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Comparison of host response to polypropylene and non-cross-linked porcine small intestine serosal-derived collagen implants in a rat model

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Objective To compare the host response, architectural integration and tensile strength of polypropylene and porcine small intestine submucosa-derived implants in a rat model.

Design Experimental study.

Setting Center for Surgical Technologies, Faculty of Medicine, Katholieke Universiteit Leuven, Belgium.

Sample Forty-eight adult male Wistar rats weighing 220–250 g randomised to receive either implant.

Methods Full thickness abdominal wall defects were primarily repaired with polypropylene mesh (Marlex) (MX group) or porcine small intestine submucosa (Surgisis) (SIS group). Animals were sacrificed at 7, 14, 30 and 90 days after implantation.

Main outcome measures The presence of herniation, infection and intra-peritoneal adhesions. Change in thickness and tensile strength of implant. Histopathological and immunohistochemical appearances of inflammatory response and collagen deposition.

Results Implants from the SIS group showed a short term increase in thickness in the first 14 days. Formation of adhesions was significantly more intense in the MX group at 30 days, and more extensive in the SIS group at 90 days. Tensile strength increased over time in both groups but was significantly lower in the SIS group than the MX group at 30 days. Implants in the MX group showed a more pronounced inflammatory response and more pronounced new vessel formation than the SIS group. Collagen formation was initially more fibrous and better organised in the MX group but became greater in the SIS group at 90 days.

Conclusions Biologically derived implant material induced a less pronounced inflammatory response and differences in collagen deposition. At 30 days tensile strength was weaker in the biological implant group but was equivalent by 90 days. These differences may have implications for the *in vivo* performance of the materials.

INTRODUCTION

About 35–50% of elderly women develop genital prolapse which is associated with urinary incontinence in up to 38% of cases.[1,2] Failure rates of primary surgery are high and 29% of women who have undergone surgery for prolapse will require re-intervention within 12 years.[2] Increasingly, surgical repairs are reinforced with different implant materials.[3–5] The 'ideal' implant should be biocompatible, sterile, non-carcinogenic, resistant to mechanical stress, affordable and available in a convenient format for clinical use. It should not provoke allergic or excessive inflammatory reactions, allow adequate collagen ingrowth and become well incorporated into the host tissue.[6,7] In reality no material fulfils all these criteria.

Synthetic materials such as polypropylene induce an intensive inflammatory response,[8,9] which may be responsible for poor tissue compatibility, and lead to adhesion formation, infection and other complications,[10] such as dyspareunia, pain, bladder dysfunction, stone formation and infection, bowel obstruction and abdominal pain.[11]

There are newer implant materials derived from biological sources available, one of which is porcine small intestine submucosa (SIS)-derived, non-cross-linked collagen matrix, marketed as SIS (Cook, Strombeek-Bever, Belgium). Experimental studies repairing abdominal wall defects in dogs and rats showed that SIS provides a strong

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repair but is replaced by organised collagen within four months, with long term results up to two years.[12–15]

We have conducted an experimental study to document the early inflammatory response and integration of SIS implants compared with a commercially available polypropylene mesh (Marlex, CR Bard, Haasrode, Belgium).[16–18] We used the previously described rat model for reconstruction of full thickness abdominal wall defects.[19,20]

MATERIALS AND METHODS

Marlex is a synthetic monofilament polypropylene fabric with a pore size of minimum 190 μm[21] and is classified as a type I, macroporous implant.[10] It is not degradable. Surgisis is a xenograft of porcine origin prepared as follows. In specially raised market-weight (118 kg) pigs, the small intestine is harvested immediately after euthanasia. The superficial mucosal and abluminal muscular layers and serosa are surgically removed, leaving an 80-μm-thick layer of tunica submucosa with basal layers of the tunica mucosa. This small intestinal submucosa (SIS) is treated with 0.1% paracetic acid and rinsed in hypotonic saline to lyse all remaining cells. The resulting biomaterial is acellular. Individual sheets are subjected to vacuum compression to obtain a multilayered implant. After drying, it is sterilized with ethylene oxide to eliminate concerns for cell-borne pathogens.[14] It contains collagen types I, III and V and growth factors such as transforming growth factor-β (TGF-β) and basic fibroblast growth factor (b-FGF). TGF-β and b-FGF play an important role in the initiation and modulation of tissue repair and both target fibroblasts.[22] Prior to use, SIS is rehydrated in sterile saline for at least 3 minutes. In this study we used a four-layered preparation, which was the proposed product for pelvic floor reconstruction at the time of the experiment. Both sterile products were purchased via the hospital pharmacy and this study was performed independently from the two manufacturers.

Adult male Wistar rats weighing 220–250 g were used in this study. Animals were housed in the animal facility of the Faculty of Medicine of the Katholieke Universiteit of Leuven and treated in accordance with current national guidelines on animal welfare. The study was approved by the Ethics Committee for Animal Experimentation of the Faculty of Medicine of the KU Leuven. The rats were randomly divided into two treatment groups of 24 rats each to receive either a Marlex (MX group) or Surgisis implant (SIS group). Rats were anaesthetised with 2.5% isoflurane mask inhalation with oxygen (0.5 L/min). The abdomen was shaved, disinfected with povidone iodine (IsoBetadine; Astra Medica, Brussels, Belgium) and covered with sterile draping. A vertical midline skin incision was made and skin flaps were raised. A 1.5 × 3.0-cm longitudinal full-thickness defect was created in the left lateral anterior abdominal wall, using a grid. The defect, consisting of fascia, muscle, and peritoneum, was primarily repaired with either the polypropylene mesh or collagen matrix according to a randomisation table. The implant was trimmed to a fixed 2.0 × 3.5-cm using a second grid, thus oversizing the defect by 0.25 cm. Prior to repair, the initial thickness of the hydrated implant was measured with a digital micrometer (Quick Mini, Mitutoyo, Kawasaki, Japan) and noted. Then the implant was laid over the defect, by definition slightly overlapping the defect (overlay technique). It was fixed without tension to the abdominal wall by four non-absorbable polypropylene 4/0 sutures at its four corners, followed by a continuous polypropylene suture between the corners (Prolene, Ethicon, Dilbeek, Belgium).[23,24] Finally, subcutaneous tissues and skin were closed with interrupted or continuous resorbable 3/0 polyglactin (Vicryl, Ethicon).

Following recovery, rats were returned to their cages with free access to food and drinking. Animals were weekly clinically checked for local and systemic complications until euthanasia by intracardial injection of 1 mL of a mixture of embutramide 200 mg, mebezonium 50 mg and tetracaine hydrochloride 5 mg (T61; Hoechst Marion Roussel, Brussels, Belgium). From each group, six rats were sacrificed after 7, 14, 30 and 90 days, respectively. During necropsy, location and size of re-herniation (if any) were noted, as well as the presence of fluid collection, infection, erosion or other signs of rejection. Then almost the entire anterior abdominal wall was resected 'en bloc', including (1) the initial implant, (2) the interface and (3) a 1-cm border of neighbouring native tissue (the 'explant'). During resection, the presence of adhesions was quantified by extent and density and the organs connected by these, using a validated scoring system.[25] Extent was scored by area (%) of the implant surface covered by adhesions. The density of adhesions was graded on a scale of 0–III, where 0 = represents no adhesions; I = adhesions that can be easily separated; (I) = mild adhesions that are more difficult to separate; and III = dense adhesions which can only be surgically divided. Thickness of the implant at sacrifice was measured by three random measurements over the central area, and its mean was noted. From this the proportional change in thickness was calculated as Δ% thickness = (mean thickness at sacrifice − initial mean thickness)/initial mean thickness. Explants were then cut into three strips of at least 1 cm wide, perpendicular to the long axis of the animal. The first was cut in two pieces to be fixed in 6% formalin, and the second and third one were put in normal saline at room temperature for tensiometry, at the latest 10 hours after sacrifice. A tensiometer (Instron frame F-DM-H 4467, High Wycombe, England) was used running at a crosshead speed of 5 cm/min. The maximum load required to disrupt the strip and the location of breakage (either at the interface or within the implant) were recorded.[26] Due to the different physical characteristics of the implant materials used, blinding of the investigators was not possible.

Formalin-fixed explant specimens were embedded in paraffin and cut into 5-μm-thick slices in a longitudinal fashion, so that each slice would contain the implant, interface as

well as surrounding native tissue. Sections were stained with haematoxylin and eosin (H&E) and Movat stain.[27] The latter stains nuclei of the cells black, elastic fibres dark purple to black, collagen and reticular fibres yellow, muscular tissue red and the ground substance blue to bluish green. Microscopic evaluation on H&E stains was performed to quantify the presence of foreign body giant cells (FBGC), polymorphonuclear (PMN) and mononuclear (MN) cells and newly formed vessels. Five non-overlapping fields per slide were counted at a magnification ×400 by two investigators (M.K. & P.L.) using an Axioplan 40 microscope (Carl Zeiss, Oberkochen, Germany) and the average cell count calculated. Fields were randomly selected at the interface between implant and surrounding tissue. A scale was used analogous to that described by Badylak.[15,20] The organisation, composition and amount of collagen were assessed semi-quantitatively on Movat stains. The organisation of collagen was scored between totally disorganised to a well-organised scar tissue (0–3).[15] We supplemented this by a scale for its composition, ranging from absent (0), cellular (1), mixed (2), to a (nearly) acellular (3) collagen scar. Also the amount of collagen was ranked as absent (0), minimal (1), moderate (2) to abundant (3) (Table 1).

Immunohistochemical staining was determined with a primary monoclonal mouse ED1 antibody (1:50, Serotec, Kidlington, UK). This is binding a lysosomal membrane-antigen specific for rat macrophages/monocytes.[28] As a secondary antibody we used EnVision+TM System (Dako, Carpinteria, California, USA); these immunoglobulins are conjugated with a peroxidase-labeled polymer. Endogenous peroxidase activity was blocked during a 30-minute incubation period in 0.3% hydrogen peroxide/methanol. 3,3-Diaminobenzidine tetrahydrochloride (DAB) was used as chromogen for peroxidase activity. The counterstaining process was determined by haematoxylin and destaining with 1% HCl/ethanol. The amounts of positive stained macrophages/monocytes in each slide were counted by analysing five non-overlapping high power fields per slide at a magnification ×400. A descriptive categorical scoring system was used (0 = none, to 3 = power field dominated by macrophages).[20]

Results are reported using medians and interquartile ranges. Mann–Whitney *U* tests were used to assess differences between the two materials at each given time point. Kruskal–Wallis ANOVA, followed by Mann–Whitney *U* tests for pairwise comparisons, has been used to compare within each material the different time points. P values < 0.05 were considered as statistically significant. Bonferroni corrections were applied for the pairwise comparisons within each material. Because there was no evidence that distributions were asymmetrical, graphs were presented with means and confidence intervals. All analyses have been performed using Statistica (Statsoft, Tulsa, Oklahoma, USA).

Table 1. Histological scoring criteria during microscopic examination.

Cellular infiltration	**Score**			
	0	1	2	3
Foreign body giant cells[a]	0	1–5	6–10	>10
Polymorphonuclear cells[a]	0	1–5	6–10	>10
Mononuclear cells[a]	0	1–5	6–10	>10
Vascularity[a]	0	1–3	4–10	>10
Collagen deposition				
Organisation	Totally disorganised	Slightly organised	Moderately organised	Well organised
Composition	0	Cellular[b]	Mixed[c]	Collagen[d]
Amount	0	Mild	Moderate	Abundant

[a] Number per high power field.
[b] Blue.
[c] Blue and yellow.
[d] Yellow colour stains of connective tissues on Movat staining.

RESULTS

All animals had a normal post-operative recovery and none died during the study period. There was no evidence of herniation around or through the implant site. In seven animals in the SIS group at either 7 or 14 days, a fluid collection in the implant area was noted after incision of the skin over the implant at the time of necropsy. In two of them, accumulation of pus between the layers of the implant could be seen. On histology this corresponded to a purulent inflammatory reaction with architectural degradation of the material. Further observations in these two animals were excluded in the analysis of microscopy results below. In the five other ones, there was no such evidence of a purulent or granulomatous inflammatory response and they have been included in the analysis.

The data from macroscopic inspection are shown in Table 2. Implants in the SIS group were significantly thicker in the first 14 days, due to fluid accumulation, with a return to baseline thereafter. The MX implants increased less in thickness, but this change persisted. There was no difference in the grade of adhesions between groups, except at 30 days when it was higher in the MX treated group ($P = 0.004$). There was no difference in the extent of adhesion formation except at 90 days when SIS rats showed more adhesions ($P = 0.03$). Adhesions usually involved the omentum, but at seven days there were two animals with bowel adhesions and one with perisplenic adhesions in the SIS group, and eight with adhesions to the liver at different times in the MX group. Explants from the MX group showed a gradual, and at 30 days a significant ($P = 0.0065$) increase in tensile strength (Table 2 and Fig. 1). SIS explants had a comparable strength over the course of the experiment, but were significantly weaker than MX at 30 days ($P = 0.037$). MX explants always failed at the interface between mesh and tissue. In the SIS group, five explants (21%) ruptured through the material.

The microscopy results are shown in Table 3 and Fig. 2. There was a more pronounced inflammatory reaction (assessed by cell numbers) in the MX group than the SIS group over the entire study period. Animals where seroma formation developed had no different scores.

Data on newly formed vessels and collagen deposition are shown in Table 4 and Fig. 3. Active neo-vascularisation was occurred in both groups, but was more pronounced in the MX group at 90 days ($P = 0.02$). The rate of mature collagen formation was different between the two groups, but reached similar levels by 90 days. Within the MX group, the composition of collagen was more fibrous and better organised initially, but organisation was finally more orderly in the SIS group.

DISCUSSION

The present experimental study shows that SIS implants induce less dense adhesions, a less severe inflammatory reaction and a more orderly deposition of collagen than MX. After an initial period of decreased tensile strength at one

Table 2. Macroscopic appearance of implant site.

Days after implantation	Group	Delta thickness (mm)	Extent of adhesions (% of implant area)	Grade of adhesions (score)[25]	Tensile strength (N/cm)
7	MX	0.5 (0.1)*	48 (20)	1.8 (0.5)	7.5 (1.5)
	SIS	8.4 (6.0)	18 (25)	1.0 (0.5)	9.8 (9.1)
14	MX	0.5 (0.2)*	28 (15)	1.5 (0.5)	7.3 (2.1)
	SIS	5.0 (1.3)	35 (50)	1.5 (0.5)	8.5 (3.4)
30	MX	0.5 (0.1)*	20 (20)	2.0 (1.5)*	13.7 (3.7)*
	SIS	−0.2 (0.5)	5 (5)	0.5 (0.0)	6.1 (6.1)
90	MX	0.7 (0.1)*	18 (10)*	1.0 (1.5)	19.6 (4.9)
	SIS	0 (0.2)	48 (30)	1.3 (0.5)	13.3 (6.1)

Data are presented as medians and interquartile range, and rounded to one decimal place for clarity. There were six animals in each group at each time point.
* $P < 0.05$ MX *versus* SIS.

Table 3. Microscopy results.

Days after implantation	Group	Foreign body giant cells	Polymorphonuclear cells	Mononuclear cells
7	MX	0.8 (0.2)*	2.2 (0.6)*	1.0 (0.2)*
	SIS	0 (0)	2.6 (0.2)	0.1 (0.4)
14	MX	0.6 (0.2)*	2.4 (0.6)*	1.6 (0.8)
	SIS	0.1 (0.3)	0.6 (0.1)	1.2 (1.1)
30	MX	0.8 (0.4)*	2.7 (0.8)*	2.4 (0.2)
	SIS	0.3 (0.4)	0.4 (0)	2.2 (1.6)
90	MX	0.8 (0)*	1.2 (0.4)*	1.3 (0.2)
	SIS	0.1 (0.2)	0.4 (0.4)	1.3 (1.0)

Six animals per group at each time point, except for 14 days SIS group (four animals).
Data are given as medians and interquartile ranges of average cell count per high-powered field.
* $P < 0.05$ MX *versus* SIS.

Table 4. Vessel formation and collagen deposition.

Days after implantation	**Group**	**Vascularity**	**Collagen**		
			Amount	Composition	Organisation
7	MX	1.2 (0.6)*	1.5 (0.6)*	1.4 (0.4)*	0.6 (0.6)
	SIS	0.4 (0.4)	0.1 (0.2)	0.9 (0.1)	0.4 (0.4)
14	MX	2.0 (0.2)	2.0 (0.4)*	2.2 (0.3)*	1.4 (0.3)*
	SIS	1.8 (0.7)	0.8 (0.4)	0.7 (0.2)	0.6 (0.4)
30	MX	2.1 (0.6)*	2.2 (0.1)*	2.2 (0.4)*	2.0 (0.2)*
	SIS	2.7 (0.4)	1.4 (0)	1.0 (0)	1.3 (0.2)
90	MX	2.6 (0.2)*	2.4 (0.4)	2.5 (0.4)	2.1 (0.2)*
	SIS	1.7 (0.8)	2.5 (0.2)	2.6 (0)	2.4 (0.2)

Six animals per group at each time point, except for 14 days SIS group (four animals).
Data are given as medians and interquartile ranges, of average vessel count per high-powered field, and the scoring system for collagen (Table 1).
* $P < 0.05$ MX *versus* SIS.

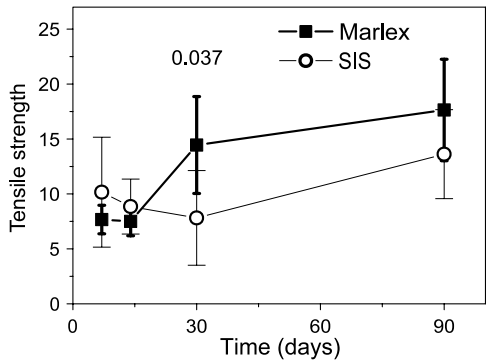

Fig. 1. Graphic representation of the data presented in Table 2. Tensile strength measured in N/cm for Marlex *versus* SIS over time; mean ± 0.95 confidence intervals, $P < 0.05$ mentioned as statistically significant (*x*-axis represents a proportionate scale of time).

month, both implant materials have comparable strength at 90 days. SIS induced a similar amount, but less dense type of adhesions, in accordance with previous studies.[12] The lower density of adhesions may be directly related to a less severe inflammatory reaction, a known determinant of adhesion formation.[10,29]

The two products caused different local fluid shifts during the post-operative period. At explantation, MX explants were 50% thicker than prior to implantation at all time points. This increase in thickness may represent a well-described severe and persistent chronic inflammatory process.[30,31] Initially SIS implants accumulated large amounts of fluid between the different layers of the product, causing formation of a seroma.[32] This may be related to the absence of pores in the material and/or ingrowth of new vessels. Fluid accumulation disappeared in SIS implants after a month. MX explants were free of fluid collections.

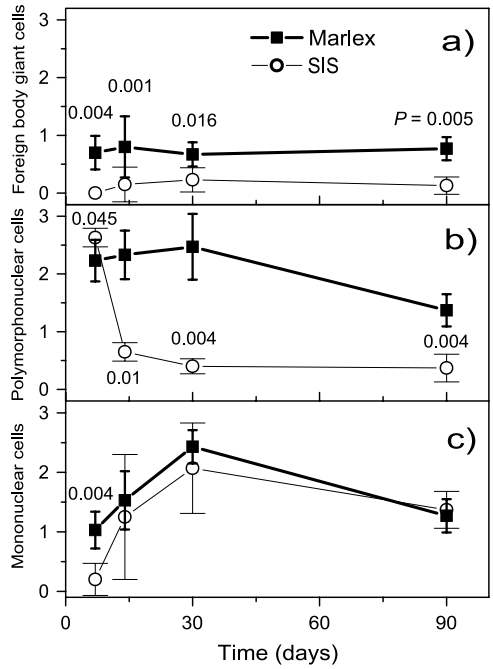

Fig. 2. Graphic representation of the data presented in Table 3. Scores for (a) foreign body giant cells, (b) polymorphonuclear cells, (c) mononuclear cells for Marlex *versus* SIS over time; mean ± 0.95 confidence intervals, $P < 0.05$ mentioned as statistically significant (*x*-axis represents a proportionate scale of time).

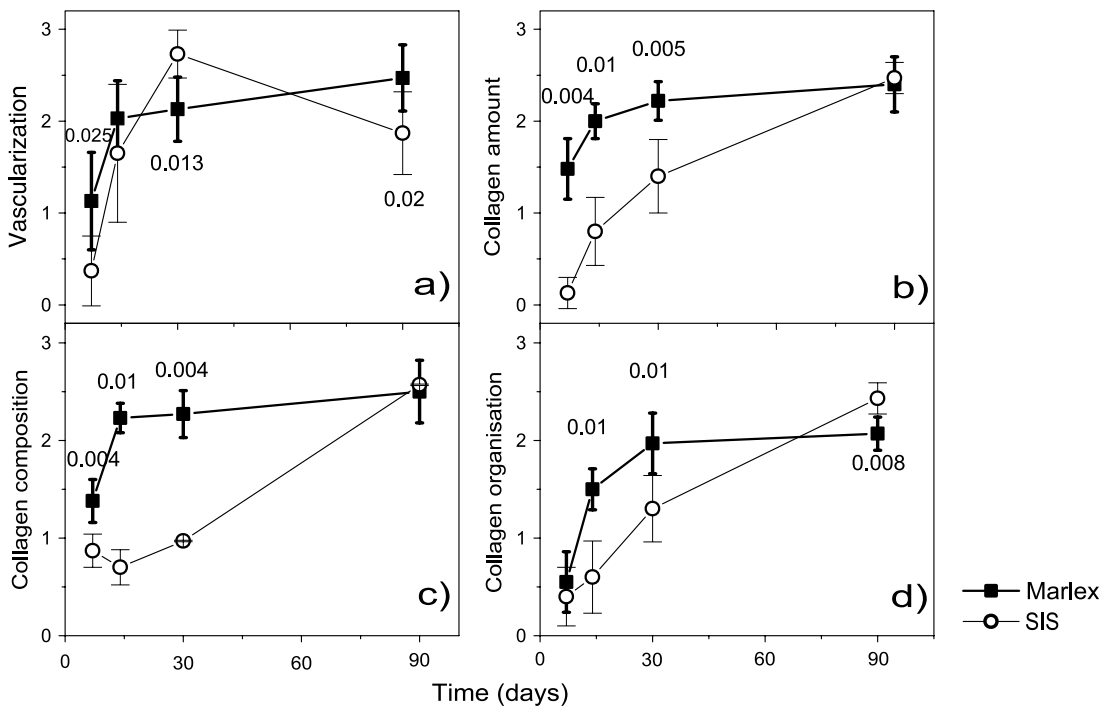

Fig. 3. Graphic representation of the data presented in Table 4. Scores for (a) vascularisation, (b) amount, (c) composition and (d) organisation of collagen for Marlex *versus* SIS over time; mean ± 0.95 confidence intervals, $P < 0.05$ mentioned as statistically significant (*x*-axis represents a proportionate scale of time).

Explants from the SIS group were weaker than those from the MX group at 30 days. At 90 days, two-thirds of the SIS group explants ruptured through the material, indicating that the implant was weaker than the interface with normal tissue. In contrast, MX explants always tore at the level of interface, as observed previously.[33] There was also concern about the values obtained during tensiometry in SIS explants. A level of 16 N/cm is often claimed to be clinically relevant, as this would be the minimal force to which the abdominal wall is exposed.[34] SIS explants always failed before this theoretical level was reached. The clinical relevance of this observation remains uncertain, and the absence of reherniation in this study is not completely reassuring in this respect. The rat model does not have high intra-abdominal pressures, and may actually not be a good model for reherniation.

In our study, SIS caused a very mild inflammatory response, confirming the low immunogenicity reported by others.[35–37] The weak inflammation process was also reflected in a slower and different process of collagen deposition than around MX implants. This slow collagen deposition coincides with the previously mentioned changes in strength of the material.[14,38] Ninety percent of the SIS material degrades four weeks after implantation, and is replaced by an infiltrate of macrophages and only later on by a stronger scar tissue with deposition of novel collagen. This is much different from other cross-linked porcine dermal collagens, which become encapsulated.[20] In contrast, MX implants caused an immediate and vigorous inflammatory response, with a faster and more marked connective tissue production and increased tensile strength at an early stage.[4,12,39–41]

In order to tackle the early, but transient relative weakness of SIS implants one can increase the number of layers in the SIS implant (as is currently done in the marketed eight-layer version of the product). This may certainly make the implant more resistant to physical forces, but also has some disadvantages, in terms of seroma formation and as a consequence the potential for infectious sequelae.

In summary, SIS induced a less pronounced inflammatory reaction, less dense adhesions and an architecturally better collagen organisation than MX. SIS shows an obvious transient weakness in tensile strength at 30 days compared with MX but this difference does not persist.

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