ANIMAL STUDY SERIES IN BIORESORBABLE TECHNOLOGY

Evaluation of a Resorbable Polylactide Film for the Reduction of Pelvic Adhesions in a Porcine Animal Model. Part 1: Adhesion Scores

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ABSTRACT
A large animal (porcine) model was used to evaluate the formation of adhesions 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 an adhesion barrier film made from a bioresorbable polylactide polymer. The placement strategy for the adhesion barrier was to place two films: one between the bladder and the abdominal wall, and the second between the bladder and the uterus. After the four-week and twelve-week survival periods, the severity and location of adhesions were assessed using a zero to three-point scale. The resorbable adhesion barrier film was found to provide an effective barrier between the anatomical structures in question and reduce the amount of adhesions observed between the treated and the control groups.

INTRODUCTION

Pelvic adhesions following laparotomy are 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 adhesions can lead to intraoperative complications, prolonged operative time (Ellis, 1997; Van Der Krabben, 2000), and higher costs associated with the procedure (Ivarsson, 1998).

Many different types of materials have been used to prevent or minimize postoperative adhesions 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 adhesion formation was used via a transperitoneal laparotomy approach. The goal of the study was to evaluate the effectiveness of a treatment consisting of a bioresorbable polymer film (SurgiWrapi) compared with no treatment (Control) on the formation of adhesions between the pelvic contents.

MATERIALS AND METHODS

Study Design

Adult female porcine (70 kg) were used in accordance with institutional ethics approval. Animals were allocated to either a control group or to the treatment group; both groups had two different survival periods of four weeks and twelve weeks. The treatment group consisted of a 0.02 mm thick polylactide adhesion barrier film (SurgiWrapi, MacroPore Biosurgery, San Diego, CA) with dimensions of 130 mm by 200 mm. The films were placed between the abdominal wall and the bladder and between the bladder and the uterus.

Table 1. **Study Design**

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

The SurgiWrapi adhesion barrier film 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 are 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 the skin prepped and draped in a sterile manner. All surgeons used powder free gloves.

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

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 had two 0.02 mm bioresorbable adhesion barrier films placed; one between the bladder and the uterus followed by a separate film placed between the bladder and the abdominal wall. No suture was used to fix either piece of film 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 porcine 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 Adhesion Formation

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

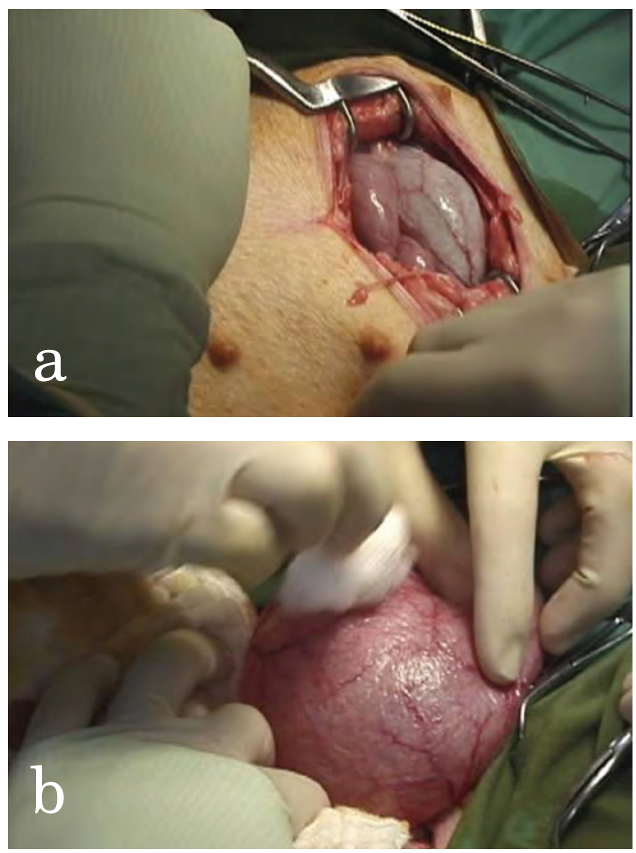

Figure 1.
Photograph of surgical technique illustrating the (a) laparotomy, (b) the abrasion to the bladder. The uterus (located dorsal to the bladder) was also abraded with 30 controlled strokes.

Table 2. **Matrix Used to Grade Adhesions Between Various Anatomic Structures of the Female Porcine Pelvis**

	ABW	BLAD	UTER	L FT	L OV	R FT	R OV	Lrg IN	Sm IN	Total
ABW										
BLAD										
UTER										
L FT										
L OV										
R FT										
R OV										
Lrg IN										
Sm IN										
Total										

assessment of the adhesions in the pelvic region. The matrix shown in Table 2 was used to assess the adhesions between the various anatomic structures. The specific abbreviations for the anatomic structures listed in Table 2 are:

ABW = Abdominal Wall
BLAD = Bladder
UTER = Uterus
L FT = Left Fallopian Tube
L OV = Left Ovary
R FT = Right Fallopian Tube
R OV = Right Ovary
Lrg IN = Large Intestine
Sm IN = Small Intestine

A graded scale ranging from zero to three (0 to 3) was used to assess the pelvic adhesions where:
0 = none
1 = sparse to infrequent, can easily be dissected manually (quantity $\leq$ 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. Adhesion scores were assigned using the scale described (0-1-2-3) at 40 separate locations, as summarized in Table 2. At the four week survival time, it was possible to find remnants of the resorbable film at the operative site. At the 12 week survival time, the film was difficult to observe and locate macroscopically but it was possible to palpate regions where the film was present.

Data analysis included determining the mean and standard deviations for each adhesion interaction (each cell in the Table 2 matrix) 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, respiratory or gastrointestinal complications in any animal. Placement and manipulation of the polylactide film was easily achieved during surgery. The film did not crack or break during manipulation between the soft tissues. The film 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.

Adhesion Formation

The adhesion scores from all reviewers for all animals at all locations were tabulated for analysis. The total score for all locations for each animal (sum of all locations) was examined prior to focusing on the results for specific locations of interest. 2 animals received scores of 0 at all locations from all 4 reviewers (both were 12-week film treated animals). For the 4-week animals, the total scores for the control animals ranged from 11 to 42 (mean of 25.5, standard deviation of 9.31). The film treated animals after 4 weeks had total scores ranging from 1 to 6 (mean of 3.7, standard deviation of 1.58). After 12 weeks, the control animals had total scores ranging from 4 to 23 (mean of 14.8, standard deviation of 6.15). The film treated animals at 12 weeks had scores ranging from 0 to 15 (Including 2 animals with scores of 0 at all locations), and had an average total score of 3.13 (standard deviation of 5.08).

In 8 locations, no adhesions were observed in any animal at either time period (abdominal wall-uterus, abdominal wall-left ovary, uterus-right ovary, left ovary-right fallopian tube, left ovary-right ovary, right fallopian tube-small intestine, right ovary-large intestine, and right ovary-small intestine).

In general, gross tenacious adhesions were noted in the control group and typical examples are shown in Figure 2. The treated animals had fewer adhesions at the specific sites where the resorbable barrier film was placed as shown in Figure 3 and appeared to have fewer adhesions in general during macroscopic dissection.

For clinical relevance, the adhesion scores were examined at each of the 40 specific locations, with focus directed toward adhesions that occurred involving the most important gynecological structures (for example, the fallopian tubes, ovaries, 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 adhesion 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 red boxes.

Adhesion Observations – 4-Week Time Period

After 4 weeks, adhesions were observed in 24 of 40 locations for the control animals (60% of locations), whereas in the film treated animals, adhesions were observed in only 8 of 40 of the locations (20% of locations) as summarized in Table 3. The average

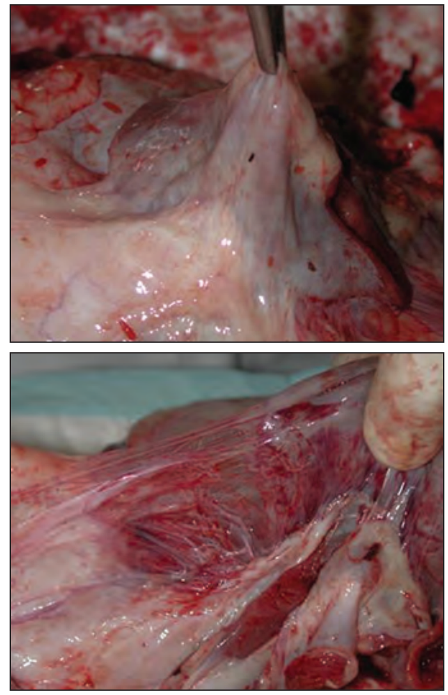

Figure 2.
Gross photograph of control specimen – the adhesions were thick and tenacious and the score was 3 for most anatomic regions shown on the adhesion grading matrix.

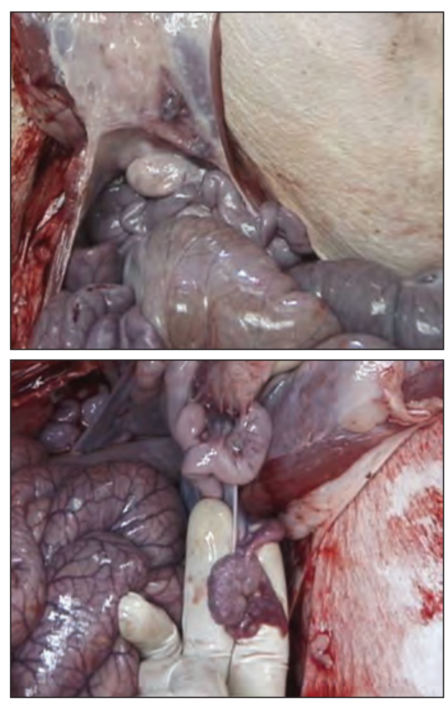

Figure 3.
Gross photograph of treated specimen – there were fewer adhesions throughout the specimen.

Table 3. **4-Week Adhesion Grading Results**

	ABW	BLAD	UTER	L FT	L OV	R FT	R OV	Lrg IN	Sm IN	Total
ABW										
BLAD	2.88 0.75									
UTER	0 0	0.88 0.75								
L FT	0 0	2.00 0.50	1.00 0.31	2.38 0.13						
L OV	0 0	0 0	0 0	1.13 0						
R FT	0 0	2.06 0.88	1.00 0.25	0.19 0	0 0	1.81 0.13				
R OV	0 0	0.19 0	0 0	0 0	0 0	0 0				
Lrg IN	1.94 0	1.13 0	0.19 0	0.75 0	0.31 0	0.56 0	0 0	1.25 0		
Sm IN	1.88 0	1.06 0	0.19 0	0.38 0	0 0	0 0	0 0	0.19 0	0.19 0	
Total										25.5 3.7

The Control score is over the Treated score. Significant differences are indicated by red.

Table 4. **12-Week Adhesion Grading Results**

	ABW	BLAD	UTER	L FT	L OV	R FT	R OV	Lrg IN	Sm IN	Total
ABW										
BLAD	1.05 0.08									
UTER	0 0	1.50 0.24								
L FT	0.20 0	1.90 0.25	0.20 0	1.90 0.42						
L OV	0 0	0.35 0 *	0.10 0	1.15 0.50						
R FT	0.20 0	2.10 0.42	0.20 0	0.30 0 *	0 0	1.40 0.42				
R OV	0.10 0	0.20 0	0 0	0.10 0	0 0	0.55 0.46				
Lrg IN	0.75 0	0 0	0 0	0 0	0.15 0	0 0	0 0	0 0		
Sm IN	0.30 0	0 0	0 0	0 0	0.10 0.29	0 0	0 0	0 0	0 0	
Total										14.8 3.7

The Control score is over the Treated score. Significant differences are indicated by red.
** The difference for these regions is $p<0.052$*

adhesion scores for the film treated animals were less than or equal to the average of the control animals at every location. At 16 locations the film treated and control scores were 0 for all observations.

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 2.38 (left fallopian tube-left fallopian tube). Overall, in 4 locations the average score ranged from 2-3 (frequent to numerous adhesions), in 9 locations the average score ranged from 1-2 (sparse to frequent adhesions), in 11 locations the average scores ranged from 0-1 (none to sparse adhesions), and there were no adhesions in 16 locations.

In the 4-week film 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 8 locations the average score ranged from 0-1 (none to sparse adhesions), and there were no adhesions in the remaining 32 locations.

Adhesion Observations – 12-Week Time Period

After 12 weeks, adhesions were observed in 22 of 40 locations for the control animals (55% of locations), whereas in the film treated animals adhesions were observed in only 9 of 40 of the locations (23% of locations) as summarized in Table 4. The average adhesion scores for the film treated animals were less than or equal to the average of the control animals at every location. At 18 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 (in two locations, bladder-left fallopian tube, and left fallopian tube-left fallopian tube). Overall, in 1 location the average score was in the range of 2-3 (frequent to numerous adhesions), in 6 locations the average score ranged from 1-2 (sparse to frequent adhesions), in 15 locations the average scores ranged from 0-1 (none to sparse adhesions), and there were no adhesions in 18 locations.

In the 12-week film treated animals, the maximum average location score was 0.5 (for the left fallopian tube-left ovary location), followed by an

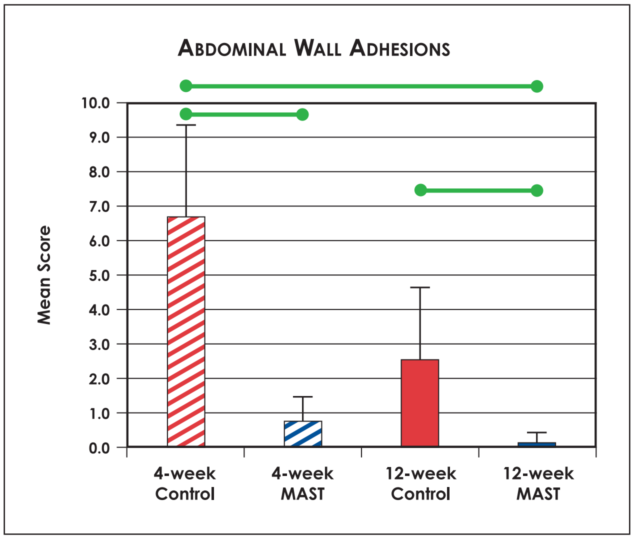

FIGURE 4.
Summary of the mean adhesion score for each interaction with the Abdominal Wall comparing 4-week control, 4-week treated, 12-week control and 12-week treated. The mean scored is compiled by the sum of each average interaction. The green bars indicate a significant difference.

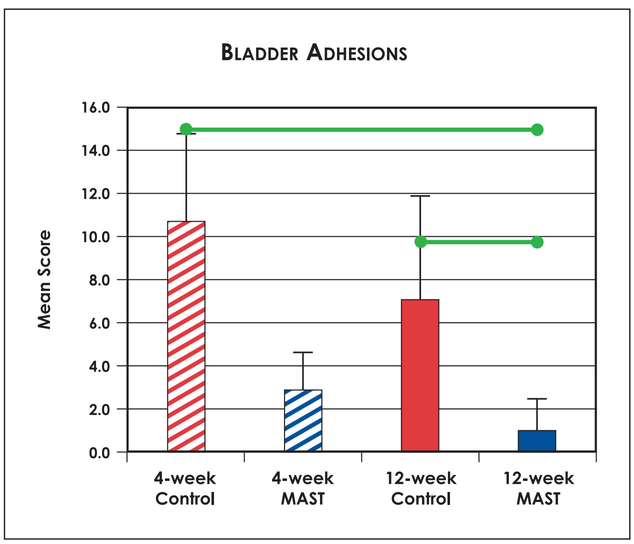

FIGURE 5.
Summary of the mean adhesion score for each interaction with the Bladder comparing 4-week control, 4-week treated, 12-week control and 12-week treated. The mean scored is compiled by the sum of each average interaction. The green bars indicate a significant difference.

average score of 0.46 (right fallopian tube-right ovary location). Overall, in 9 locations the average score ranged from 0-1 (none to sparse adhesions), and there were no adhesions in the remaining 31 locations.

Adhesion Observations – Anatomic Structures

The numeric data summarized in Tables 3 and 4 was compared relative to the total adhesion interactions affecting specific pelvic anatomic structures. The mean and standard deviations were computed for any interaction with each of the specific anatomic structures. The right and left ovaries were combined into one group and the right and left fallopian tubes were combined into one group. 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 (Figure 4)

The mean adhesion score at the abdominal wall for the 4-week control animals was 6.7 (standard deviation of 2.6) and for the film treated animals after 4 weeks, the mean adhesion score was 0.75 (standard deviation of 0.68). After 12 weeks, the control animals had a mean score of 2.6 (standard deviation of 1.96) while the film treated animals at 12 weeks had a mean score of 0.08 (standard deviation of 0.28). The results of the abdominal wall adhesion scores are summarized in Figure 4.

Bladder (Figure 5)

The mean adhesion score at the bladder for the 4-week control animals was 10.2 (standard deviation of 4.6) and for the film treated animals after 4 weeks, the mean adhesion score was 2.9 (standard deviation of 1.7). After 12 weeks, the control animals had a mean score of 7.1 (standard deviation of 4.66) while the film treated animals at 12 weeks had a mean score of 1.0 (standard deviation of 1.4). The results of the bladder adhesion scores are summarized in Figure 5.

Uterus (Figure 6)

The mean adhesion score at the uterus for the 4-week control animals was 3.3 (standard deviation of 3.9) and for the film treated animals after 4 weeks, the mean adhesion score was 1.3 (standard deviation of 1.2). After 12 weeks, the control animals had a mean score of 2.0 (standard deviation of 1.9) while the film treated animals at 12 weeks

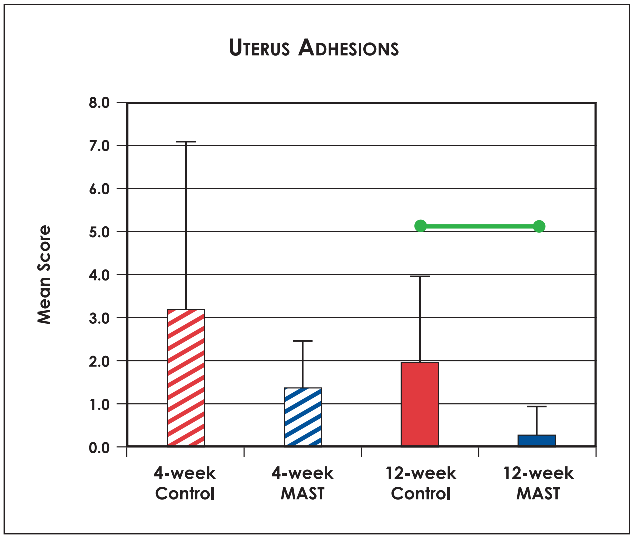

FIGURE 6.
Summary of the mean adhesion score for each interaction with the Uterus comparing 4-week control, 4-week treated, 12-week control and 12-week treated. The mean scored is compiled by the sum of each average interaction. The green bar indicates a significant difference.

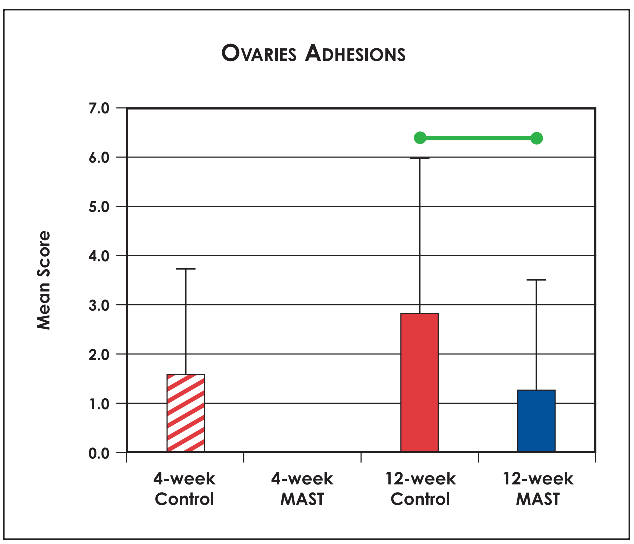

FIGURE 7.
Summary of the mean adhesion score for each interaction with the Ovaries comparing 4-week control, 4-week treated, 12-week control and 12-week treated. The mean scored is compiled by the sum of each average interaction. The green bar indicates a significant difference.

had a mean score of 0.3 (standard deviation of 0.6). The results of the uterus adhesion scores are summarized in Figure 6.

Ovaries (Figure 7)
The mean adhesion score for the ovaries for the 4-week control animals was 1.6 (standard deviation of 2.1) and for the film treated animals after 4 weeks, there were no adhesions observed. After 12 weeks, the control animals had a mean score of 2.8 (standard deviation of 3.1) while the film treated animals at 12 weeks had a mean score of 1.3 (standard deviation of 2.2). The results of the ovaries adhesion scores are summarized in Figure 7.

Fallopian Tubes (Figure 8)
For the fallopian tubes, the mean adhesion for the 4-week control animals was 13.25 (standard deviation of 6.7) and for the film treated animals after 4 weeks, the mean adhesion score was 2.2 (standard deviation of 1.6). After 12 weeks, the control animals had a mean score of 10.2 (standard deviation of 5.3) while the film treated animals at 12 weeks had a mean score of 2.5 (standard deviation of 5.2). The results of the combined fallopian tube adhesion scores are summarized in Figure 8.

Total Mean Adhesion Score (Figure 9)
For the total combined adhesion scores, the mean value for the 4-week control animals was 25.5 (standard deviation of 9.3) and for the film treated animals after 4 weeks, the mean adhesion score was 3.7 (standard deviation of 1.6). After 12 weeks, the control animals had a mean score of 14.8 (standard deviation of 6.2) while the film treated animals at 12 weeks had a mean score of 3.1 (standard deviation of 5.1). The results of the combined total adhesion scores are summarized in Figure 9.

DISCUSSION
Preventing or limiting adhesion formation following surgery has significant clinical and revision surgery implications. Adhesions 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 adhesions have had limited success.

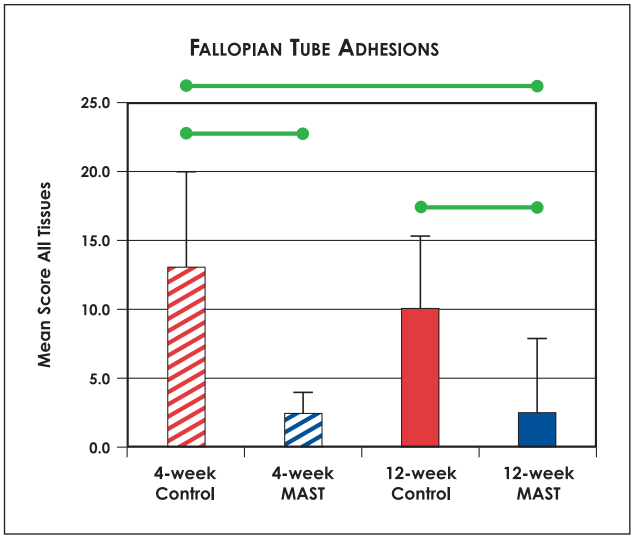

FIGURE 8.
Summary of the mean adhesion score for each interaction with the Fallopian Tubes comparing 4-week control, 4-week treated, 12-week control and 12-week treated. The mean scored is compiled by the sum of each average interaction. The green bars indicate a significant difference.

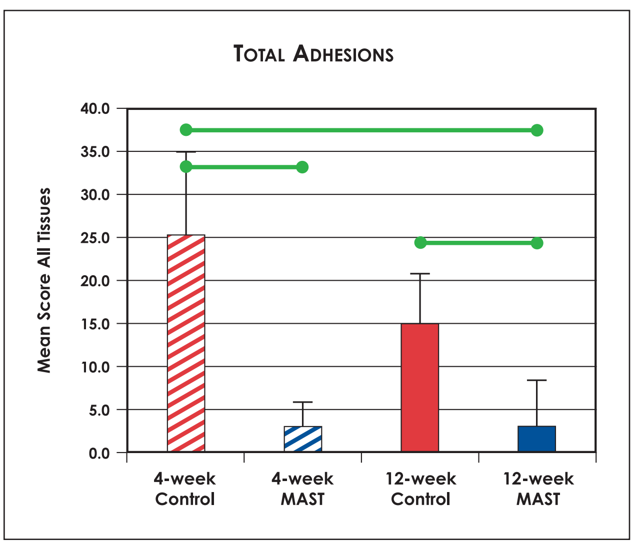

FIGURE 9.
Summary of the Total Mean adhesion score for each interaction comparing 4-week control, 4-week treated, 12-week control and 12-week treated. The total mean scored is compiled by the sum of each average interaction. The green bars indicate a significant difference.

The use of an off-the-shelf biomaterial which does not complicate the surgical procedure or impede healing while controlling the formation of postsurgical adhesions would be a significant achievement. The ideal material would be easy to use in the operating environment, biocompatible, provide adhesion prevention during healing, and would facilitate reentry if required for subsequent surgery. The current study explored the use of a bioresorbable polylactide polymer film that meets these requirements.

Intraoperatively the film was very easy to manipulate and position into the appropriate anatomic location. When placed adjacent to the bladder, it was possible to slide the film and reposition it with ease. The film did not crack or break during surgical manipulation in any case. These results confirm our previous experience with a similar bioresorbable polylactide barrier film in a cardiothoracic porcine model (Iliopoulos et al., 2003). The tensile properties 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 film, 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 13 locations, were equal in 8 locations, and were lower after 12 weeks than at 4 weeks in 19 locations. In contrast, for the film treated animals the average location scores were higher at 12 weeks than at 4 weeks in only 5 locations, were equal in 29 locations, and were lower at 12 weeks than at 4 weeks in 6 locations. These results suggest that in both treatment groups adhesions do not form continuously throughout the postoperative healing period. The fact that in some control group animals the scores decreased from 4 to 12 weeks also suggests that some early adhesions do not persist during the healing period. This has been observed in other preclinical studies. Haney observed a decrease in adhesions from 75% at 2 weeks to 49% at 5 weeks (Haney, 1998).

As summarized in Tables 3 and 4, there were 20 locations involving the fallopian tubes and ovaries. After 4 weeks, in 5 of the locations, the film-treated scores were significantly lower than the control scores. After 12 weeks, in 4 of the locations, the film-treated scores were significantly lower than the control scores, and in 2 additional locations the film-treated scores were marginally lower ($p<0.052$) than the control scores.

At the other 20 locations (not involving the fallopian tubes or ovaries), after 4 weeks the adhesion scores for the film treated group were significantly different from the controls at 8 more locations, and after 12 weeks there were 2 more significant locations.

SUMMARY

- The gross dissection and adhesion 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 (SurgiWrapi™ adhesion barrier film) throughout their scheduled survival times of 4 or 12 weeks.

- A clear dissection plane was observed in gross dissection and there were notably less adhesions with the SurgiWrapi™ film treated animals as compared to the control animals.

- There was a statistically significant difference in the graded adhesion score between the control (no treatment) and animals treated with SurgiWrapi™ film. The significant reduction in adhesions associated with the use of the film was observed at both the 4 and 12 week time periods.

REFERENCES

Al-Took S, Platt R, and Tulandi T: Adhesion-related small-bowel obstruction after gynecologic operations. Am J Obstet Gynecol 180: 313-15, 1999.

Burns JW, Skinner K, Colt MJ, Burgess L, Rose R, and Diamond MP: A hyaluronate based gel for the prevention of postsurgical adhesions: evaluation in two animal species. Fertil Steril 66(5): 814-21, 1996.

Ellis H, Moran BJ, Thompson JN, Parker MC, Wilson MS, Menzies D, McGuire A, Lower AM, Hawthorn RJ, O'Brien F, Buchan S, and Crowe AM: Adhesion-related hospital readmissions after abdominal and pelvic surgery: a retrospective cohort study. Lancet 353: 1476-80, 1999.

Ellis H: The Clinical Significance of Adhesions: focus on intestinal obstruction. Eur J Surg 163(Supp 577): 5-9, 1997.

Fukasawa M, Girgis W, and diZerega GS: Inhibition of postsurgical adhesions in a standardized rabbit model: II. Intraperitoneal treatment with heparin. In J Fertil. 36(5): 296-301, 1991.

Haney AF and Doty E: The temporal efficacy of early second-look lysis of adhesions in reducing postoperative adhesions in a murine model. Am J Obstet Gynecol 179: 368-73, 1998.

Haney AF, Hesla J, Hurst BS, Kettel LM, Murphy AA, Rock JA, Rowe G, and Schlaff WD: Expanded polytetrafluoroethylene (Gore-Tex Surgical Membrane) is superior to oxidized regenerated cellulose (Interceed TC7+) in preventing adhesions. Fertil Steril 63(5): 1021-6, 1995.

Hill-West JL, Dunn RC, Hubbell JA: Local release of fibrinolytic agents for adhesion prevention. J Surg Res 59(6) 759-63, 1995.

Hollinger JO and Battistone GC: Biodegradable bone repair materials. Synthetic polymers and ceramics. Clin Orthop. 207: 290-305, 1986.

Howard FM: Chronic pelvic pain. Obstet Gynecol 101(3): 594-611, 2003.

Iliopoulos J, Cornwall GB, Evans R, Thomas KA, Manganas C, Newman D, and Walsh WR: Evolution of Bioresorbable PLa Film for the Reduction of Pericardial and Retrosternal Adhesions in a Large Animal Model. Submitted: Journal of Surgical Research.

Ivarsson ML, Bergstrom M, Eriksson E, Risberg B, and Holmdahl L: Tissue markers as predictors of postoperative adhesions. Br J Surg 85: 1549-54, 1988.

Linsky CB, Diamond MP, Cunningham T, Constantine B, DeCherney AH, and diZerega GS: Adhesion reduction in the rabbit uterine horn model using an absorbable barrier, TC-7. J Reprod Med 32(1): 17-20, 1987.

Menzies D and Ellis H: Intestinal obstruction from adhesions--how big is the problem? Ann R Coll Surg Engl 72: 60-63, 1990.

Montz FJ, Wheeler JH, and Lau LM: Inability of polyglycolic acid mesh to inhibit immediate post-radical pelvic surgery adhesions. Gynecol Oncol 38(2): 230-3, 1990.

Montz FJ, Holschneider CH, Solh S, Schuricht LC, and Monk BJ: Small bowel obstruction following radical hysterectomy: risk factors, incidence, and operative findings. Gynecol Oncol 53: 114-20, 1994.

Muller SA, Treutner KH, Haase G, Kinzel S, Tietze L, and Schumpelick V: Effect of intraperitoneal antiadhesive fluids in a rat peritonitis model. Arch Surg 138: 286-90, 2003.

Rice VM, Shanti A, Moghissi KS, and Leach RE: A comparative evaluation of Poloxmer 407 and oxidized regenerated cellulose (Interceed [TC7]) to reduce postoperative adhesion formation in the rat uterine horn model. Fertil Steril 59(4): 901-6, 1993.

Rosner BA: Fundamentals of Biostatistics. Duxbury Press (PWS Publishers, Boston, MA), 467-73, 1986.

Shimanuki T, Nishimura K, Montz FJ, Nakamura RM, and diZerega GS: Localized prevention of postsurgical adhesion formation and reformation with oxidized regenerated cellulose. J Biomed Mater Res 21: 173-85, 1987.

Sulaiman H, Gabella G, Davis C, Mutsaers SE, Boulos P, Laurent GJ, and Herrick SE: Presence and distribution of sensory nerve fibers in human peritoneal adhesions. Ann of Surg 234(2): 256-61, 2001.

Thomas KA, McManus AJ, Moser RC, Kisselburgh C, and Cornwall GB: Strength Retention of 70:30 Poly(L-lactide-co-D,L-lactide) Films Following Real Time Ageing. Society For Biomaterials 29th Annual Meeting Transactions 29: 390, 2003. (Abstract)

Tulandi T, Collins JA, Burrows E, Jarrell JF, McInnes RA, Wrixon W, and Simpson CW: Treatment-dependent and treatment-independent pregnancy among women with periadnexal adhesions. Am J Obstet Gynecol 162: 354-7, 1990.

Van Der Krabben AA, Dijkstra FR, Nieuwenhuijzen M, Reijnen MM, Schaapveld M, and Van Goor H: Morbidity and mortality of inadvertent enterotomy during adhesiotomy. Br J Surg 87: 467-71, 2000.

Vrijland W, Tseng LM, Eijkman HJ, Hop WC, Jakimowicz JJ, Leguit P, Stassen LP, Swank DJ, Haverlag R, Bonjer HJ, and Jeekel H: Fewer intraperitoneal adhesions with use of hyaluronic acid-carboxymethylcellulose membrane: a randomized clinical trial. Ann Surg 235: 193-7, 2002.

Wiseman DM, Huang WJ, Johns DB, Rodgers KE, and diZerega GS: Time-dependent effect of tolmetin sodium in a rabbit uterine adhesion model. J Invest Surg 7: 527-32, 1994.

Yemini M, Meshorer A, Katz Z, Rozenman D, and Lancet M: Prevention of reformation of pelvic adhesions by "Barrier" methods. Int J Fertil 29: 194-6, 1984.

Yoldermir T, Sagol S, Adakan S, Oztekin K, Ozsener S, and Karadadas N: Comparison of the reduction of postoperative adhesions by two barriers, one solution, and two pharmacologic agents in the rat uterine model. Fertil Steril 78(2): 335-9, 2002.

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