Reduction of de novo postsurgical adhesions by intraoperative precoating with Sepracoat* (HAL-C) solution: a prospective, randomized, blinded, placebo-controlled multicenter study

Michael P. Diamond, M.D. and The Sepracoat Adhesion Study Group†

Hutzel Hospital, Wayne State University, Detroit, Michigan

Objective: To assess the efficacy and safety of Sepracoat (HAL-C; Genzyme Corporation, Cambridge, MA) solution in reducing the incidence, severity, and extent of de novo adhesion formation at sites without direct surgical trauma or adhesiolysis at the time of gynecologic laparotomy.

Design: Prospective, randomized, blinded, placebo-controlled multicenter study. Patients underwent gynecologic procedures via laparotomy; approximately 40 days later, surgeons assessed their adhesions during second-look laparoscopy.

Setting: Twenty-three North American institutions.

Patient(s): Two hundred seventy-seven women for safety evaluations; 245 women for efficacy studies.

Intervention(s): Intraoperative serosal coating with Sepracoat (treatment) or phosphate-buffered saline (placebo) after opening of the abdominal cavity, after irrigation or every 30 minutes during surgery, and at the completion of surgery.

Main Outcome Measure(s): Incidence, severity, and extent of de novo adhesions to 23 intraabdominal sites.

Result(s): The Sepracoat group had a significantly lower incidence of de novo adhesions than the placebo group as assessed by the proportion of sites involved (0.23 ± 0.02 versus 0.30 ± 0.02, respectively) and the percentage of patients without de novo adhesions (13.1% versus 4.6%, respectively), as well as significantly reduced adhesion extent and severity. Sepracoat was well tolerated, with a safety profile nearly identical to that of the placebo.

Conclusion(s): Sepracoat was significantly more effective than placebo and was safe in reducing the incidence, extent, and severity of de novo adhesions to multiple sites indirectly traumatized by gynecologic surgery via laparotomy. (Fertil Steril 1998;69:1067-74. ©1998 by American Society for Reproductive Medicine.)

Key Words: Adhesions, indirect surgical trauma, Sepracoat, HAL-C, gynecologic surgery, de novo adhesions, adhesion formation, postoperative adhesions

Intraperitoneal adhesions are a major clinical problem; they cause small bowel obstruction, infertility, and abdominopelvic pain, and they contribute to lengthened surgical procedures and increased morbidity in patients who require reoperation (1-3). The annual cost of adhesions in the United States alone has been estimated at $1.2 billion per year, not including outpatient expenditures and the expense of loss of work (4).

Postoperative adhesions develop in a surprisingly large number of patients. In women who undergo gynecologic surgical procedures, followed by early second-look laparoscopies, the incidence is 55%-100%, and the rate is similar in men and women who undergo general surgical procedures (2, 5). These adhesions represent a combination of adhesion re-formation (the redevelopment of adhesions after adhesiolysis) and de novo adhesion formation (the development of adhesions at sites that initially did not undergo adhesiolysis) (6). Each of these categories, re-formation and de novo formation, can be segregated further according to whether an additional surgical procedure was performed at that site.

To date, surgical adjuvants used in human clinical trials have addressed the issue of adhesion re-formation or de novo adhesion formation at sites undergoing additional surgical
procedures. Although de novo adhesion formation at sites that have not been subject to surgical procedures has been shown to occur at more than 50% of tubes and ovaries, other than the use of good surgical technique, there have been no attempts to use adjuvant approaches to reduce these adhesions. The purpose of this study was to assess the efficacy of Seprocoat (HAL-C; Genzyme Corporation, Cambridge, MA), a dilute solution of hyaluronic acid, in reducing such de novo adhesions.

MATERIALS AND METHODS

Study Design

This prospective, randomized, blinded, placebo-controlled multicenter study compared the efficacy and safety of Seprocoat, an investigational agent, in reducing the incidence, extent, and severity of de novo adhesion formation throughout the pelvis after gynecologic surgery performed via laparotomy. Institutional review board approval was obtained at each of the participating institutions. All subjects gave informed, written consent before participation in this study.

Each patient underwent two surgeries. At the first surgery, a test solution (either Seprocoat or phosphate-buffered saline [PBS]) was applied intraoperatively to coat the serosal surfaces. The second surgery was a planned, second-look laparoscopy performed to assess and surgically treat adhesions. During the second-look laparoscopy, adhesions were documented and scored by the attending surgeon. In addition, a videotape recording of the abdominopelvic cavity was made at this time; the video was reviewed later by a blinded, independent reviewer, and the adhesions were evaluated with the use of the scoring criteria that were used by the attending surgeon.

Randomization

Before their initial procedure, patients at each center were assigned randomly according to a computer-generated list to receive either Seprocoat (treatment group) or PBS (placebo group). Patients were assigned a number that corresponded to an identically numbered set of 2,500-mL bottles of blinded solution. The surgeons who performed the initial procedures, the surgeons who performed the second-look laparoscopies, and the independent reviewer were blinded to the randomization.

Seprocoat coating solution is a liquid composed of 0.4% sodium hyaluronate (hyaluronic acid) in PBS. Sodium hyaluronate is a high–molecular-weight polysaccharide that is found naturally in connective tissue, synovial fluid, and vitreous humor, and is used widely in ophthalmologic surgery. Seprocoat is bioresorbable, with an intraabdominal residence time of <24 hours and complete clearance in <5 days (7). This solution coats tissues with a temporary, protective, viscous barrier. Preclinical studies have shown Seprocoat to be safe and effective in reducing and preventing de novo adhesion formation in animal models (8).

Test Solutions

Both the Seprocoat and the PBS were packaged in identical 500-mL stoppered bottles and stored at temperatures of 2°–8°C. Before use, the solutions were warmed to room temperature and applied according to the same protocol:

1. Up to 250 mL at the start of the procedures, after incision into the abdominal cavity and before any tissue manipulation.
2. After irrigation and/or at least every 30 minutes during the procedures, to a volume of 100 mL per application.
3. Just before closure of the abdominopelvic cavity, to a volume of 250 mL.
4. To a maximum total volume of 1,000 mL.

All serosal tissues were coated by gently distributing the solution throughout the abdominopelvic cavity for at least 1 minute. After each application, test solution was left standing for at least 1 minute, after which all excess fluid was removed by suctioning. The volume of excess fluid was measured and the fluid was discarded.

Study Population

Seventeen principal investigators at 23 institutions enrolled a total of 277 adult women in the Seprocoat 0.4% and PBS groups from June 10, 1992 to March 2, 1995. The patients were women ≥18 years of age who were scheduled to undergo laparotomy for gynecologic surgery, followed by second-look laparoscopy performed an average of 40 days later. To optimize safety and to minimize variability and confounding factors, the protocol excluded patients who were pregnant or who had cancer or active pelvic inflammatory disease. The protocol excluded the use of instillants and/or irrigants containing dextran, heparin, corticosteroids, or nonsteroidal antiinflammatory agents during surgery, as well as the use of antiadhesion barriers.

Surgery

Throughout the initial procedure, the second-look laparoscopy, and thereafter, the methodology and care of all patients were consistent with the investigators’ standard surgical and medical practices. The methodology and care of patients in the treatment and placebo groups differed only in the test solution they received.

During the initial procedure, baseline adhesions, the volume of test solution applied, the times of test solution application, the volume of fluids used for irrigation or hydroflotation, the approximate volume of excess fluid removed, and all anesthetic and surgical medications administered were recorded.

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Key demographic parameters in the Sepracoat and placebo groups.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PBS (n = 120)</th>
<th>Sepracoat (n = 157)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>33.4 ± 0.5</td>
<td>33.1 ± 0.4</td>
<td>0.69</td>
</tr>
<tr>
<td>Height (in.)</td>
<td>63.9 ± 0.3</td>
<td>63.8 ± 0.2</td>
<td>0.81</td>
</tr>
<tr>
<td>Weight (lb)</td>
<td>149.4 ± 3.0</td>
<td>147.2 ± 2.5</td>
<td>0.58</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.6 ± 0.5</td>
<td>25.4 ± 0.4</td>
<td>0.83</td>
</tr>
<tr>
<td>Percentage of patients given GnRH analogues within 31 days of initial procedure(s)</td>
<td>10.8</td>
<td>10.2</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Note: Values are means ± SEM, except for the percentage of patients given GnRH analogues within 31 days of initial procedure. PBS = phosphate-buffered saline.

Evaluation

Preoperative Baseline Evaluation

Within 1 week before the initial procedure, a medical/surgical history was obtained and all concomitant medications (including GnRH agonists), vital signs, laboratory values, eligibility criteria, and informed consent were documented. A serum or urine pregnancy test was performed for each patient. Vital signs included oral temperature, blood pressure, and heart rate. Laboratory values included the following: complete blood count, prothrombin time, partial thromboplastin time, blood urea nitrogen, creatinine, glucose, sodium, chloride, potassium, carbon dioxide, phosphorus, calcium, alkaline phosphatase, total protein, albumin, total bilirubin, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, lactate dehydrogenase, and creatine phosphokinase.

Adhesion Evaluation During the Surgical Procedures

The presence or absence of adhesions was documented at 23 sites during both the initial and second-look procedures using a previously described adhesion scoring system (9). Any of the 23 locations that were totally free of adhesions at the time of the initial surgery and did not receive direct surgical intervention (ablation of endometriosis, incision, suture, cautery, or laser) were considered an available site for efficacy evaluation. The extent of adhesions was graded as follows: 0 = no adhesions; 1 = up to 25% of total area/length of the site; 2 = 26%–50% of total area/length of the site; and 3 = >50% of total area/length of the site. The severity of adhesions was graded as follows: 0 = no adhesions; 1 = filmy, avascular adhesions; 2 = vascular and/or dense adhesions; and 3 = cohesive adhesions (9).

Evaluation of Safety

Vital signs and laboratory values were monitored for 2–5 days and 2–4 weeks, respectively, after the initial procedure. Throughout the study, adverse events, defined as any undesirable physical, psychological, or behavioral effects experienced by a patient, were recorded as to their nature and severity, as well as the investigator’s assessment of their relation to the test solution. In addition to those reports received spontaneously, information on adverse events was solicited from patients at 1 week and 1 month after the initial procedure.

Statistical Analysis

Statistical analysis was performed with the use of SAS 6.07 software (SAS Institute, Inc., Cary, NC) on VAX/VMS computers. Clinical data were double-entered in an Oracle database and validated by Clintrial software (BBN Domain, Cambridge, MA). In general, all variables were summarized with descriptive statistics, including number, mean, median, SD, and range for continuous variables, and number and percentage in each category for categorical variables. In general, continuous variables were compared with the use of the Student’s t-test and categorical variables were compared with the use of the Fisher’s exact test. Baseline comparisons were two-tailed; all efficacy analyses were one-tailed. Data on proportions were normalized with the arcsine transformation before analysis; the arcsine-transformed proportions then were compared with the Student’s t-test.

The potential for bias in scoring of adhesions on the part of the attending surgeons was assessed by comparison with scoring of adhesions by the independent reviewer (via the videotapes) using McNemar’s test and the Jonkheere-Terpstra test of homogeneity. Differences for all analyses were considered statistically significant if the P value was <0.05. Any baseline or surgical characteristic found to differ significantly between the Sepracoat and placebo solution groups, and those characteristics considered to be potential predictors of adhesiogenesis, were examined as covariates in an analysis of variance (ANOVA) model, with the proportion of available sites with de novo adhesions as the outcome.

RESULTS

Patient Demographics

There were no statistically significant differences between the groups in patient demographic criteria (Table 1). The
Key surgical parameters in the Sepracoat and placebo groups.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PBS (n = 109)</th>
<th>Sepracoat (n = 137)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of sites with adhesions at baseline</td>
<td>0.20 ± 0.02</td>
<td>0.17 ± 0.02</td>
<td>0.09</td>
</tr>
<tr>
<td>No. of sites available for de novo adhesions</td>
<td>16.1 ± 0.4</td>
<td>16.3 ± 0.4</td>
<td>0.62</td>
</tr>
<tr>
<td>Time to second-look laparoscopy (d)</td>
<td>41.3 ± 4.2</td>
<td>38.6 ± 3.0</td>
<td>0.64</td>
</tr>
<tr>
<td>Volume of solution applied (mL)</td>
<td>661.8 ± 16.5</td>
<td>652.0 ± 15.8</td>
<td>0.49</td>
</tr>
<tr>
<td>No. of applications</td>
<td>4.89 ± 0.15</td>
<td>4.77 ± 0.14</td>
<td>0.56</td>
</tr>
<tr>
<td>Rate of application (mL/h)</td>
<td>471.1 ± 22.4</td>
<td>463.0 ± 15.9</td>
<td>0.78</td>
</tr>
<tr>
<td>Volume of excess fluid removed (mL)</td>
<td>558.9 ± 19.5</td>
<td>505.2 ± 14.7</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Note: Values are means ± SEM.

most common presurgical diagnoses were leiomyomata of the uterus (133 patients), infertility of tubal or unspecified origin (89 patients), pelvic peritoneal adhesions (37 patients), endometriosis (31 patients), and other female genital symptoms (13 patients) (some patients had multiple diagnoses). Most patients (78% [217 of 277]) had a history of surgery (446 procedures, or a mean of 1.61 per patient), with laparoscopy (99 surgeries), tubal surgeries (59 surgeries), dilation and curettage (32 surgeries), cesarean section (28 surgeries), and laparotomy (21 surgeries) being the most common interventions. The time difference between surgical procedures for the control PBS (41.3 ± 4.2 days; range, 7–223 days) and Sepracoat (38.6 ± 3.0 days; range, 6–188 days) groups was not statistically significant.

Efficacy

The Sepracoat group had a statistically significant reduction in the proportion of available sites with de novo adhesions after indirect surgical trauma (0.23 ± 0.19 versus 0.30 ± 0.22, respectively; P = 0.003 by Student’s t-test) compared with the placebo group (Fig. 1A). In addition, the Sepracoat group had 2.8 times as many patients without de novo adhesions (18 [13.1%] of 137 versus 5 [4.6%] of 108 patients, respectively) a difference that also was statistically significant (P = 0.018 by Fisher’s exact test) (Fig. 1B).

The Sepracoat group also had a lower incidence of de novo adhesion formation than the placebo group at 18 of the 22 available sites (data not shown). The difference was statistically significant for 3 sites: the posterior uterus, the right pelvic sidewall, and the right ovary (P = 0.001, 0.012, and 0.010, respectively, by Fisher’s exact test). Moreover, a greater percentage of Sepracoat-treated patients (80.4%) had at least one ovary that was completely free of adhesions compared with placebo-treated patients (57.8%; P = 0.014 by Fisher’s exact test).

The mean of the median de novo adhesion extent score for each patient was 42% less in the Sepracoat group than in the placebo group (0.11 ± 0.03 versus 0.19 ± 0.04, respectively; P = 0.014 by Wilcoxon’s rank sum test) (Fig. 1C). The mean of the median de novo adhesion severity score for each patient was significantly reduced by 38% in the Sepracoat group compared with the placebo group (0.20 ± 0.06
Figure 1

(A), Incidence of de novo adhesions at second-look laparoscopy: proportion of available sites involved (mean ± SEM; *P = 0.003). (B), Incidence of de novo adhesions at second-look laparoscopy: percentage of patients free of adhesions (mean ± SEM; *P = 0.018). (C), Extent of de novo adhesions at second-look laparoscopy (mean ± SEM of the median scores for each patient’s adhered sites; *P = 0.004). (D), Severity of de novo adhesions at second-look laparoscopy (mean ± SEM of the median scores for each patient’s de novo adhered sites; *P = 0.026). PBS = phosphate-buffered saline.

versus 0.32 ± 0.07, respectively; *P = 0.026 by Wilcoxon’s rank sum test) (Fig. 1D).

At sites of direct surgical trauma, type Ib de novo adhesions developed at 0.50 ± 0.42 of the available sites in the control group patients as opposed to 0.49 ± 0.36 of those in the Sepracoat group patients (not significant, *P = 0.40).

Covariate Analysis

An ANOVA model was used to examine a variety of possible covariates in the study for any effects on the primary efficacy parameter (i.e., the proportion of available sites with de novo adhesions). No covariate was found to have a statistically significant effect on the comparative efficacy of Sepracoat and placebo (data not shown).

The following covariates were found not to have a statistically significant correlation with de novo adhesion formation: patient age, preoperative use of GnRH analogues within 31 days of the initial procedure, time to second-look laparoscopy, volume of test solution applied, and volume of excess fluid removed and remaining. The following covariates were found to correlate significantly with a greater incidence of adhesions: higher patient body mass index (weight in kilograms and height in square meters; *P<0.001 by ANOVA), greater proportion of sites with adhesions at baseline evaluation (*P = 0.017 by ANOVA), greater decrease in hematocrit between baseline and postoperative day 2–5 (*P<0.001 by ANOVA), and lower rate of test solution application (in milliliters per hour; *P = 0.010 by ANOVA).

Importantly, when analyzed controlling for each of the
Number of sites with preexisting adhesions compared with number of sites at which de novo adhesions formed in the placebo group ($r = -0.31; P = \text{not significant}$).

As can be seen in Figure 2, among the women in the control group, a greater number of sites with preexisting adhesions was not predictive of the number of sites at which de novo adhesions formed.

**Video Analysis**

At each of the 23 abdominopelvic locations evaluated in the study, no bias was found on the part of the attending surgeon with respect to the distribution of higher adhesion scores across treatment groups compared with the scores of the independent reviewer ($P > 0.05$ by the Jonckheere-Terpstra test of homogeneity).

**Safety**

The safety profiles of Sepracoat and the placebo were comparable. Sepracoat had no adverse effect on hematologic parameters, blood chemistry values, liver and renal function tests, or serum electrolytes (data not shown). There was no statistically significant difference between the treatment and placebo groups in the incidence of the five most common adverse events: pain, location unspecified; abdominal pain; nausea; fever; and headache. Among the more than 100 other parameters assessed, the Sepracoat group had a significantly greater incidence of dizziness (15.9% versus 6.7%) and pharyngitis (7.0% versus 1.7%) than the placebo group ($P < 0.05$ by Fisher’s exact test, two-tailed). However, these reactions generally were mild or moderate and were not...
attributed to the test solution by the attending surgeons. Mechanisms for these differences remain unclear.

DISCUSSION

It generally is accepted that the best approach to reducing postoperative adhesion development is strict attention to surgical technique (to the extent possible for the surgical procedure being performed). These principles are contained within the tenets of gynecologic microsurgery and include minimization of tissue handling (and atraumatic handling of tissue that must be handled), achievement of meticulous hemostasis, use of fine suture of low reactivity, prevention of tissue drying, use of magnification as appropriate, and avoidance of introduction of foreign bodies (3). Thus, these issues address both the site of surgical injury and the surrounding nonsurgical sites. The development of adhesions at these latter sites has been called de novo adhesion formation or, more specifically, type Ia de novo adhesions (6). Reduction of adhesions at these sites is the subject of this study.

The extent to which de novo adhesions occur after surgery has been unappreciated because the early second-look laparoscopic procedure required to identify them has been performed in only a limited number of subjects. Further, in the many studies that have evaluated adhesion re-formation at second-look laparoscopy, few have reported the development of adhesions (or lack thereof) at areas distant from the site of interest for that study. However, previous studies indicate that de novo adhesions occur in 51% of subjects and at 31% of their available sites after gynecologic laparotomy (10), and in 12% of subjects and 23% of their available sites after gynecologic laparoscopy (11).

Tissue precoating with a protective sodium hyaluronate solution would be expected to reduce de novo adhesion development by minimizing tissue drying and reducing tissue trauma (e.g., serosal abrasion by lap pads, handling). In animal studies, tissue precoating with Sepracoat significantly reduced de novo adhesion formation compared with non-treated control animals (8, 12). Consistent with those observations, in this clinical trial, Sepracoat significantly increased the percentage of patients who were free of de novo adhesion formation to 13.1%, compared with 4.6% of the control group. The use of Sepracoat also was associated with significant reductions in the proportion of available sites with de novo adhesion formation, as well as the severity and extent of de novo adhesion formation.

Because efficacy evaluations were performed by the attending surgeons, a videotape review by a blinded observer was included in the study design to rule out surgeon bias. Comparison of adhesion scoring by the surgeons and the reviewer using the Jonkheere-Terpstra test of homogeneity demonstrated that no bias existed.

It is important to note that in animal studies, Sepracoat has not been shown to be effective in reducing adhesion formation at sites of surgical injuries when applied after lesioning (13). This study also concluded that Sepracoat was not effective in reducing postoperative adhesion development at sites of direct surgical trauma. These observations suggest that this solution does not reduce de novo adhesion formation by a pharmacologic action, but rather by limiting tissue trauma at the time of tissue injury. If, in fact, hyaluronate solutions also have pharmacologic activity, failure of postcoating to manifest this ability by significantly reducing adhesion formation may be due to the limited residence time in the peritoneal cavity. Sepracoat, which is composed of 0.4% hyaluronic acid, persists at its site of application for approximately 24 hours, which may be insufficient to coat tissues during the process of reepithelialization.

Several interesting observations can be made from these data regarding the nature of peritoneal healing. First, no significant relation was identified between the time to the second-look laparoscopy and the incidence of de novo adhesions resulting from indirect trauma. This observation is consistent with similar findings for de novo adhesions resulting from direct surgical trauma (14) and for adhesion re-formation (11, 15). However, whereas the interval between the first surgical procedure and the second-look procedure in previous studies has been ≤3 months, in this study, the interval extended to 270 days. Second, the likelihood that sites with de novo adhesions would develop in an individual patient could not be predicted by the number of sites with preexisting adhesions.

Therefore, in this study population, individuals with adhesions at multiple sites did not have a greater propensity toward the development of de novo adhesions. Finally, data from the control subjects validated the concept that there is a difference in de novo adhesion development at sites of indirect and direct surgical trauma. Further, the data from the Sepracoat-treated subjects demonstrated for the first time the ability of an adjuvant to reduce the incidence of one type of adhesion without affecting the development of adhesions resulting from direct surgical insult.

Greater reduction of de novo adhesion formation by precoating with Sepracoat may have been limited due to the prescribed method of use of Sepracoat in the study protocol. The ability of dilute hyaluronate solutions to reduce adhesions probably results from the viscous protective nature of the solutions, which limits intraoperative tissue damage and thereby decreases the ensuing inflammatory process that leads to adhesion development. If the coating was thin, or if it was wiped off, its protective properties would be expected to be reduced.

In fact, the rate of Sepracoat application was a significant cofactor such that those subjects with the lowest rate of application had greater de novo adhesion formation. Further, the protocol dictated that pooled solution be aspirated after each application. Future studies may determine whether limiting the aspiration of Sepracoat, presoaking lap pads, and
precoating more generously will reduce de novo adhesion formation further.

In summary, Sepracoat precoating significantly reduced the likelihood of de novo adhesion formation at nonsurgical sites with regard to the incidence, severity, and extent of adhesions. Its use had a safety profile nearly identical to that of placebo; only dizziness and pharyngitis occurred more frequently. This unique surgical approach may be combined with other existing methods of adhesion reduction to provide a significant breakthrough in the reduction of overall postoperative adhesion development.

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