes, mainly in terms of their susceptibility to adhesion formation.

*Methods* Two 3-cm x 3-cm fragments of prosthetic material were placed on the parietal peritoneum in male New Zealand White rabbits in the following combinations: PTFE and CollaMend®, PTFE and Permacol®, or PTFE and Surgisis®. The meshes were fixed at the four corners with individual 4/0 polypropylene sutures. Adhesion formation was quantified by sequential laparoscopy and image analysis performed at 3, 7, 14, and 90 days postimplant. All animals were killed at 90 days and the mesh specimens were subjected to microscopy and immunohistochemistry.

*Results* Intensely vascularized adhesions to all the implants were observed, although Surgisis showed the lowest percentage of adhesions at each follow-up time. Adhesions had stabilized by 7-14 days. The PTFE meshes were enveloped by a layer of macrophages and connective tissue, bounded by a monolayer of mesothelial cells. Permacol and CollaMend showed similar histological behavior, including cell ingrowth through their fenestrations with no signs of degradation detected at 90 days. In contrast, the Surgisis mesh at 90 days was practically replaced with neoformed tissue.

*Conclusions* No difference in susceptibility to adhesion formation was noted in the crosslinked collagen meshes compared to PTFE meshes. The noncrosslinked collagen mesh Surgisis showed the best behavior in that it induced fewer adhesions. Ninety days after implant, a more intense macrophage response was observed in CollaMend and Permacol than in PTFE or Surgisis.

**Keywords** Collagen mesh · Intraperitoneal · Peritoneal adhesions · Laparoscopy · Hernia repair · Abdominal wall · Biomeshes

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The peritoneal interface is the key focus of any attempt to improve the behavior of a prosthetic material designed to repair an abdominal wall defect such as an incisional hernia. In some cases (full abdominal wall defects and/or laparoscopic repair of a defect), the biomaterial needs to be placed in contact with the visceral peritoneum which can lead to postoperative complications. Adhesions that form at this interface can result in intestinal obstruction [1] or intestinal fistulas [2].

In prior in vitro studies [3], we observed that when mesothelial cells were seeded on different types of biomaterials, mesothelialization of the mesh surface was deficient when the material was of a reticular structure, while better results were observed with the laminar meshes. In vivo, mesothelialization is also rapidly achieved when the expansion surface is smooth.

Included in the available laminar prosthetic materials are biomeshes derived from animal or human collagen. These laminar biomeshes are a current option for the repair of an abdominal wall defect [4]. Besides repair, the aim of these biomaterials is to regenerate new tissue [5, 6]. Thus, once implanted, biomeshes induce elements of the host extracellular matrix to promote angiogenesis [7] and maybe even to recruit growth factors to create new tissue [8] or, in the case at hand, a neoabdominal wall.

To prepare these collagen biomeshes, the collagen has to be extracted and treated (lyophilized) to eliminate cells and leave behind only the matrix components collagen types I, III, and IV and elastin. After the purification process, there should be no immune response induced in the host and the inflammatory response to the implant should be minimal.

In in vivo conditions, collagens are degraded by enzymes such as metalloproteases or even by microbes in a setting of infection. Thus, implants in which the collagen fibers are not intensely crosslinked tend to be rapidly absorbed and consequently do not act as good tissue support. The ideal situation in terms of function is that the biomesh should remain stable long enough to gradually become fully incorporated in the host tissue. To achieve this, links at the level of the triple helix comprising the collagen molecule need to be as efficient as possible [9, 10]. For this purpose, there are several crosslinking methods that use substances such as glutaraldehyde or hexamethylene diisocianate (HMDI).

To date, the clinical use of biologic prostheses has been limited for several reasons. First, other available inert materials (e.g., polypropylene, polyester, expanded polytetrafluoroethylene) have provided excellent outcomes in patients. Second, biomeshes have precise indications and have been used principally in repair zones compromised by infection [11, 12]. Third, these materials are expensive.

Published reports on the use of biomeshes lack sufficient mid- and long-term follow-up results for conclusions to be drawn regarding their benefits. Many studies are short retrospective case series that have been inconclusive as to the real utility of this type of prosthesis [13–17]. Because of the appearance of new bioprostheses and concerns about the intraperitoneal behavior of such prosthetic materials, the objective of this experimental study was to examine adhesion formation with and the peritoneal response to several different biomeshes, using expanded polytetrafluoroethylene (PTFE) mesh as the control. We selected PTFE since it has been the most used prosthetic material at this interface in laparoscopic repair procedures [18, 19] and in the form of a composite mesh [20]. Peritoneal behavior was assessed using sequential laparoscopy performed in each group of animals. This enabled us to follow the postoperative course of the different meshes implanted.

## Materials and methods

## Mesh material

The following prosthetic materials were employed:

- Gore Preclude® (Gore, Flagstaff, AZ, USA), a synthetic, nonporous biomaterial composed of expanded polytetrafluoroethylene (PTFE). This material was used as the control in each study group.
- CollaMend® (Bard Inc., Cranston, RI, USA), a bioreabsorbable laminar material made of lyophilized acellular porcine dermal collagen that is partially perforated (crosslinked).
- Permacol® (Covidien, Dublin, Ireland), a collagen material composed of porcine dermis treated with hexamethylene diisocianate (HMDI) to maintain the stability of collagen fibers (crosslinked).
- Surgisis® (Cook Inc., West Lafayette, IN, USA), collagen derived from porcine small intestine submucosa with an intact extracellular matrix (noncrosslinked).

## Experimental protocol

New Zealand White rabbits (mean weight = 3,000 g) were housed and handled during the entire study period in accordance with European Union guidelines for animal care (European Directive 609/86/CEE and European Convention of Council of Europe ETS123).

The animals were anesthetized with a mixture of ketamine hydrochloride (Ketolar®, Parke-Davis, Spain) (70 mg/kg), diazepam (Valium®, Roche, Spain) (1.5 mg/ kg), and chlorpromazine (Largactil®, Rhone-Poulenc, Spain) (1.5 mg/kg) administered intramuscularly. In some cases, an additional dose of anesthetic was injected directly into the abdominal cavity during the course of surgery.

Using a sterile surgical technique, each animal under- went a midline laparotomy approximately 6 cm long and about 4 cm from the xiphoid process. On either side of the laparotomy and 1 cm from the linea alba, 3-cm x 3-cm fragments of each of the prosthetic materials were placed on the parietal peritoneum and fixed using four individual 4/0 polypropylene sutures at the implant corners (Fig. 1).

The following study groups were established: group I ($n = 6$): PTFE and CollaMend, group II ($n = 6$): PTFE and Permacol, and group III ($n = 6$): PTFE and Surgisis. All 18 animals were killed at 90 days postimplant.

## Laparoscopy study

On postoperative days 3, 7, 14, and 90, each animal was anesthetized and examined laparoscopically to quantify adhesions between the visceral peritoneum and the implants. Laparoscopy was performed by introducing a 3-mm, 0° laparoscope (Karl Storz, Tuttlingen, Germany) into the peritoneal cavity through a metal trocar (Karl Storz). Access was gained through the linea alba 1 cm from the lower end of the laparotomy. Pneumoperitoneum was achieved using $CO_2$ at a maximum pressure of 8 mmHg. When the examination was completed, the laparoscopy equipment was removed and the skin closed. Observations were photographed and video recorded for subsequent review.

The surface areas of the meshes that were covered with adhesions were measured at each follow-up time. This was done by tracing the outlines of the adhesions on transparent polyethylene templates the same size as the implants using the photographs taken during the laparoscopic study. The surface areas of the meshes covered by adhesions could then be determined by computerized image analysis of the templates.

Images obtained by digitizing the templates were evaluated by the MIP program incorporated in the image analyzer (MICRON, Barcelona, Spain). Results are expressed as the percentage of implant covered by adhesions, ranging from 0 to 100% (no adhesions to completely covered). The intra-abdominal structure involved (epiploon or intestine), location of adhesions, and appearance of the implant's surface were noted.

Adhesions were classified, according to their consistency, as (1) loose, transparent, and easily dissected; (2) firm, whitish, and more difficult to dissect; or (3) integrated within the prosthesis/visceral peritoneum interface and difficult to dissect away from the biomaterial and intestinal serosa.

## Histology

The entire prosthetic mesh and surrounding tissue were removed. Each specimen was cut into quarters to produce four samples, each of which included normal abdominal wall, the mesh, and the transition zone between them. Tissues were processed for light microscopy (LM) and scanning electron microscopy (SEM). For LM, specimens were fixed in Bouin's fluid, embedded in paraffin, sliced into 5-μm sections, and stained with hematoxylin-eosin and Masson's trichrome (Goldner–Gabe) stains. Specimens for SEM were fixed in 3% glutaraldehyde, placed in Millonig's buffer (pH 7.3), and dehydrated in a graded series of ethanol. Critical point was reached in an E-3000 Polaron (Quorum Technologies Ltd., West Sussex, UK) with carbon dioxide. After metalizing with gold palladium, speci- mens were examined under a Zeiss scanning electron microscope (DSM-950) (Carl Zeiss, Oberkochen, Germany).

## Morphometric analysis of the peritoneum

The neoperitoneum formed over each implant was morphometrically evaluated on 25 histological sections (in microscopy fields of magnification 920) per group using a computerized image analyzer (MICRON, Barcelona, Spain). In each tissue section, two random measurements were made of the thickness of the neoperitoneum, defined as the distance between the prosthetic material and the neoformed mesothelium.

## Immunohistochemistry

Paraffin-embedded tissues were immunolabeled using RAM-11, a monoclonal antibody against rabbit macrophages (M-633, Dako, Carpinteria, CA, USA) in the alkaline phosphatase-labeled avidin-biotin procedure. The method consists of the following steps: incubation with the primary antibody (1:50 in tris-buffered saline [TBS]) for 60 min; incubation with immunoglobulin G (IgG) and biotin (1:1,000 in TBS) for 45 min; and labeling with avidin (1:200 in TBS) for 60 min. These steps were conducted at room temperature. The images were developed using a chromogenic substrate containing naphthol phosphate and Fast Red. Nuclei were contrasted for 5 min with acid hematoxylin. Labeled macrophages were quantified by performing counts in 30 microscopy fields (magnification 920) for each biomaterial.

## Statistical analysis

Adhesions expressed as percentages of implant covered, neoperitoneum thickness, and macrophage counts for the different study groups (expressed as mean ± standard deviation) were compared using the Mann-Whitney *U*-test. All statistical analyses were

performed using the GraphPad Prism 5 computer package for Windows (GraphPad Software, Inc., La Jolla, CA, USA). Probability ($p$) values $< .05$ were considered statistically significant.

## Results

No signs of infection or rejection of the prosthetic meshes were observed. One animal died at 14 days postimplant due to an overdose of anesthesia while conducting the laparoscopic examination.

### Laparoscopy study (Fig. 2)

*PTFE* Most of the PTFE implants had no surface adhesions, and the formation of a neoperitoneum on the prosthetic's surface was clearly observed at 3 days postimplant. Only in one animal was the presence of a small, loose, intensely vascularized adhesion evident at the level of one of the polypropylene suture stitches.

*CollaMend* At 3 days postimplant, adhesions of the loose type, showing an intense vascular network, were observed. In each case, the adhered material corresponded to epiploon. At 7 days, the mean percentage of adhesions was slightly higher than the percentage recorded at 3 days. Adhesions to the implants seemed to stabilize between days 7 and 14. The only observations were their increased consistency and degree of adhesion to the biomaterial, with adhesions at 90 days being of the firm type.

*Permacol* This biomesh showed behavior similar to that of CollaMend in terms of inducing adhesions. Most adhesions appeared in the areas of suture stitches.

Surgisis This biomesh showed the least adhesion formation, with no adhesions observed at 3 and 7 days postimplant. At 14 days, only a small amount of fibrous tissue appeared at the suture stitches that anchored the mesh to the abdominal wall. At 90 days, the laparoscopy examination revealed a lack of adhesions and the almost complete disappearance of the biomaterial; only a small remnant was visible in the area of the sutures.

Figure 3 shows the mean adhesion percentages obtained for each biomaterial at each follow-up time.

### Histological study

*PTFE* Three months after implant, the PTFE meshes had been enveloped by a thick fibrous capsule of connective tissue, which was delineated toward the peritoneal side by a monolayer of mesothelial cells. Scanning electron microscopy revealed that the cells comprising the neoperitoneum seemed to migrate from the abdominal wall toward the prosthesis (Fig. 4A, B). The thickness of the neoperitoneum formed on the PTFE was $355.90 \pm 39.94$ μm.

*CollaMend* Compared to the PTFE, a greater number of cells were seen to infiltrate the collagen matrix and giant foreign-body reaction cells were observed in the interior and at the periphery of the biomaterial. At the fenestration points, connective tissue fibers and cells penetrated toward the inside of the mesh. There were no signs of degradation on the biomaterial. In areas free of adhesions, the neoperitoneum was composed of connective tissue organized as fiber bundles running parallel to the CollaMend sheet (Fig. 4C–E). The thickness of the neoperitoneum was $501.60 \pm 39.94$ μm.

*Permacol* This mesh showed a similar integration within the host tissue as CollaMend. Cell ingrowth occurred through the natural pores of the prosthesis. The main cell types

observed were fibroblasts and white blood cells. The spaces left by the pores were occupied by newly formed tissue with the presence of blood vessels. Neither degradation of the collagen matrix nor loss of the structural integrity of the Permacol were observed. The neoperitoneum was significantly thinner (77.11 ± 9.21 μm thick) than that of CollaMend and PTFE. A uniform layer of mesothelial cells lined the intraperitoneal side of the mesh (Fig. 5A–C).

*Surgisis* At 90 days postimplant, the biomesh had almost disappeared. The small fragments of biomaterial that remained in the neoformed tissue appeared inside granulomas formed of several layers of white blood cells. Neoperitoneal thickness was the lowest of all the meshes at 53.23 ± 1.91 μm. Mesothelial cells with a very smooth surface were interspersed with cells with a rougher surface indicating greater activity in the latter. In zones in which the continuity of the mesothelial layer was interrupted, we could see that its cells lay on a dense, fibrous extracellular matrix (Fig. 5D, E).

Immunohistochemistry study

In the immunohistological analysis performed using the monoclonal RAM-11 antibody specific for rabbit macrophages, a more marked inflammatory reaction was observed in the collagen biomeshes. Macrophages formed a barrier around the PTFE sheet. RAM-11-positive cells infiltrated the CollaMend and Permacol interstices and the tissue adjacent to the biomaterial. CollaMend and Permacol showed a similar distribution of macrophages around the mesh perimeter, but they also penetrated within the meshes through the interstices left by the collagen fibers and the small perforations existing between the sheets of collagen comprising the CollaMend. The remains of Surgisis that persisted at this time point (90 days), were surrounded by granulomas.

Macrophage counts were significantly higher for CollaMend and Permacol compared to PTFE and Surgisis. The lowest macrophage count was for the Surgisis meshes due to reabsorption of the biomaterial (Fig. 6).

## Discussion

The repair of incisional hernias using a laparoscopic approach requires the use of appropriate materials such that behavior at the peritoneal interface is optimal. This type of repair usually involves the use of a laminar type of biomaterial of which PTFE has been the most commonly employed. Over time, however, other prosthetic materials have appeared, including composite types. The rationale behind the use of a composite is that good tissue ingrowth is achieved by the reticular component and a good peritoneal response is obtained by the smooth laminar component [21, 22].

Another important innovation has been the advent of biological prostheses, mainly those based on animal or human collagen. These prostheses of laminar architecture were first used in the laparoscopic repair of incisional hernias by Franklin et al. [8], with good behavior observed at the peritoneal interface. In those patients who needed to be reoperated on after mesh implantation [23], it was confirmed that the mesh surface was well mesothelialized and devoid of adhesions.

The experimental model of sequential laparotomy, introduced by Baptista et al. [24], enabled us to follow, in real-time, the behavior of a prosthetic mesh in the same animal. Our final goal was to identify the possible benefits of the use of a collagen biomesh over the more conventional biomaterial PTFE. Unlike classic experimental studies, we were able to follow the postimplant course of the mesh over 3 months at the intraperitoneal level.

No morbidity or mortality was caused by the laparoscopic investigation (one animal died because of an anesthesia overdose), despite the use of intra-abdominal pressures of 8 mmHg. Other authors [25] work with pressures as low as 3 mmHg or even insufflate the abdomen using ambient air without manometrically controlling pressure [26].

All the biomeshes used in our study were laminar, and all but one of the materials, Surgisis, were crosslinked. The variable that we believe best reflects the behavior of a mesh at the peritoneal interface is adhesion formation. Thus, in terms of scarce adhesion formation, the mesh that showed the best behavior was Surgisis. This bioprosthesis was practically indistinguishable from the parietal peritoneum and had significantly fewer adhesions than the other meshes. In general, adhesions to the implants were visible at 3 days postimplant. In some of the meshes, the proportion of mesh covered by adhesions increased slightly until 7 days postimplant, but no difference in this variable was detected between day 7 and day 90, with the exception of Surgisis. In agreement with the findings of others [27], the first 7 days after implant seem to be crucial for formation of adhesions. As described by Petter-Puchner et al. [28], in our model, adhesions appeared mainly at the borders of the mesh in the areas of polypropylene sutures. We observed few adhesions in the central zone, suggesting that adhesions affect mostly sites of incomplete mesothelial cell deposition. In other experimental studies [29–31] conducted in different animal species (rat/pig), results in terms of the extent of adhesions have been quantitatively similar to ours. It has also been possible to reduce adhesion formation using a composite prosthesis in which the peritoneal barrier material was a biomesh [32, 33].

The thickness of the neoperitoneum formed did not correlate with adhesion formation. Obviously, thickness measurements made at 90 days were markedly lower for the Surgisis implant due to its degradation.

The foreign body reaction immunohistochemically assessed by macrophage counts using a specific monoclonal antibody (RAM-11) was greater for CollaMend and Permacol than for PTFE; the lowest count was for Surgisis. The low adhesion response is Surgisis is related to the biodegradation of this material. It is likely that an earlier assessment of the immune reaction in this implant would have yielded similar results for the different meshes, as reported in previous studies [34].

In conclusion, our findings indicate (1) that there are no differences in adhesion-inducing behavior among the crosslinked collagen prostheses compared to PTFE, (2) that the behavior of the noncrosslinked collagen mesh (Surgisis) in terms of adhesion formation is better than that of the other implants at all the time points established, and (3) there is a more intense macrophage response at 90 days postimplant in CollaMend and Permacol than in PTFE or Surgisis.

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**Disclosure** Drs. Juan M. Bellón, Marta Rodríguez, Gemma Pascual, Verónica Gómez-Gil, Sandra Sotomayor, and Julia Buján have no conflicts of interest or financial ties to disclose.

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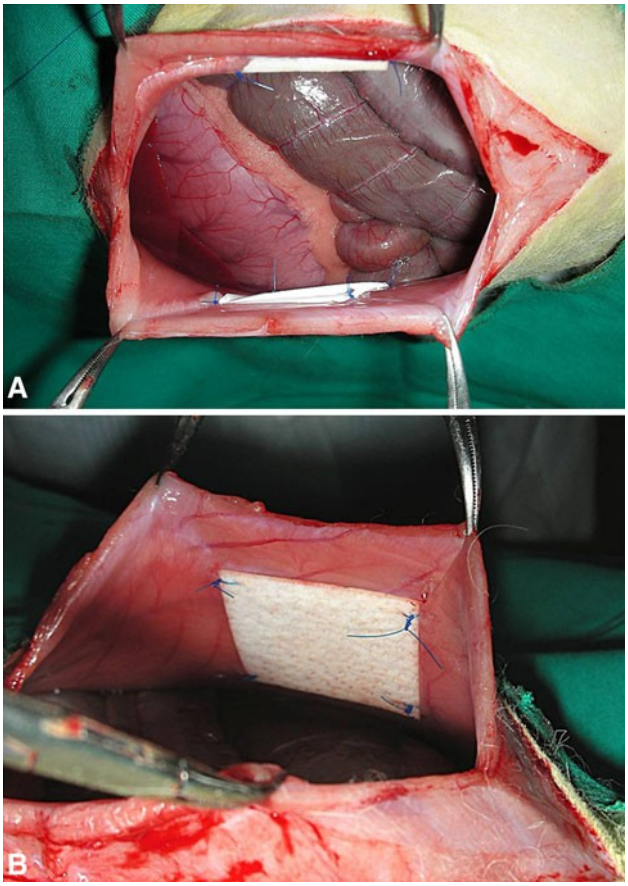


**Fig. 1** Surgical technique. **A** Detail showing how the prosthetic mesh is fixed onto the parietal peritoneum using four stitches. **B** Final appearance of the CollaMend mesh on the right side

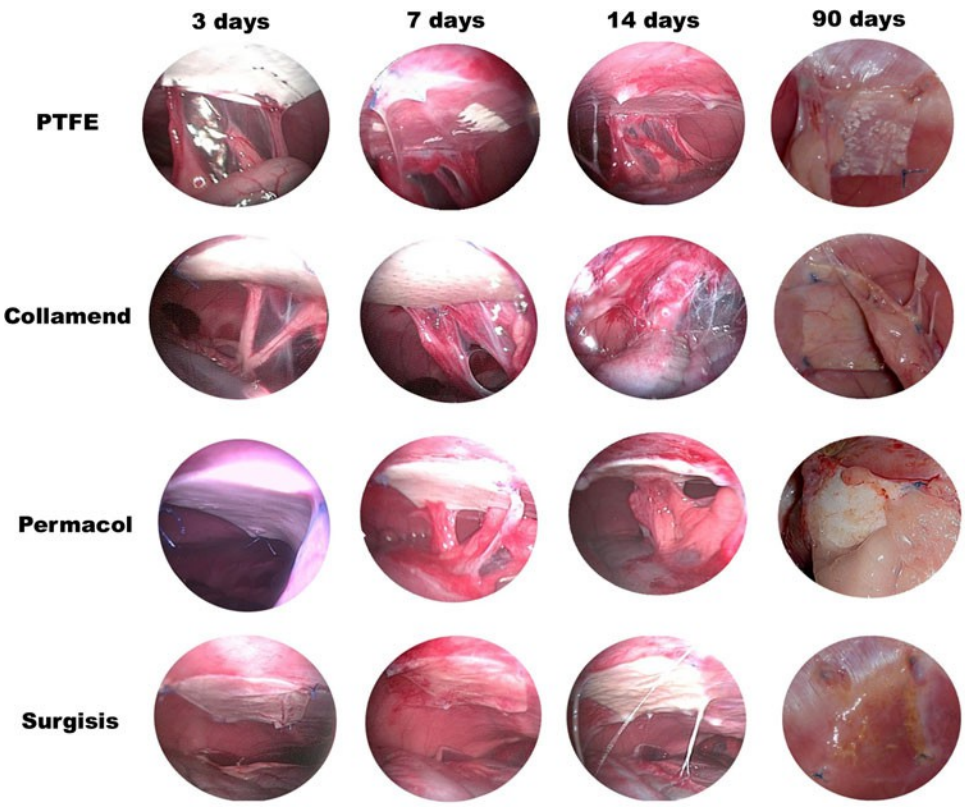


**Fig. 2** Sequential laparoscopic view of the adhesions formed to the meshes

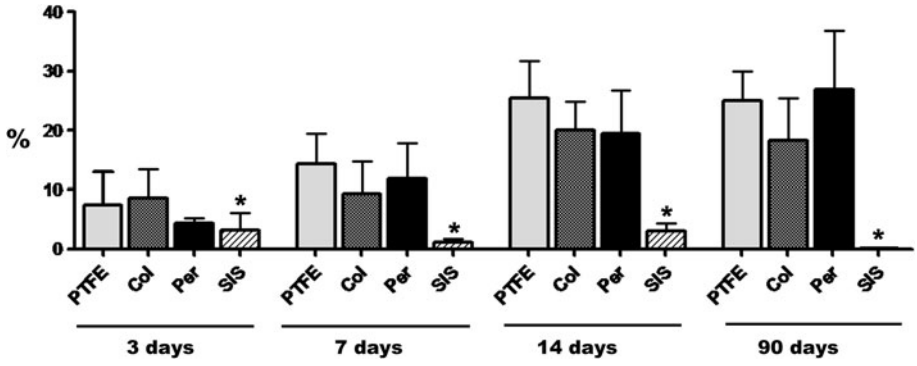


**Fig. 3** Mean percentage adhesion scores recorded in each study group (*$p < 0.05$). *Col* CollaMend, *Per* permacol, *SIS* surgisis

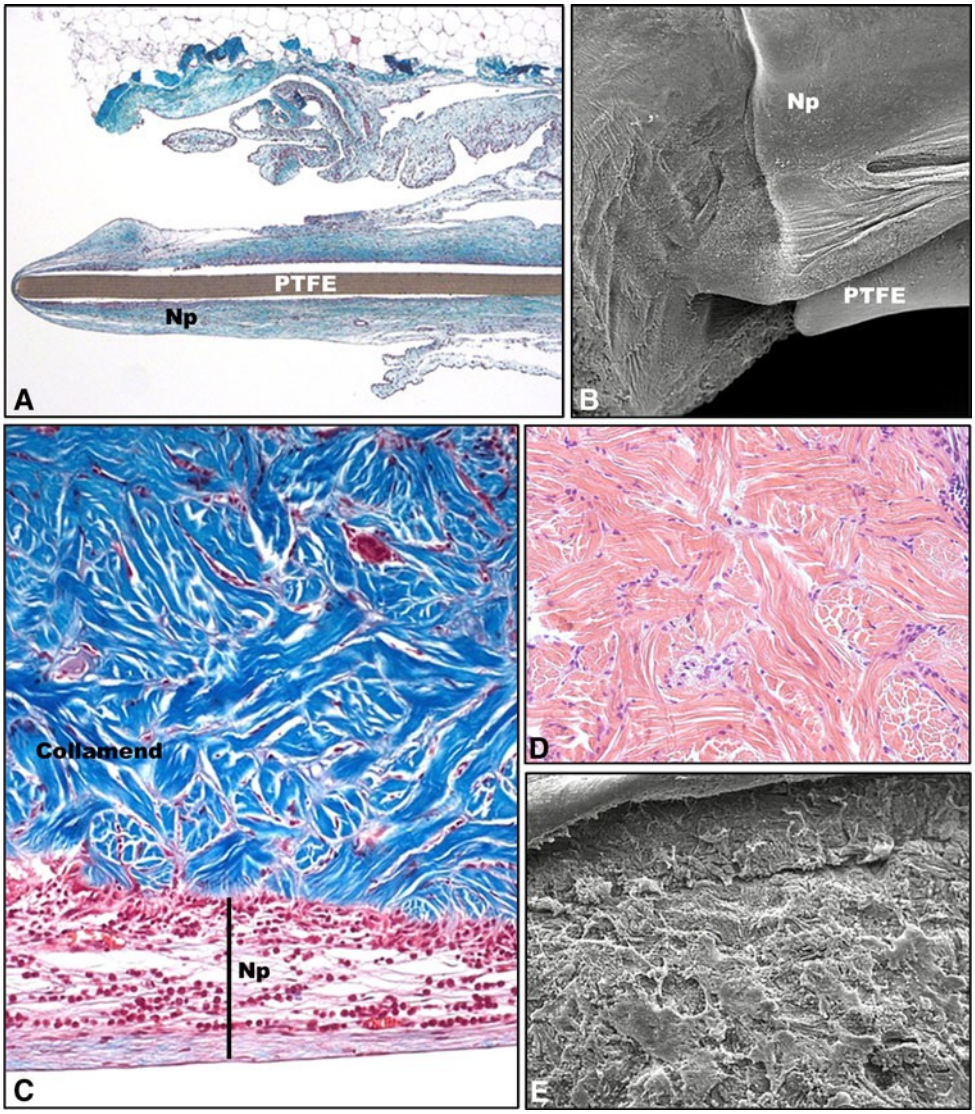


**Fig. 4** **A** Panoramic view of a PTFE mesh (×50). **B** SEM micrograph of PTFE showing cell migration from the peritoneum to the biomaterial (×20). **C** Photomicrograph of CollaMend showing the neoformed peritoneum (×200). **D** Detail showing cell infiltration inside the CollaMend (×400). **E** Panoramic view showing the CollaMend surface at the peritoneal interface (×500). *Np* neoperitoneum

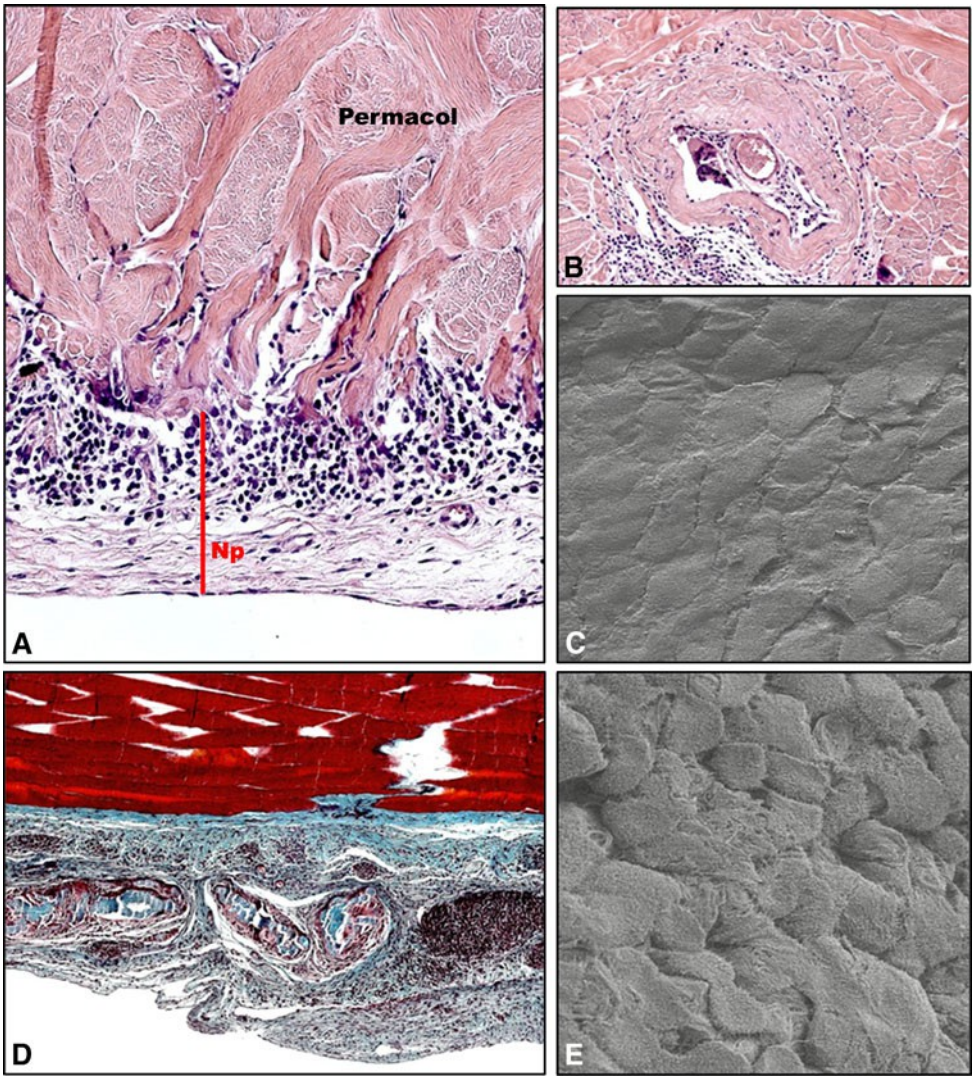


**Fig. 5** **A** Light microscopy image of Permacol showing neoformed tissue and cell ingrowth between the collagen bundles that comprise the prosthetic material (×200). **B** Small blood vessels forming inside the biomesh's natural pores (×200). **C** Mesothelium on Permacol (×500). **D** Connective tissue substituting for Surgisis showing the presence of granulomas corresponding to remains of the biomaterial (×100). **E** SEM micrograph of the mesothelium (×1000). *Np* neoperitoneum

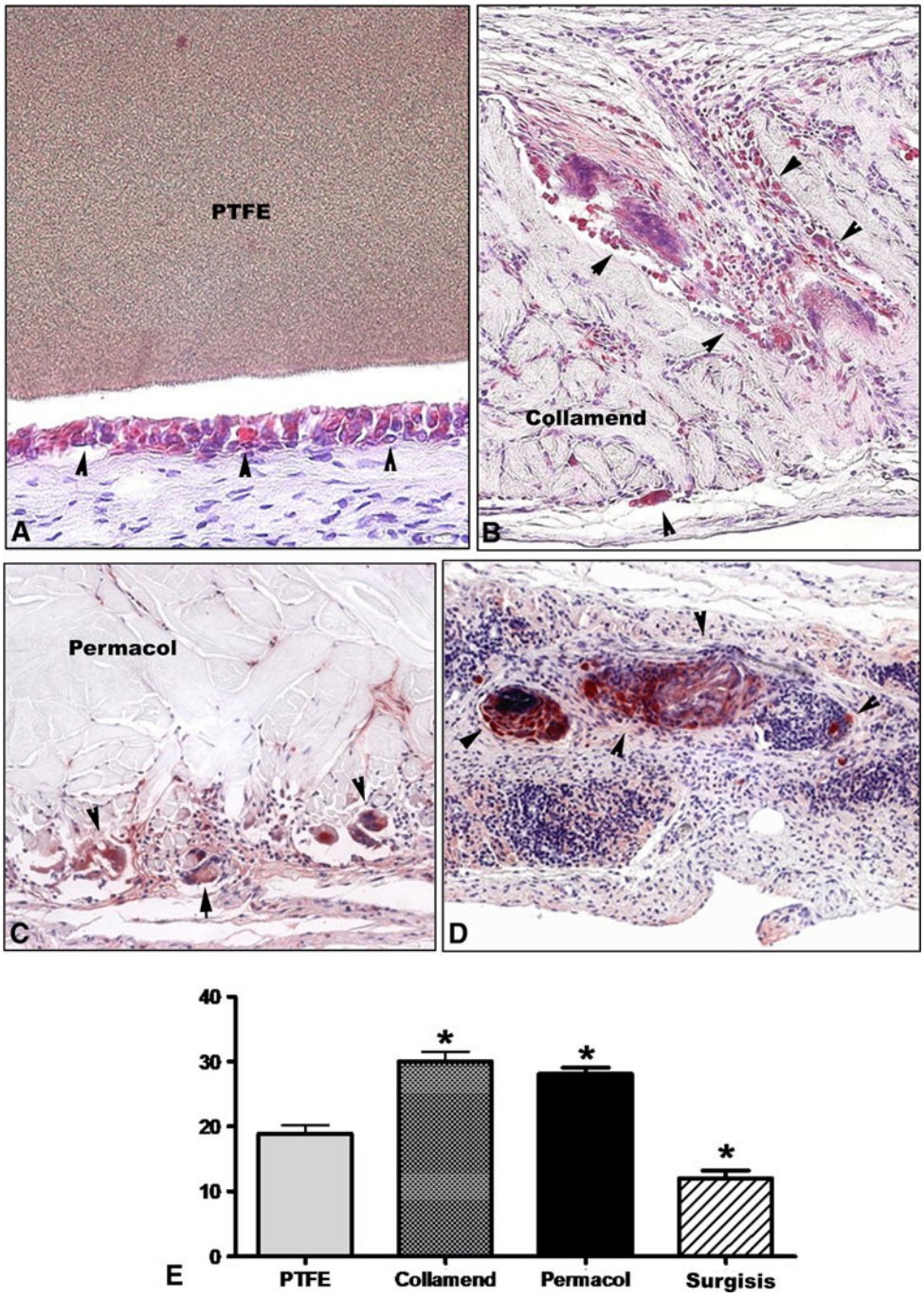


**Fig. 6** Immunohistochemical labeling of rabbit macrophages (*arrows*) using the RAM-11 monoclonal antibody. **A** PTFE (×400). **B** CollaMend (×200). **C** Permacol (×200). **D** Surgisis (×200). **E** Mean macrophage cell counts recorded for each study group indicating significant differences between the study groups (*$p < 0.05$)