

Gynecologic use of Sepraspay Adhesion Barrier for reduction of adhesion development after laparoscopic myomectomy: a pilot study

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Objective: To assess the safety and efficacy of Sepraspay Adhesion Barrier (a modified hyaluronic acid and carboxymethylcellulose powder) after laparoscopic surgery, in view of both the high efficacy of Seprafilm Adhesion Barrier in reducing postoperative adhesions after open surgical procedures and the difficulty with laparoscopic delivery.

Design: Multicenter, randomized, reviewer-blinded trial.

Setting: Reproductive endocrinology and infertility clinics.

Patient(s): Women undergoing laparoscopic myomectomy for indications including infertility.

Intervention(s): Randomization to treatment with (n = 21) or without (n = 20) Sepraspay Adhesion Barrier.

Main Outcome Measure(s): Postoperative adhesions development was assessed at early second-look laparoscopy. Adhesions were scored using the modified American Fertility Society scoring system.

Result(s): Surgical procedure duration length was 99 versus 102 minutes in the control versus Sepraspay Adhesion Barrier groups, respectively, with the median number of fibroids removed being two in each group and corresponding fibroid weights of 134 ± 103 versus 113 ± 161 g, respectively. Adhesions scores increased in both the control and Sepraspay Adhesion Barrier groups, with larger although nonstatistically significant increases noted in control subjects when evaluating for the anterior uterus, the posterior uterus, and the entire uterus.

Conclusion(s): Laparoscopic application of Sepraspay Adhesion Barrier after myomectomy in this pilot study was associated with a trend toward a reduction in postoperative adhesion development, as well as an encouraging safety profile. Further evaluation is warranted.

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Postsurgical adhesions are an exceedingly frequent complication of operations involving sites throughout the body, with many reports describing an incidence as high as over 90% after certain types of procedures (1, 2). Adhesions are associated with large health care expenditures that are estimated to exceed 1 billion dollars per year for gynecologic procedures in the United States alone (3–6). This is due not only to the procedures themselves but also to significant sequelae, including patient morbidity, rehospitalization and additional procedures, prolonged recuperation, and subsequent complications including adhesion reformation.

Seprafilm Adhesion Barrier (Genzyme Biosurgery) is a US Food and Drug Administration (FDA) and European CE Mark approved product that can be applied over intraperitoneal surfaces at the completion of surgical procedures before closure of the abdom-

inal cavity. It is formulated as a sheet composed of hyaluronic acid and carboxymethylcellulose, which has been chemically modified to prolong its residence time at the site of application. Before its degradation, Seprafilm Adhesion Barrier acts as a barrier to allow separation of adjoining tissues to reduce adhesion development while reperitonealization occurs. The FDA approval of Seprafilm Adhesion Barrier for use in abdominopelvic procedures performed by laparotomy was based on two randomized clinical trials in which Seprafilm Adhesion Barrier was shown to be efficacious in adhesion reduction, one in men and women undergoing colectomy for ulcerative colitis and familial polyposis (7) and the other in women undergoing uterine myomectomy (8).

Advances in laparoscopic surgical procedures have been variably associated with decreased length of hospital stay and/or reduced patient morbidity (9–11). However, postoperative adhesion development remains a frequent occurrence and complication after such procedures (12, 13). Seprafilm Adhesion Barrier is designed and approved for use in reducing adhesions after abdominal and pelvic laparotomy. Seprafilm Adhesion Barrier has not been formally studied in laparoscopic procedures owing to difficulty applying it laparoscopically. While individual surgeons have recently experimented with various methods of endoscopic delivery of Seprafilm Adhesion Barrier including placing a tightly rolled barrier through the laparoscopic trocar (14–16) or creating

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FIGURE 1

Delivery instrument for laparoscopic administration of Sepraspay Adhesion Barrier. Note the attached tube containing Sepraspay Adhesion Barrier and the bulb that is squeezed to apply the Sepraspay Adhesion Barrier.



Fossum. Reduction of adhesions with Sepraspay Adhesion Barrier. Fertil Steril 2011.

a slurry (17, 18), such approaches are not addressed in the product labeling and have not been formally evaluated in clinical studies.

This report presents results from the initial pilot clinical trial of laparoscopic application of Sepraspay Adhesion Barrier, a modified hyaluronic acid and carboxymethylcellulose powder (Genzyme Biosurgery), for reduction of postoperative adhesions after myomectomy. The primary aim of this trial was to assess the safety of Sepraspay Adhesion Barrier applied at the conclusion of laparoscopic myomectomy. Results from patients in the study group were compared with those from a control group, who underwent myomectomy without the application of an adhesion prevention barrier. The secondary aim of this study was to assess efficacy findings at early second-look laparoscopy.

MATERIALS AND METHODS

This prospective randomized, patient- and assessment-blinded pilot trial was conducted at three clinical sites. Each site obtained Institutional Review Board (IRB) approval for the trial. Women participating in the study were all scheduled to undergo a laparoscopic myomectomy for indications including infertility, as well as a planned early second-look laparoscopy. All subjects executed an IRB-approved written informed consent before participation.

Study inclusion criteria included nonpregnant women between the ages of 18 and 49 who were scheduled to undergo laparoscopic myomectomy for the resection of at least one uterine fibroid. Intraoperatively, patients were excluded if an intra-abdominal infection or abscess was identified, if entry into the endometrial cavity or the bowel lumen was noted, if adhesiolysis involving the bowel wall was performed, or if a concurrent, nongynecologic procedure was performed. At the conclusion of the procedure, just before closure, all patients who met all inclusion and exclusion criteria were randomized to either the control or the treatment group.

For patients who were randomized to the treatment group, Sepraspay Adhesion Barrier was introduced as follows: after attaching a tube containing Sepraspay Adhesion Barrier powder to a specially designed laparoscopic delivery instrument (Fig. 1), the instrument was introduced into the abdominal cavity through one of the secondary ports. The tip of the delivery instrument was then positioned approximately 2–3 cm from the tissue to be treated. The bulb on the delivery device was then repeatedly squeezed, enabling Sepraspay Adhesion Barrier to cover the anterior and posterior uterine surface, the ovaries, and the tubes. At the surgeon's discretion, Sepraspay Adhesion Barrier was also applied to adjacent surfaces to ensure adequate coverage of the uterus and the adnexae. After either Sepraspay Adhesion Barrier application in the study group or randomization to the control group, the laparoscopic instruments were removed after confirmation of hemostasis and the incisions were closed.

Safety evaluations were conducted by telephone 1 week postoperatively and at an office visit 1 month postoperatively. Second-look laparoscopy was performed 4–12 weeks after the initial procedure for assessment of

TABLE 1

Demographics and clinical history of women undergoing laparoscopic myomectomy.

	Control (n = 20)	Sepraspay Adhesion Barrier (n = 21)
Age	36	37
Race, %:		
White	50	62
Black	40	29
Other	10	9
Weight, kg	75	81
Body mass index, kg/m ²	27	29
Previous abdominal/pelvic surgeries, %	25	62
Previous myomectomies, %	15	24

Fossum. Reduction of adhesions with Sepraspay Adhesion Barrier. Fertil Steril 2011.

postoperative adhesions. Surgeons performed adhesiolysis as well as any other indicated procedures at this time at their discretion.

At both the initial and second-look procedures, the presence or absence of adhesions was determined at 14 intra-abdominal and pelvic sites. These sites included the following: anterior uterus, left ovary, left fallopian tube, left pelvic sidewall, bladder, posterior cul-de-sac, large bowel, posterior uterus, right ovary, right fallopian tube, right pelvic sidewall, anterior cul-de-sac, small bowel, omentum.

Each of the surgical procedures was videotaped in its entirety. The video was then edited so that the postrandomization component of the procedure (possible application of Sepraspay Adhesion Barrier) was removed. The edited videotape of the initial procedure and the second-look video were

TABLE 2

Intraoperative characteristics at the initial procedure of women undergoing laparoscopic myomectomy in the control and Sepraspay Adhesion Barrier groups.

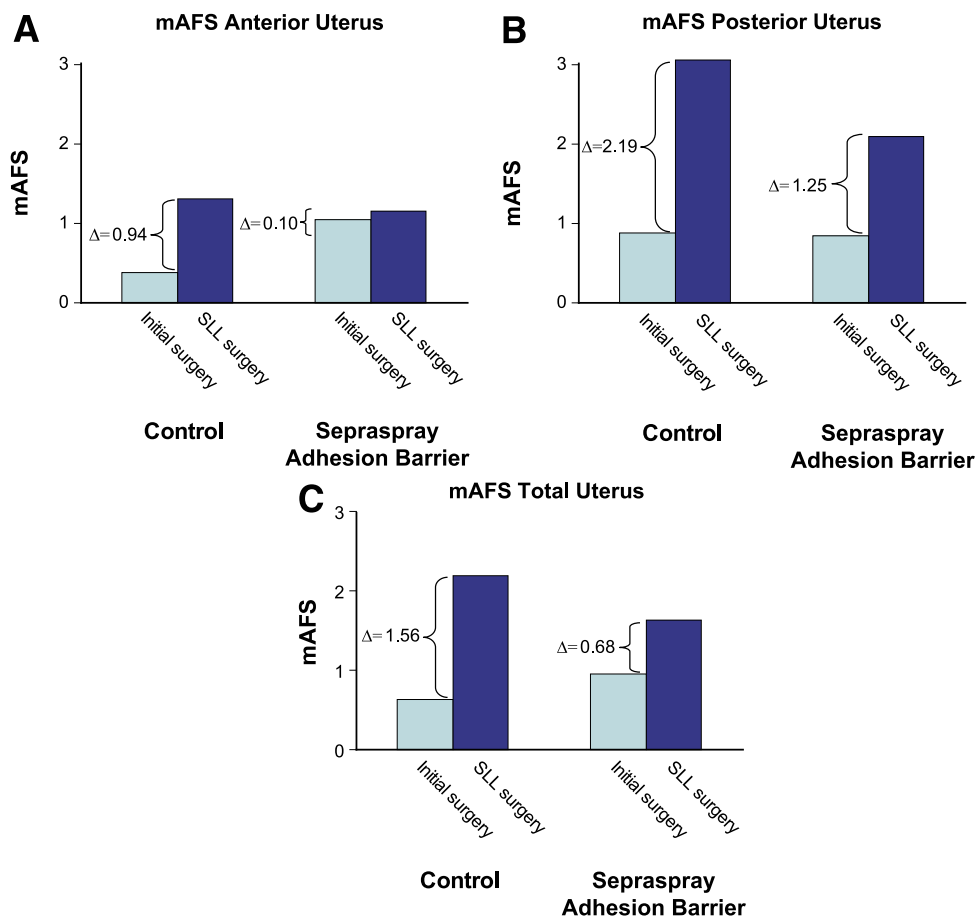
	Control (n = 20)	Sepraspay Adhesion Barrier (n = 21)
Median length of surgery, minutes	99	102
Uterine Incision method ^a (%):		
Electrosurgery	3 (15)	1 (5)
Harmonic scalpel	12 (60)	13 (62)
Laser	7 (35)	8 (38)
No. of myomas removed mean ± SD	3.6 ± 3.2	3.2 ± 27
No. of myomas removed median	2	2
Weight of myomas removed, mean ± SD, g	134 ± 103	113 ± 161
Weight of myomas removed, median, g	120	70
Adhesiolysis performed, n	10	15
Adhesiolysis time, minutes	11.6	10.6
Estimated blood loss, mL	43	62

^a More than one possible.

Fossum. Reduction of adhesions with Sepraspay Adhesion Barrier. Fertil Steril 2011.

FIGURE 2

Modified AFS adhesion scores at initial and second-look procedures after laparoscopic myomectomy in women in the control and Sepraspay Adhesion Barrier-treated groups for (A) the anterior uterus, (B) the posterior uterus, and (C) the entire uterus.



Fossum. Reduction of adhesions with Sepraspay Adhesion Barrier. Fertil Steril 2011.

then reviewed and scored by a blinded evaluator. Evaluation of each of the 14 sites included an assessment of the presence or absence of adhesions, as well as the extent (localized, moderate, or extensive) and severity (filmy, dense) of adhesions, using a modified American Fertility Society (mAFS) scoring system.

RESULTS

Fifty-one women consented to inclusion in this trial. Ten failed screening criteria before randomization. Of the 41 women who were randomized, 21 were randomized to receive Sepraspay Adhesion Barrier, while 20 were randomized to the control group. All of the Sepraspay Adhesion Barrier-treated women underwent second-look laparoscopy and were included in the efficacy analysis; three control subjects failed to complete the second-look laparoscopy (one owing to a postoperative diagnosis of leukemia and two who withdrew because they did not want to undergo the second-look procedure).

As shown in Table 1, there were no differences in patient demographics including age, racial distribution, height, or body mass index. However, a higher percentage of patients in the Sepraspay Adhesion Barrier group were noted to have undergone previous abdominal/pelvic surgery, including myomectomy. Table 2 provides intraoperative and perioperative surgical procedure comparisons.

There were no differences between the groups in the length of surgery, the modalities used for uterine incisions, the number of myomas removed, the weight of myomas removed, adhesiolysis time, or intraoperative estimated blood loss.

As shown in Figure 2A and B, which demonstrate the anterior and posterior surfaces of the uterus, respectively, creation of one or more uterine incisions at initial laparoscopy was associated with an increase in the mAFS adhesion score to the uterus in both the control and Sepraspay Adhesion Barrier groups at second-look laparoscopy. However, in the Sepraspay Adhesion Barrier-treated group, the increases in adhesion score after laparoscopic myomectomy tended to be smaller for both the anterior (Fig. 2A) and posterior (Fig. 2B) uterine surfaces.

Similar results were identified for the mAFS adhesion score for the uterus as a whole (Fig. 2C), as patients in the control group had an increase in their score that was more than twice as large as that of patients in the Sepraspay Adhesion Barrier group. Patients in the Sepraspay Adhesion Barrier group also exhibited a trend toward having no adhesions to the anterior uterus, posterior uterus, and total uterus, when compared with patients in the control group. Compared with control patients, Sepraspay Adhesion Barrier group patients were also more likely to have either side of the uterus free of

dense adhesions at second-look laparoscopy (control, 70% vs. Sepraspay Adhesion Barrier, 95%).

Only one patient in this trial developed a serious adverse event, as she was diagnosed with leukemia after her initial laparoscopy. This patient had been randomized to the control group and therefore did not receive Sepraspay Adhesion Barrier. No overall difference was noted in the number of patients with adverse events in either the control ($n = 12$; 60% of patients) or Sepraspay Adhesion Barrier-treated ($n = 14$; 67% of patients) groups. No adverse event directly related to Sepraspay Adhesion Barrier was identified by the surgeons, nor was there any report of surgical site infection, intra-abdominal abscess formation, or deep vein thrombosis.

DISCUSSION

The pathophysiological state under which adhesions develop is becoming increasingly understood. Teleologically, a postsurgical adhesion represents a mechanism by which the body reestablishes a supply of oxygen and nutrients to tissues that have undergone hypoxic injury during a surgical procedure. Tissue hypoxia initiates synchronized and cascading responses which, in combination with the fibrinous collection of blood and serosanguineous fluid at the tissue surface, may result in adhesion development. These responses include a reduction in plasminogen activator activity, chemotaxis of macrophages and other host defense cells, migration of fibroblasts to the site of injury (and into the persisting fibrinous mass), enhancement of extracellular matrix deposition including collagen and fibronectin, remesothelialization, and stimulation of angiogenesis (19, 20).

As noted earlier, antiadhesion barriers typically function by separating tissue surfaces during reoperation, which is thought to be initiated within hours of a surgical injury and completed within 3–5 days (21–26). This period of time becomes the critical window during which a barrier needs to function.

In studies conducted to date, there does not appear to be a biologic effect of modified hyaluronic acid and carboxymethylcellulose, which are the components of Seprafilin Adhesion Barrier and Sepraspay Adhesion Barrier, on adhesion development. Neither one of the present authors (MD) nor others (27–30) have been able to identify molecular biologic evidence of an impact of modified hyaluronic acid and carboxymethylcellulose on mRNA expression of tissue plasminogen activator (28), collagen I, transforming growth factor beta (28), matrix metalloproteinase I (28), tissue plasminogen activator activity (28), vascular endothelial growth factor expression (29), or polymorphonuclear neutrophil (PMN) phagocytosis.

Similarly, there does not appear to be a change in the rate of PMN apoptosis/necrosis, production of cytokines (tumor necrosis factor-alpha, interleukin-1 α , interleukin-6, interleukin-8, interleukin-1 receptor antagonist), or PMN elastase in response to the use of this product (30). Thus it appears that the primary mode of action of modified hyaluronic acid and carboxymethylcellulose is to function as a resorbable barrier that separates tissues during reoperation.

In the pivotal clinical trials leading to FDA approval, Seprafilin Adhesion Barrier successfully reduced the percentage of patients with midline abdominal adhesions from 94% in the control group to 49% in the Seprafilin Adhesion Barrier-treated patients ($P < 10^{-11}$). Furthermore, among those patients who did develop midline adhesions, the extent of involvement of the midline incision was significantly less in the Seprafilin Adhesion Barrier-treated subjects.

In the gynecologic myomectomy trial, covering the uterus with Seprafilin Adhesion Barrier at the completion of the procedure reduced the number of sites adherent to the uterus. Furthermore, the use of Seprafilin Adhesion Barrier was associated with a significant reduction in patients with adhesions to the anterior uterus (94% vs. 61%; $P < .0001$) and in the number of women with at least one adnexa free of adhesions to the posterior uterus ($P < .05$).

In this study, we evaluated the use, safety, and efficacy trends of laparoscopic application of Sepraspay Adhesion Barrier after laparoscopic myomectomy. Although not powered for statistical significance in this pilot study, and while a higher percentage of Sepraspay Adhesion Barrier group patients had undergone previous abdominopelvic surgery, Sepraspay Adhesion Barrier showed clear efficacy trends in the reduction of adhesions to the anterior and posterior uterus and the proportion of patients with either side of the uterus free from dense adhesions at second-look laparoscopy. Furthermore, there were no serious adverse events resulting from the use of Sepraspay Adhesion Barrier.

Based on the trends favoring efficacy in the use of Sepraspay Adhesion Barrier demonstrated in this trial, as well as the historically demonstrated efficacy of Seprafilin Adhesion Barrier in reducing postoperative adhesions, we believe that additional, larger clinical trials to further evaluate the safety and efficacy of Sepraspay Adhesion Barrier in reducing postoperative adhesions are warranted.

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