ANIMAL STUDY SERIES IN BIORESORBABLE TECHNOLOGY

Evaluation of a Bioresorbable Polylactide Sheet for the Reduction of Soft Tissue Attachment in a Porcine Pelvic Animal Model

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ABSTRACT

As a means to characterize the additional benefits of minimizing soft tissue attachment (STA) to a bioresorbable sheet following soft tissue repair, an animal study was conducted to focus exclusively on minimizing STA without a soft tissue defect. A large animal (porcine) model was used to evaluate the formation of undesirable STA in a female pelvic surgery model. Through a midline incision using a transperitoneal laparotomy, the bladder and uterus of the porcine were abraded. Two survival periods were used to compare groups with no treatment (control) or treatment with a thin bioresorbable sheet intended to minimize STA. Two bioresorbable sheets were placed within each treatment specimen: one between the bladder and the abdominal wall, and the second between the bladder and the uterus. After the 4-week and 12-week survival periods, the severity and location of STA to the sheet was assessed using a zero to three-point scale. The resorbable sheet was found to provide an effective barrier between the anatomical structures in question and to reduce the interaction of soft tissue to the device observed between the treated and the control groups.

INTRODUCTION

There are two major product categories utilized to address the problems associated with uncontrolled postsurgical healing. One group of products performs at the tissue level and the other group of products performs at the cellular level.

The SurgiWrap® Bioresorbable Sheet performs at the tissue level and is regulated by the United States Food and Drug Administration (FDA) as a Surgical Mesh. The SurgiWrap® sheet is utilized to reinforce soft tissues and minimize STA to the device (sheet) in case of contact with the surrounding viscera. The SurgiWrap® sheet creates a physical barrier between healing tissues, thereby minimizing undesired tissue attachments immediately adjacent to the sheet.

Unlike SurgiWrap®, resorbable adhesion barrier products perform at the cellular level without the additional benefit of reinforcing soft tissues. Typically of a gelatinous or semi-solid consistency, these products attempt to retard uncontrolled healing by interacting with various cellular functions. Problems associated with these types of gelatinous adhesion barrier products include difficulty in placement or repositioning and difficulty in localizing to a specific anatomical region (Vrijland, 2002); potential interference with the normal healing process, causing delayed healing at the site or of the external wound (Hieb, 2001), which may lead to increased risk of infection at the surgical site (Van Goor, 2003). Uncontrollable migration throughout the anatomic region may indiscriminately retard the healing of both desirable and undesirable tissues.

As a solid sheet, the SurgiWrap® device is not susceptible to the same undesirable clinical sequelae associated with gelatinous products.

Following laparotomy, STA in the pelvic region is associated with several postoperative complications including pelvic pain (Sulaiman, 2001; Howard, 2003), fertility impairment (Tulandi, 1990; Vrijland, 2002), and bowel obstruction (Ellis, 1999; Al-Took, 1999; Montz, 1994; Menzies, 1990). Upon abdominal cavity re-entry, dissection through undesirable STAs can lead to intraoperative complications, prolonged operative time (Ellis, 1997; Van Der Krabben, 2000), and higher costs associated with the procedure (Ivarsson, 1998).

Table 1. **Study Design**

Groups	4 Week Survival	12 Week Survival
1: Control	n=4	n=6
2: Treated with 0.02 mm bioresorbable sheet	n=4	n=5

Many different types of materials have been used to prevent or minimize postoperative STA after pelvic surgery. Materials studied include oxidized regenerated cellulose (Shimanuki, 1987; Rice, 1993), chemically modified composition of sodium hyaluronate and carboxymethylcellulose (Burns, 1996), expanded polytetraflouroethylene (Haney, 1998), silicon (Yemini, 1984), pharmceutical agents (Fukasawa, 1991; Yoldermir et al., 2002), and in-situ polymerized hydrogels (Hill-West, 1995). Also, a variety of animal models have been used in these studies including:

- Mouse (Haney, 1995 & 1998)
- Rat (Muller, 2003; Yoldermir et al., 2002; Elbert, 1998; Herslag, 1991)
- Rabbit (Wiseman, 1994; Linsky, 1987; Yemini, 1984)
- Dog (Montz, 1990)
- Pig (Montz, 1994)

In this investigation, a porcine model of pelvic surgery was used to assess soft tissue interactions employing a transperitoneal laparotomy approach. The goal of the study was to evaluate the effectiveness of a treatment consisting of a bioresorbable polymer sheet (SurgiWrap®) compared with no treatment (Control) on the formation of STAs between the pelvic contents immediately adjacent to the sheet.

MATERIALS AND METHODS

Study Design

Adult female porcine (60 kg) were used in accordance with institutional ethics approval. Animals were allocated to either a Control group or to the treatment group; both groups included two survival periods (four and twelve week). The treatment group consisted of a 0.02mm thick polylactide bioresorbable sheet (SurgiWrap®, MAST Biosurgery, San Diego, CA) with dimensions of 130mm by 200mm. The sheets were placed between the abdominal wall and the bladder and between the bladder and the uterus. The SurgiWrap Bioresorbable Sheet is an amorphous copolymer of poly(L-lactide-co-D,L-lactide) sterilized by electron-beam irradiation. A minimum of 4 animals was used in each group and for each survival period. The specific number of animals used in each group is summarized in Table 1.

Surgical Procedure

Anesthesia was induced with intramuscular injection of Ketamine (10-15 mg/kg, Parnell Laboratories, Sydney, Australia), followed by spraying of the vocal chords with lignocaine and endotracheal intubation. Anesthesia was maintained with halothane and oxygen. Temgesic (0.324 mg Buprenorphine IM, Schering Plough Pty Ltd, North Ryde, Australia) was used for analgesia prior to the start of the surgical procedure. Intravenous Keflin (1 g Cephalozin IV, Eli Lily, Rome, Italy) was used for antibiotic prophylaxis. The animal was positioned supine, the operative site was marked, and

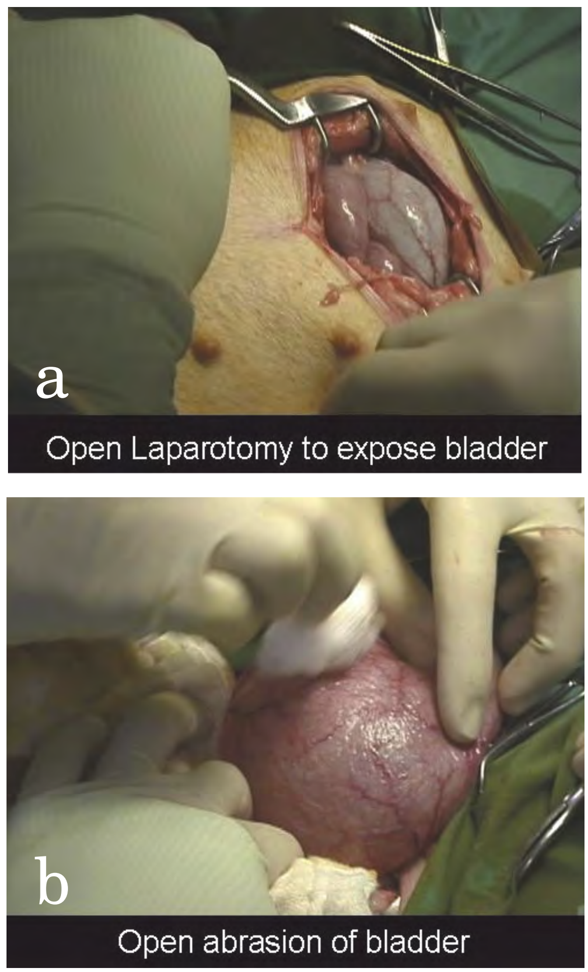

Figure 1.
Photograph of surgical technique illustrating the (a) laparotomy, (b) the abrasion to the bladder. The uterus (located dorsal to the bladder) was also abraded with 30 controlled strokes.

TABLE 2. **Soft Tissue Interactions Between Various Anatomic Structures of the Female Porcine Pelvis**

Location of Soft Tissue Attachment			Weeks Postoperative	
			4 weeks	12 weeks
Abdominal Wall	AND	Bladder	■	■
Abdominal Wall	AND	Large Intestine	■	■
Abdominal Wall	AND	Small Intestine	■	■
Bladder	AND	Uterus	■	■
Bladder	AND	Left Fallopian Tube	■	■
Bladder	AND	Right Fallopian Tube	■	■
Bladder	AND	Large Intestine	■	■
Bladder	AND	Small Intestine	■	■

the skin prepped and draped in a sterile manner. All surgeons used powder free gloves.

A 3cm midline skin incision was made with a #10 scalpel blade followed by blunt dissection to divide the soft tissues.

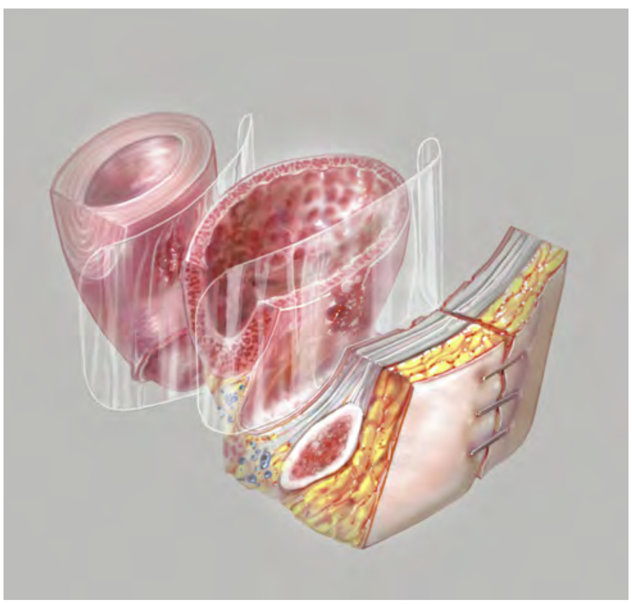

FIGURE 2.
Illustration showing placement strategy for bioresorbable polylactide sheet.

The bladder was delivered and was abraded using 30 controlled firm strokes with a 4 by 4 gauze. The uterus was also abraded deep in the peritoneal cavity with 30 controlled strokes (Figure 1). Finally, the peritoneal space was infused with 50 ml of cold sterile saline. The deep soft tissues were repositioned and the fascia and skin closed in layers with 3-0 Dexon (Davis and Geck, North Ryde, NSW).

Treatments

No material was used in the Control group of animals. The treated groups received two 0.02mm bioresorbable sheets; one between the bladder and the uterus followed by a separate sheet placed between the bladder and the abdominal wall (as shown in Figure 2). No suture was used to fix either piece of sheet in place. No drains were used for either the control or the treated animals.

Recovery

Animals were recovered and monitored daily during the first seven postoperative days. All porcine received postoperative analgesia as required (0.324 mg Buprenorphine IM, Schering Plough Pty Ltd, North Ryde, Australia). The pigs were housed in individual pens for the survival period of the study. They were humanely euthanized at 4 or 12 weeks postoperatively with a lethal dose of sodium pentothal (Lethobarb, Virbac Australia Pty Ltd, Sydney, Australia) administered via an ear vein.

Macroscopic Grading of Soft Tissue Interactions

The original incision was identified prior to a dissection of the surgical site. A U-shaped incision was created surrounding the original midline incision. Careful dissection was performed to allow assessment of the STAs in the pelvic region. Table 2 was used to assess the soft tissue interactions between the various anatomic structures immediately adjacent to the sheet.

A graded scale ranging from zero to three (0 to 3) was used to assess STA in the pelvic region where:

- 0 = none
- 1 = sparse to infrequent, can easily be dissected manually (quantity 4)
- 2 = frequent, requires difficult manual dissection, or light sharp dissection, (quantity > 4)
- 3 = numerous, requires sharp dissection, very difficult to dissect (not focal but disperse)

The dissections of each animal were graded separately by four independent reviewers, who were blinded to the treatment group and to the scoring results from the other reviewers and who did not perform the initial surgery. STA scores were assigned using the scale described (0-1-2-3) at 8 separate locations, as summarized in Table 2. At the 4-week survival time, it was possible to find remnants of the resorbable sheet at the operative site. At the 12-week survival time, the sheet was difficult to observe and locate macroscopically but it was possible to palpate regions where the sheet was present.

Data analysis included determining the mean and standard deviations for each soft tissue interaction (each cell in the Table 2) for all animals within a group and time period and each of four independent assessments. All interactions with each anatomic structure were compiled and a non-parametric comparison between the groups was performed using the Kruskal-Wallis test (Rosner, 1986). A p-value less than or equal to 0.05 was considered statistically significant. Comparison of the pooled data for anatomical structures was also conducted comparing the two treatments at each survival time, and between the two survival periods (Kruskal-Wallis test). SPSS statistical software was used to perform all data analysis (SPSS, Inc., Chicago IL).

Results

Surgery

There were no operative or postoperative complications. Specifically, there was no evidence of wound infection, wound dehiscence, hemodynamic compromise, or respiratory/gastrointestinal complications in any animal. Placement and manipulation of the polylactide sheet was easily achieved during surgery. The sheet did not crack or break during manipulation between the soft tissues. The sheet could be removed or repositioned if the placement was not satisfactory.

All animals recovered well from the procedure and were standing and drinking within a few hours, and mobilized and eating by the first postoperative day. Postoperative analgesia was not required beyond the first postoperative day. All wounds were observed to be macroscopically well healed after the 4- and 12-week survival periods.

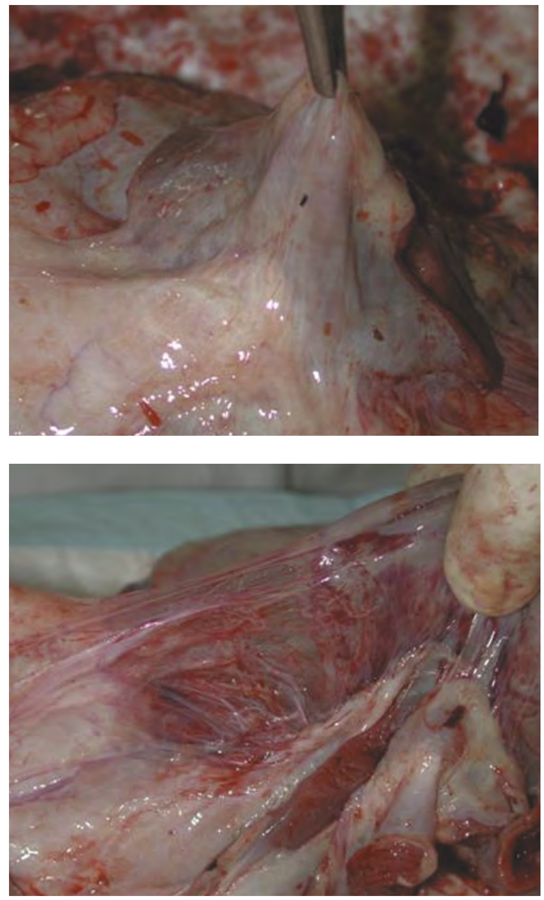

FIGURE 3.
Gross photograph of control specimen – the STAs were thick and tenacious and the score was 3 for most anatomic regions shown on the soft tissue attachment grading matrix.

Soft Tissue Attachment Formation

In general, gross, tenacious and undesireable STAs were noted in the Control group and typical examples are shown in Figure 3. The treated animals had fewer tissue attachments to the sheet at the specific sites where the resorbable sheet was placed as

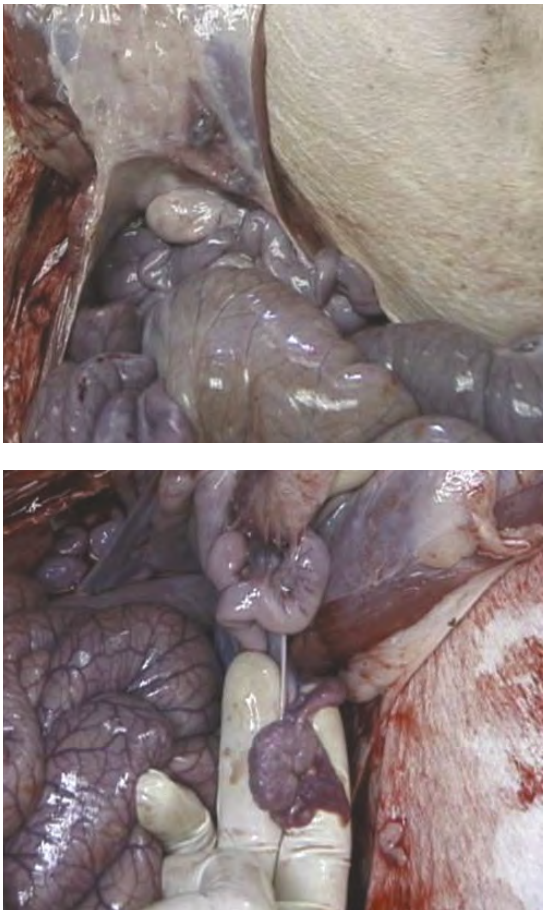

FIGURE 4.
Gross photograph of treated specimen – there were fewer STAs throughout the specimen.

shown in Figure 4 and appeared to have fewer tissue attachments in general during macroscopic dissection.

For clinical relevance, the STA scores were examined at each of the 8 specific locations (Table 2), with focus directed toward tissue attachments to the sheet that occurred involving important gynecological structures (for example, the fallopian tubes, and uterus). For this analysis, the scores from all reviewers and all animals within a treatment group were tabulated at each location; the 4-week and 12-week data were considered separately. The mean values for soft tissue interactions between the specific anatomic structures for the 4-week survival period are summarized in Table 3 and the mean values for the 12-week survival period are summarized in Table 4. Significant differences ($p<0.05$) between the Control and treated groups are identified in shaded boxes.

Soft Tissue Interaction Observations – 4-Week Time Period

After 4 weeks, soft tissue interaction was observed in all 8 locations for the Control animals (100% of locations), whereas in the device treated animals, STAs were observed in only 4 of 8 of the locations (50% of locations) as summarized in Table 3. The average scores for the sheet treated animals were less than the average of the Control animals at each location.

In the 4-week Control animals, the maximum average location score was 2.88 (for the abdominal wall-bladder location), followed by an average score of 2.06 (bladder – right fallopian tube). Overall, in 3 locations the average score ranged from 2-3 (frequent to numerous STAs), in 4 locations the average score ranged from 1-2 (sparse to frequent STAs), and in 1 location the average scores ranged from 0-1 (none to sparse STAs).

In the 4-week sheet treated animals, the maximum average location score was only 0.88 (for the bladder-right fallopian tube location), followed by an average score of 0.75 (in two locations, abdominal wall-bladder, and bladder-uterus). Overall, in all 8 locations the average score ranged from 0-1 (none to sparse STAs).

Soft Tissue Interaction Observations – 12-Week Time Period

After 12 weeks, STA was observed in 6 of 8 locations for the Control animals (75% of locations), whereas in the sheet treated animals STAs were observed in only 4 of 8 of the locations (50% of locations) as summarized in Table 4. The average scores for the sheet treated animals were less than or equal to the average of the Control animals at each location. At 2 locations the treated and control scores were 0 for all observations.

In the 12-week Control animals, the maximum average location score was 2.1 (for the bladder – right fallopian tube location), followed by an average score of 1.9 (for the bladder-left fallopian tube). Overall, in 1 location the average score was in the range of 2-3 (frequent to numerous STAs), in 3 locations the average score ranged from 1-2 (sparse to frequent STAs), in 4 locations the average scores ranged from 0-1 (none to sparse STAs), and there were no STAs in 2 locations.

In the 12-week sheet treated animals, the maximum average location score was 0.42 (for the bladder–right

Table 3. **4-Week Soft Tissue Interaction Scores**

Location of Soft Tissue Attachment				Mean Independant Reviewer Scores (All animals pooled) (scale = 0 – 3)	
				Mean of All 4 Reviewers*	Standard Deviation (between animals)
Abdominal Wall	AND	Bladder		2.88	0.34
				0.75	0.68
Abdominal Wall	AND	Large Intestine		1.94	1.39
				0	0
Abdominal Wall	AND	Small Intestine		1.88	1.50
				0	0
Bladder	AND	Uterus		0.88	1.36
				0.75	0.68
Bladder	AND	Left Fallopian Tube		2.00	1.26
				0.50	0.63
Bladder	AND	Right Fallopian Tube		2.06	1.29
				0.88	1.09
Bladder	AND	Large Intestine		1.13	1.50
				0	0
Bladder	AND	Small Intestine		1.06	1.44
				0	0

*The control score is over the treated score. Shaded boxes indicate statistically significant differences

Table 4. **12-Week Soft Tissue Interaction Scores**

Location of Soft Tissue Attachment				Mean Independant Reviewer Scores (All animals pooled) (scale = 0 – 3)	
				Mean of All 4 Reviewers*	Standard Deviation (between animals)
Abdominal Wall	AND	Bladder		1.05	1.23
				0.08	0.28
Abdominal Wall	AND	Large Intestine		0.75	1.21
				0	0
Abdominal Wall	AND	Small Intestine		0.30	0.92
				0	0
				0.29	0.62
Bladder	AND	Left Fallopian Tube		1.90	1.33
				0.25	0.61
Bladder	AND	Right Fallopian Tube		2.10	1.17
				0.42	0.97
Bladder	AND	Large Intestine		0	0
				0	0
Bladder	AND	Small Intestine		0	0
				0	0

*The control score is over the treated score. Shaded boxes indicate statistically significant differences

Table 5. **Mean Cumulative Soft Tissue Interaction Scores at the Abdominal Wall, Bladder and Total Combined Soft Tissue Interactions.**

Location of Soft Tissue Attachment	Weeks Postoperative			
	4 weeks		12 weeks	
	Control	Treated	Control	Treated
Abdominal Wall	6.69 (2.60)	0.75 (0.68)	2.10 (1.02)	0.08 (0.28)
Bladder	7.13 (4.49)	2.13 (1.86)	5.50 (3.50)	0.96 (1.46)
	Total Combined Soft Tissue Attachment			
Abdominal Wall and Bladder	13.83 (6.76)	2.88 (1.71)	7.60 (3.47)	1.04 (1.43)

Numbers in parenthesis represent standard deviation

fallopian tube), followed by an average score of 0.29 (bladder – uterus). Overall, in each of the 8 locations the average score ranged from 0-1 (none to sparse STAs).

Soft Tissue Interaction Observations – Anatomic Structures

The numeric data summarized in Tables 3 and 4 was compared relative to the total soft tissue interactions affecting specific pelvic anatomic structures and is summarized in Table 5. The mean and standard deviations were computed for any interaction with each of the specific anatomic structures. The Kruskal-Wallis non-parametric comparison (Rosner 1986) was used to determine any significant differences between the treatment groups at each of the two time points.

Abdominal Wall (Table 5 and Figure 5)

The mean STA score at the abdominal wall for the 4-week Control animals was 6.69 (standard deviation of 2.60) and for the sheet treated animals after 4 weeks, the mean soft tissue interaction score was 0.75 (standard deviation of 0.68). After 12 weeks, the Control animals had a mean score of 2.10 (standard deviation of 1.02) while the sheet treated animals at 12 weeks had a mean score of 0.08 (standard deviation of 0.28). The results of the abdominal wall STA scores are summarized in Figure 5. Statistically significant differences between the Control and SurgiWrap® treated groups are identified with a green bar.

Bladder (Table 5 and Figure 6)

The mean STA score at the bladder for the 4-week Control animals was 7.13 (standard deviation of 4.49) and for the sheet treated animals after 4 weeks, the mean STA score was 2.13 (standard deviation of 1.86). After 12 weeks, the Control animals had a mean score of 5.5 (standard deviation of 3.50) while the sheet treated animals at 12 weeks had a mean score of 0.96 (standard deviation of 1.46). The results of the bladder STA scores are summarized in Figure 6. Statistically significant differences between the Control and SurgiWrap® treated groups are identified with a green bar.

Total Mean Soft Tissue Interaction (Table 5 and Figure 7)

For the total combined STA scores, the mean value for the 4-week Control animals was 13.83 (standard deviation of 6.76) and for the sheet treated animals after 4 weeks, the mean STA score was 2.88 (standard deviation of 1.71). After 12 weeks, the Control animals had a mean score of 7.60 (standard deviation of 3.47) while the sheet treated animals at 12 weeks had a mean score of 1.04 (standard deviation of 1.43). The results of the combined total STA scores are summarized in Figure 7. Statistically significant differences between the Control and SurgiWrap® treated groups are identified with a green bar.

DISCUSSION

Preventing or limiting indiscriminate STAs following surgery has significant clinical and revision surgery implications. Undesireable STAs may be reduced or controlled through several possible mechanisms: reduction of the initial inflammatory response and subsequent exudation; inhibition of coagulation, promoting of fibrinolysis; mechanical separation of peritoneal surfaces; and inhibition of fibroblastic proliferation (Hill-West, 1995). Current techniques used to prevent the formation of postsurgical STAs have had limited success. The use of an off-the-shelf biomaterial which does not complicate the surgical procedure or impede healing while controlling the formation of postsurgical STAs would be a significant achievement. The ideal material would

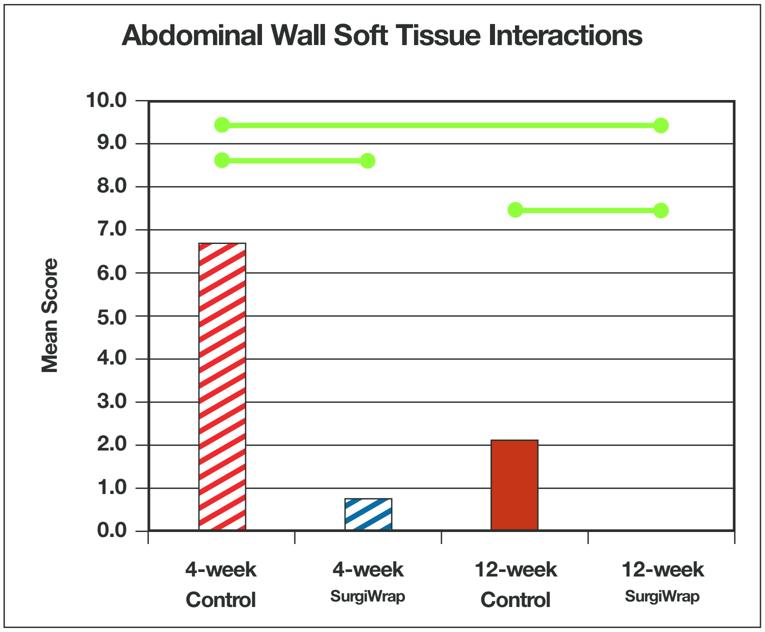

FIGURE 5.
Summary of the mean STA score for each interaction with the Abdominal Wall comparing 4-week Control, 4-week treated, 12-week Control and 12-week treated. The mean scored is compiled by the sum of each average interaction. The green bars indicate a statistically significant difference.

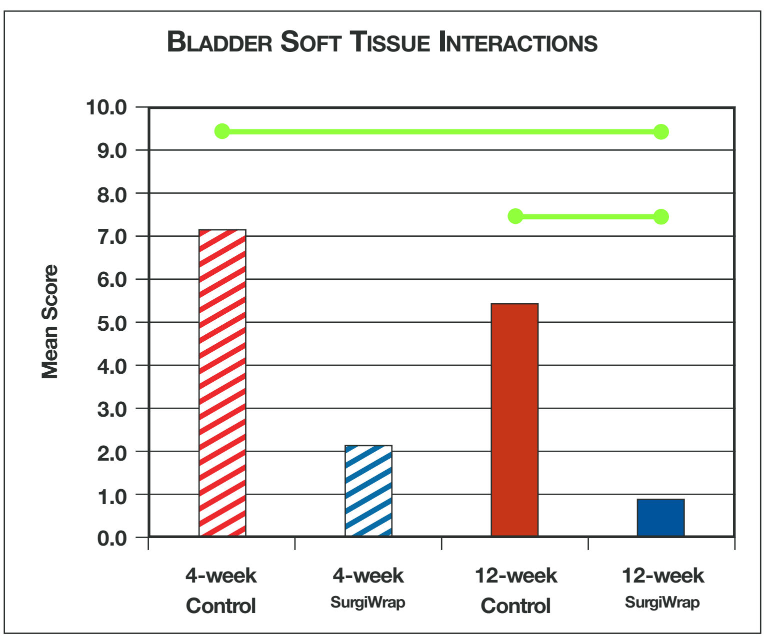

FIGURE 6.
Summary of the mean STA score for each interaction with the Bladder comparing 4-week Control, 4-week treated, 12-week Control and 12-week treated. The mean scored is compiled by the sum of each average interaction. The green bars indicate a statistically significant difference.

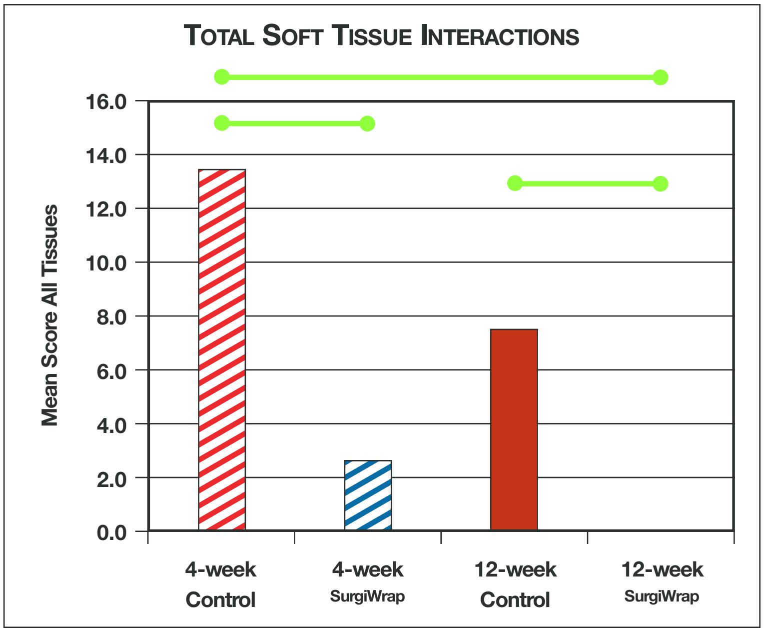

FIGURE 7.
Summary of the Total Mean STA score for each interaction comparing 4-week Control, 4-week treated, 12-week Control and 12-week treated. The total mean scored is compiled by the sum of each average interaction. The green bars indicate a statistically significant difference.

be easy to use in the operating environment, biocompatible, control STA during healing, and would facilitate reentry if required for subsequent surgery. The current study explored the use of a bioresorbable polylactide polymer sheet that meets these requirements.

Intraoperatively the sheet was very easy to manipulate and position into the appropriate anatomic location. When placed adjacent to the bladder, it was possible to slide the sheet and reposition it with ease. The sheet did not crack or break during surgical manipulation in any case. These results confirm our previous experience with a similar bioresorbable polylactide sheet in a cardiothoracic porcine model (Iliopoulos et al., 2003). The tensile properties of the sheet are sufficient to sustain load and surgical handling and further in vitro aging indicates the material will maintain these mechanical properties for up to 24 weeks (Thomas et al., 2003).

Polylactide is an alpha hydroxy ester bioresorbable polymer which is degraded by hydrolytic scission (bulk hydrolysis) at the implant site, followed by metabolism in the tricarboxylic acid cycle in the liver (Hollinger and Battistone, 1986). The end products of polylactic acid degradation are carbon dioxide and water. Manufactured as a sheet, the resorption takes place macroscopically in less than one year.

Comparing the results from 4 to 12 weeks for the Control animals, the average location scores were higher at 12 weeks than at 4 weeks in 2 locations, were not equal in any location, and were lower after 12 weeks than at 4 weeks in 6 locations. In contrast, for the sheet treated animals the average location scores were not higher at 12 weeks than at 4 weeks in any location, were equal in 4 locations, and were lower at 12 weeks than at 4 weeks in 4 locations. These results suggest that in both treatment groups STAs do not form continuously throughout the postoperative healing period. Some Control group animals had attachment scores that decreased from 4 to 12 weeks, suggesting that some early STAs do not persist throughout the healing period. This has been observed in other preclinical studies. Haney observed a decrease in STAs from 75% at 2 weeks to 49% at 5 weeks (Haney, 1998).

Summary

- The gross dissection and STA scoring observations were consistent within each treatment and within each time period group indicating the repeatability of the model used.
- All animals returned to normal behavior and did not demonstrate any obvious effects from the placement of the bioresorbable polylactide polymer (SurgiWrap® Bioresorbable Sheet) throughout their scheduled survival times of 4 or 12 weeks.
- SurgiWrap® Bioresorbable Sheet demonstrated the additional benefit of minimizing STAs secondary to the repairing of soft tissues.
- A clear dissection plane was observed in gross dissection and there were notably less STAs with the SurgiWrap® treated animals as compared to the Control animals.
- There was a statistically significant difference in the graded STA score between the Control animals (no treatment) and those animals treated with SurgiWrap® material. The significant reduction in STA scores associated with the use of the sheet was observed at both the 4 and 12 week time periods.

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