

Adept (icodextrin 4% solution) reduces adhesions after laparoscopic surgery for adhesiolysis: a double-blind, randomized, controlled study

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Objective: To evaluate the efficacy and safety of Adept (4% icodextrin solution) in reducing adhesions after laparoscopic gynecological surgery involving adhesiolysis.

Design: Multicenter, prospective, randomized, double-blind study comparing Adept with lactated Ringer's solution (LRS).

Patient(s): Four hundred two patients randomized intraoperatively to Adept (n = 203) or LRS (n = 199) returned for second laparoscopy within 4–8 weeks. Incidence, severity, and extent of adhesions were determined on both occasions.

Main Outcome Measure(s): The primary efficacy measure defined by the Food and Drug Administration was the number of patients achieving clinical success with adhesion treatment. Other measures included incidence and American Fertility Society (AFS) scores.

Result(s): Significantly more Adept patients achieved clinical success than did LRS patients (49% vs. 38%). In infertility patients, Adept demonstrated particular clinical success compared with LRS (55% vs. 33%). This was reflected in the number of patients with a reduced AFS score (53% vs. 30%) and in fewer patients with a moderate/severe AFS category score (43% vs. 14%). Safety was comparable in both groups. Most events were related to the surgery, with an increase in transient labial edema in the Adept group.

Conclusion(s): This is the first randomized, double-blind trial of an adhesion reduction agent. It demonstrated that Adept is a safe and effective adhesion reduction agent in laparoscopy. (Fertil Steril® 2007;88:1413–26. ©2007 by American Society for Reproductive Medicine.)

Key Words: Icodextrin 4% solution, Adept, anti-adhesion agent, adhesions, adhesion reduction, gynecologic laparoscopy, fertility, endometriosis, adhesiolysis

Adhesion formation after abdominopelvic procedures is almost inevitable (1–3). Adhesions account for approximately 20%–40% of cases of infertility in women (4, 5), are a major cause of postoperative pain (6, 7), and are the most common cause of intestinal obstruction (2, 8). They add a significant amount of time to subsequent abdominal surgery (9, 10), and the incidence of bowel injury and inadvertent enterotomy during reoperation has been shown to be high (with an incidence of 19% in open and 10%–25% in laparoscopic adhesiolysis cases) (11, 12). Adhesions adversely affect patient morbidity

(13, 14) and are an important and costly burden to health systems (15, 16) and an increasing litigation risk (17, 18).

Advances in surgical techniques are being made, and laparoscopic surgery is becoming more widespread. However, as evidenced by the recent Surgical and Clinical Adhesions Research–2 (SCAR-2) study data (14), this is not sufficient to prevent adhesion formation. There is a need for effective and safe adhesion reduction agents that are easy to use in laparoscopic surgery. These agents need to decrease both the recurrence of pre-existing adhesions and the development of de novo adhesions. This is particularly important in clinically challenging patients, such as those with endometriosis, who have an increased tendency to form adhesions (19).

In recent years, a number of devices have been evaluated. The first Food and Drug Administration (FDA)-approved product for adhesion prevention was Interceed, a bioabsorbable fabric, which is twice as effective as surgery alone in preventing adhesion formation (20, 21). However, efficacy

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is reduced in the presence of blood, the product is site-specific, and, because it is a fabric, is difficult to use during laparoscopic procedures. A second barrier, Seprafilm, a sodium hyaluronate/carboxymethylcellulose film that persists during re-epithelialization and is then absorbed, can also significantly reduce adhesions (22, 23). However, it is also difficult to use during laparoscopy, and recent data indicate that use of this device at the site of bowel anastomosis can increase the risk of anastomotic leakage (24). Both of these barriers are approved for abdominopelvic use in Europe but are only indicated for laparotomy use in the United States. None of the research with these devices has been double blinded.

The use of fluids in the peritoneal cavity to separate damaged peritoneal surfaces and prevent contact between organs during the time of postoperative repair has been proposed as a method of adhesion reduction—a process known as hydroflotation (25, 26). Crystalloid solutions, such as lactated Ringer's solution (LRS), phosphate-buffered saline (PBS), and normal saline, are commonly used but are not approved for use as adhesion reduction agents. Small volumes of 200–500 mL are usually instilled (27); however, as this type of solution is absorbed at an approximate rate of 30–50 mL/hour (27–29), 200 mL LRS would be absorbed in approximately 6 hours (27). Transvaginal ultrasound assessment of LRS has shown that within 24 hours, a 250 mL surgical instillate volume would have diminished to an undetectable level (30).

The peritoneal surface takes several days to recover after surgery (31), so solutions with a short residence time would not be expected to prevent adhesion formation. This is supported by the results of a meta-analysis of 23 published reports, which showed that the use of crystalloid instillates in volumes of up to 500 mL did not increase adhesion-free outcome in patients undergoing abdominopelvic surgery (32).

Adept (icodextrin w/v 4% solution; Baxter Healthcare, Deerfield, IL) is an adhesion reduction agent that is approved in Europe for use in both laparotomy and laparoscopy. In the United States, it was recently approved by the FDA for use in gynecologic laparoscopy with adhesiolysis and is the first and only anti-adhesion agent approved for use in laparoscopic surgery in the United States. This nonviscous, iso-osmotic, clear solution contains icodextrin, a biodegradable α -1,4-linked starch-derived glucose polymer (molecular weight \sim 16,500 Daltons), at a concentration of 4%, in a buffered electrolyte solution (sodium 133 mmol/L; chloride 96 mmol/L; calcium 1.75 mmol/L; magnesium 0.25 mmol/L; lactate 40 mmol/L, the buffer). Early work with Adept as an anti-adhesion agent showed that it is best used throughout surgery as an irrigant fluid (minimum 100 mL/30 minutes) and that, at the end of surgery once all irrigant fluid is removed, 1,000 mL should be instilled into the peritoneal cavity to remain as a postoperative instillate (33, 34).

As Adept is a free-running liquid, it can be easily administered via a laparoscope. As an instillate, Adept solution forms a fluid reservoir in the peritoneal cavity with a prolonged residence time of up to 4 days (35). Icodextrin is metabolized by

amylase, which is not present in the peritoneal cavity of humans (36). It persists for several days in the peritoneal cavity and is slowly absorbed by the lymphatic system into the systemic circulation where it is broken down by amylase and metabolized to glucose (40 g glucose/L of Adept) (35). The presence of Adept in the peritoneal cavity during this prolonged period separates damaged surfaces and minimizes contact between organs during the critical period for adhesion formation.

A pilot clinical study was undertaken previously to assess the safety, tolerability, and efficacy of Adept in reducing adhesions after laparoscopic gynecologic surgery (33). It showed that the use of Adept as an intraoperative irrigant and postoperative instillate reduced adhesion formation and reformation and was well tolerated. A large pivotal trial to confirm the clinical efficacy and safety of Adept was therefore undertaken.

METHODS

Patients

The study participants were aged ≥ 18 years and in good health. Laparoscopic surgery was planned for a gynecologic procedure that included adhesiolysis followed by a second follow-up laparoscopy 4–8 weeks later. Each patient's primary diagnosis was recorded (e.g., pelvic pain, infertility, endometriosis, and known adhesions). Preoperative exclusion criteria included: the use of concomitant systemic corticosteroids, antineoplastic agents, and/or radiation; pregnancy; diagnosis of an active pelvic or abdominal infection, or cancer; and a known allergy to starch-based polymers. Intraoperative exclusion criteria included patients requiring an additional non-obstetric/gynecologic surgical procedure to be performed during the laparoscopic procedure; unplanned surgery necessitating opening the bowel (excluding appendectomy); any laparotomy procedure; and use of another adhesion reduction agent. Adhesion site exclusion criteria included patients having fewer than three of the available anatomical study sites with adhesions or, if fewer than three were lysed, removal of any anatomical sites being scored for the purposes of the study; and an inability to visualize clearly all available anatomical score sites.

Patients were fully informed of the study procedure and gave signed informed consent. The study was approved by the Institutional Review Board at each study site and by the FDA under an Investigational Device Exemption. A data-monitoring committee was established to monitor the study and to advise on continuation of the study following a protocol planned blinded interim analysis. None of the board members participated as recruiting centers.

In total, 410 fully evaluable patients were planned to complete the study, with 205 receiving Adept and 205 receiving LRS.

Study Design

This was a double-blind, randomized study conducted at 16 referral centers. This is the first double-blind clinical study

of an anti-adhesion device. Double-blinding was possible because Adept and LRS are both clear and odorless solutions with similar viscosities to water.

Treatment was randomized by computer-generated randomization on a 1:1 basis. Patient numbers were allocated to treatment group before labeling of the blinded study treatment bags. The study solutions were presented in identical 1 L infusion bags, and each bag had an outer wrap that contained the study code and patient number on an identification label.

Study Procedures

The study involved four visits as illustrated in Figure 1.

Visit 1: A screening visit took place up to 4 weeks before the scheduled surgery, during which patients completed an informed consent and underwent a physical examination. Samples were also taken for clinical laboratory tests, and each patient's medical history was recorded.

Visit 2: The first laparoscopic procedure took place. Inclusion and pre- and intraoperative exclusion criteria were checked. Planned surgery commenced, and, after confirmation that there were no intraoperative exclusion criteria, the patient was randomized and the study treatment was allocated. Videotaping commenced with surgery to ensure that all 23 or all available anatomical sites for adhesion scoring could be captured/visualized on tape. Recording continued throughout surgery. At the beginning of surgery, the presence or absence of adhesions and their extent and severity at all anatomical sites was also recorded on the Case Report Form (CRF). Throughout the procedure, the abdomen was irrigated with a minimum of 100 mL of study solution every 30 minutes. There was no limit on the volume of fluid used for irrigation. The total was recorded in the CRF. At the end of surgery, any remaining study solution was aspirated and 1,000 mL of the study solution was instilled from a fresh bag from the randomized box of study supplies. All adverse

events and perioperative medications were recorded. Patients were issued a diary card before discharge from hospital to record adverse events and the use of concomitant medications.

Visit 3: A postoperative visit took place 1–3 weeks after the initial surgery. During this visit, patients underwent clinical laboratory tests and a physical examination. Concomitant medications and any adverse events were also recorded. Patients were issued a new diary card. In addition, patients were scheduled to return for their follow-up laparoscopy and clinical laboratory tests within 4–8 weeks of surgery.

Visit 4: At the final study visit, the second laparoscopic procedure took place and videotaping and scoring of all available anatomical sites was performed as per the initial laparoscopy. All adverse events and concomitant medications were recorded and laboratory tests performed.

Adhesion Scoring

At both the initial surgery and follow-up laparoscopy, adhesions were scored at all 23 or all available anatomical sites: anterior peritoneum (caudal anterior, cephalad anterior right, cephalad anterior left), small bowel, anterior uterus, posterior uterus, omentum, large bowel (left and right), rectosigmoid portion of the large bowel, cul-de-sac (posterior), right pelvic sidewall, left pelvic sidewall, right ovary (lateral, medial, fossa), left ovary (lateral, medial, fossa), right Fallopian tube, right ampulla, left Fallopian tube, left ampulla (33, 37, 38).

At each site, the presence or absence and extent and severity of adhesions were determined.

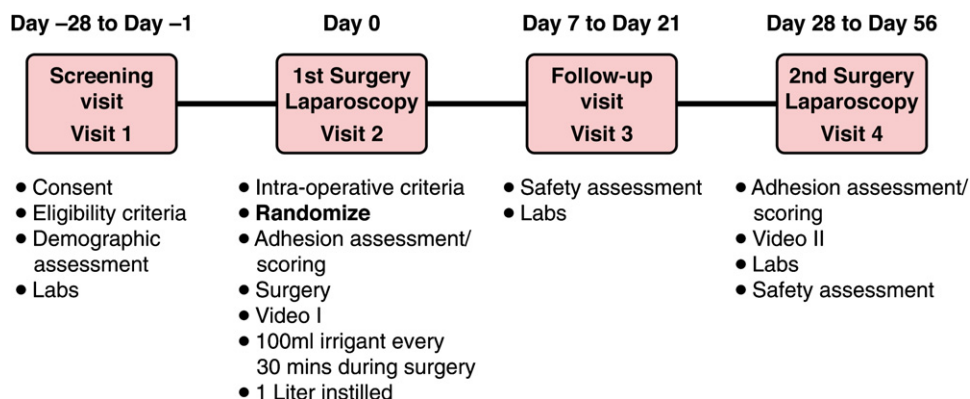
Extent was defined as

- Localized: less than 1/3 of the adhesion site (anatomical site) covered
- Moderate: 1/3–2/3 of the adhesion site covered
- Extensive: more than 2/3 of the adhesion site covered

Severity of adhesions was defined as

FIGURE 1

Study procedure flow.



Brown. Adept reduces adhesions in laparoscopy. Fertil Steril 2007.

- Mild: filmy and avascular
- Severe: dense, cohesive, or vascular

A minimum of three adhesions had to be lyzed at initial surgery and the sites recorded. An adhesion was only considered lyzed when the sites to which the adhesion was attached were freed from the adhesion.

At the time of both initial and follow-up laparoscopy, the investigator recorded the adhesion assessments and American Fertility Society (AFS) scores in the operating room. Subsequently, the investigator reviewed the video and confirmed the assessment or amended it to complete the CRF. Both the operating room scores and final CRF review sheet were used as source documents. This ensured that there was reconciliation of the video with the CRF.

Video Review Process

To ensure consistency of adhesion scoring between study sites, all investigators taking part in the study received training on the adhesion assessment process. The first three patients' videos recorded by each investigator were assessed by a single, independent, masked reviewer. If these videos were deemed acceptable, then one in every five subsequent videos was reviewed. If any video was found to be unacceptable, videos for the next three patients were reviewed until three consecutive videos were acceptable. Any queries raised by the reviewer were resolved directly with the relevant investigators, and it was the investigator's final decision that was accepted for analysis.

Study Efficacy Measures and Assessments

The following clinical parameters were used to evaluate the treatment responses: clinical success; incidence, extent, and severity of adhesions; and adhesion scoring using the AFS classification for adnexal adhesions (39). Clinical success for adhesion reduction was determined in a discussion with the FDA for an individual patient as a reduction in adhesions of at least three or 30% of sites lyzed (whichever is greater) between initial surgery and the follow-up laparoscopy.

Incidence, extent, and severity of adhesions were assessed at both surgeries at all 23 sites listed above. Comparisons of mean scores and the percentage of patients with an increase or decrease in incidence, extent, and severity were undertaken. Visceral adhesions, abdominal wall adhesions, de novo, and reformed adhesions at follow-up were also evaluated.

AFS classifications for adnexal adhesions (for Fallopian tubes and ovaries) were recorded for all patients with ovaries and/or Fallopian tubes (39). This AFS score was recorded during the first and second laparoscopies. The final AFS score was calculated by summing the component scores from the right and left side separately and then taking the lower of the two values (39).

In patients with a primary diagnosis of pelvic pain, the degree of pain was assessed at baseline and at the time of the

final visit (before the second laparoscopy) using a visual analog scale (VAS).

Safety Assessments

Safety was assessed by serious adverse events (SAEs), adverse events, and changes in laboratory values. Patients completed diary cards between initial surgery and follow-up surgery. At postoperative checkup (visits 3 and 4), cards were assessed to monitor progress. They allowed the patient to record their well-being and all concomitant medications. All adverse events whether they were considered related to study solutions or not, were investigated, and the details of nature, severity, duration, outcome, and relationship to study device were recorded.

Laboratory Tests

Clinical laboratory tests, including biochemistry, hematology, and urinalysis, were performed at study visits 1, 3, and 4, at laboratories routinely used by the investigator.

Study Populations

Safety was assessed in the intent-to-treat (ITT) population, which included all patients who had the study solution instilled. Efficacy results are presented for the per protocol (PP) population. These patients were those who had completed both first- and second-look laparoscopies without major protocol violations. Patients undergoing surgery with infertility as a primary diagnosis were assessed as an infertility subgroup for AFS scores.

Statistical Analysis

By convention, all statistical tests performed were two-tailed with significance determined at the 5% level, unless otherwise stated. All comparisons were reported with the 95% confidence intervals for the difference. For the assessment of continuous data, which included absolute and percentage changes from baseline to follow-up, a two-way analysis of covariance (ANCOVA) was performed when looking at differences between the two treatment groups. For assessment of categorical data, which included the primary endpoint definition of success and patient frequency distributions, differences between treatments were assessed using logistic regression.

Both ANCOVA and logistic regression analyses included factors for treatment group, center, and treatment group-by-center interaction and a covariate for baseline value if appropriate. If the interaction term was not significant at the 10% level, each model was refitted omitting the interaction term. For all categorical data, the odds ratios for the comparison of Adept against the LRS group were presented with the associated 95% confidence interval. An odds ratio of 1 indicates that the chances of the event occurring in both groups is equal; an odds ratio greater than 1 indicates a result in favor of Adept. For instance, if the ratio is 2, then it is twice as likely that an event occurs in the Adept group than in the

LRS group. Furthermore, if the lower bound (left side) of the 95% confidence interval is also greater than 1, then the result is significantly in favor of Adept ($P < .05$).

RESULTS

Patients

Patients were recruited between July 2001 and March 2004. From a total of 777 patients screened, 449 patients (ITT population) were randomized and received treatment with Adept (227 patients) or LRS (222 patients). A total of 29 patients were withdrawn from the study; nine of those were because of pregnancy or resolution of their pain after first surgery (five in the Adept group and four in the LRS group). A further 12 patients (six in each treatment group) declined second surgery; one patient (LRS) withdrew because of a SAE (bowel perforation, unrelated to the study device); and four patients (two in each group) were lost to follow-up. In addition, one Adept patient had her right Fallopian tube removed during surgery, one Adept patient moved away from the center before the second surgery, and one patient in the LRS group requested a hysterectomy. Overall, 6.6% of patients in the Adept group were withdrawn compared with 6.3% of patients in the LRS group ($P = .90$). Therefore, 420 patients completed the trial. Of this group, 18 patients had major protocol violations, leaving 402 patients in the PP population (Adept, 203 patients; LRS, 199 patients).

Subanalyses of the PP population were undertaken for the subgroups as follows: infertility as a primary diagnosis (Adept, 102 patients; LRS, 112 patients); patients with endometriosis (Adept, 124 patients, of whom 56 also had infertility; LRS, 119 patients, of whom 61 also had infertility);

patients with a diagnosis of infertility and pelvic pain (Adept, 45 patients; LRS, 48 patients).

Patient demographics were similar in the two treatment groups, which were balanced with respect to age, height, and weight (Table 1). A total of 89% of patients had previously undergone surgery, 78% of whom had undergone reproductive surgery and 24% of whom had previously undergone gastrointestinal surgery.

Each patient's preoperative primary diagnosis was recorded (note that patients could have more than one primary diagnosis) (Table 1). The treatment groups were balanced with respect to the presence of endometriosis, adhesions, and other primary diagnoses. The proportion of patients with pelvic pain was slightly higher in the Adept group (67%) compared with the LRS group (60%), and slightly more patients in the LRS group had fertility problems (57%) compared with those in the Adept group (51%).

Efficacy

The PP population was used for all efficacy analyses.

Clinical Success

Significantly more patients in the Adept group were classified as having undergone a successful treatment for adhesion reduction (clinical success) than in the LRS group, that is, a reduction of three or 30% of adhesions between first- and second-look surgery ($P = .018$) (Fig. 2).

In the subgroup of patients with a diagnosis of infertility at baseline, 55% of patients in the Adept group were classified

TABLE 1

Patient demographics and primary diagnosis for the ITT population.

	Adept (n = 227)	LRS (n = 222)	Overall (N = 449)
Age, years, mean \pm SD	32.6 \pm 5.9	32.3 \pm 5.7	32.4 \pm 5.8
Height in inches, mean \pm SD (n)	64.7 \pm 2.7 (225)	64.2 \pm 2.8 (221)	64.4 \pm 2.8 (446)
Weight, pounds, mean \pm SD (n)	153.2 \pm 36.9 (225)	152.0 \pm 35.0 (220)	152.6 \pm 36.0 (445)
Race, n (%):			
Caucasian	160 (70.5)	144 (64.9)	304 (67.7)
East Asian/Oriental	6 (2.6)	8 (3.6)	14 (3.1)
African American	32 (14.1)	32 (14.4)	64 (14.3)
Hispanic	24 (10.6)	35 (15.8)	59 (13.1)
Other	5 (2.2)	3 (1.3)	8 (1.8)
Primary diagnosis,* n (%):			
Pelvic pain	152 (67.0)	134 (60.4)	286 (63.7)
Endometriosis	94 (41.4)	93 (41.9)	187 (41.6)
Infertility	115 (50.7)	127 (57.2)	242 (53.9)
Adhesions	126 (55.5)	127 (57.2)	253 (56.3)
Other	36 (15.9)	43 (19.4)	79 (17.6)

* NB Patients could have more than one diagnosis.

Brown. Adept reduces adhesions in laparoscopy. *Fertil Steril* 2007.

as having undergone a successful treatment for adhesion reduction compared with 33% in the LRS group ($P=.0007$) (Fig. 3).

Adhesion Incidence

There was a significantly greater reduction in the number of adhesion sites between baseline and follow-up in the Adept group than in the LRS group (mean \pm SD: 2.6 ± 3.7 vs. 2.0 ± 3.2 , respectively; $P=.039$).

Significantly more patients were free of de novo adhesions with Adept at second-look laparoscopy compared with patients treated with LRS (53% and 43%, respectively, Fig. 4) ($P=.029$).

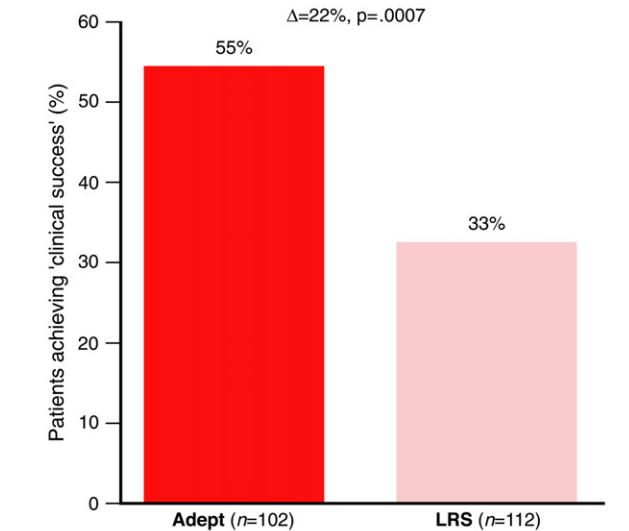
Fertility

AFS score—all patients: Forty-three percent of all Adept patients had a reduction in AFS adnexal adhesion score at follow-up compared with 35% of all LRS patients ($P=.065$). The mean reductions in AFS (\pm SD) score per patient between baseline and follow-up were 2.70 ± 6.18 for Adept and 1.19 ± 5.98 for LRS.

Of the 57 patients in the Adept treatment group and 55 patients in the LRS group who had moderate/severe AFS scores at initial surgery, 29 (51%) and 19 (35%) patients, respectively, demonstrated improvements in their AFS score by moving to a minimal/mild AFS category. For patients with

FIGURE 3

Clinical success in infertility patients (PP population; $P=.0007$).



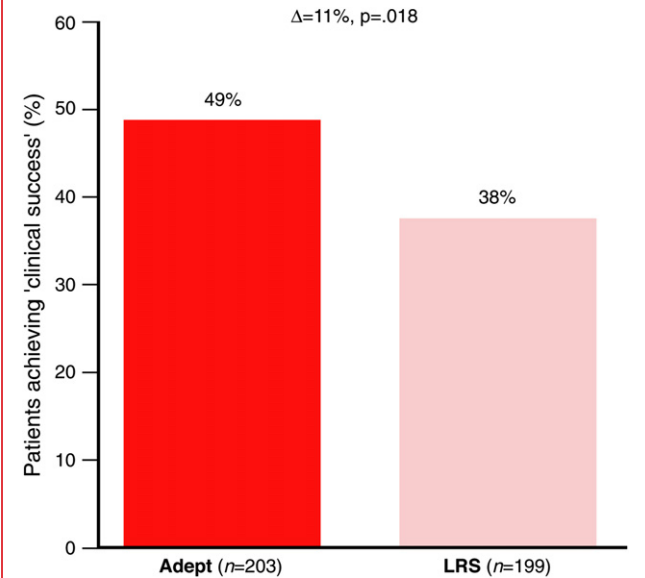
**Clinical Success defined as the percentage of patients in whom the number of sites with adhesions decreased by at least 3 or 30% of the number of sites lysed

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minimal/mild AFS scores at initial surgery, 131/134 (98%) in the Adept treatment group and 137/144 (95%) in the LRS group had AFS scores that remained minimal/mild, maintaining fertility potential.

FIGURE 2

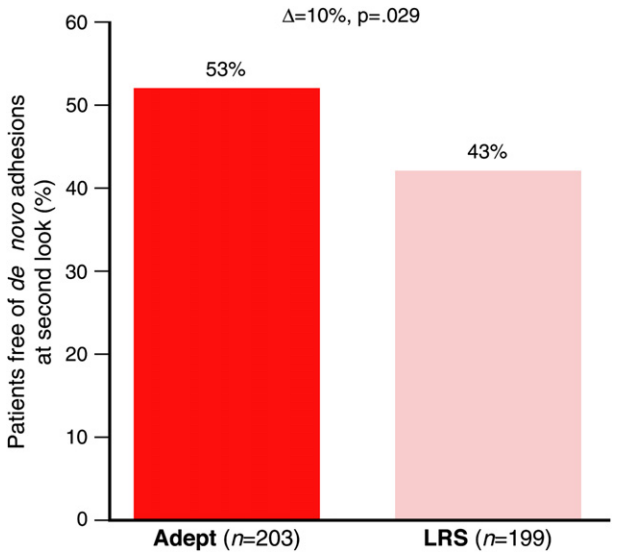
Clinical success. The percentage of patients in whom the number of sites with adhesions decreased by at least three or 30% of the number of sites lysed (PP population; $P=.018$ between groups).



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FIGURE 4

Percentage of patients free of de novo adhesions in the Adept and LRS treatment groups at second laparoscopy (PP population; $P=.029$).



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AFS score—infertility patients: Significantly more Adept -treated infertility patients (53%) had a reduction in AFS score compared with the LRS group (30%; $P=.001$) (Fig. 5). Furthermore, the mean reduction in the Adept group was significantly greater compared with the LRS group (3.46 ± 6.77 vs. 1.10 ± 6.36 ; $P=.011$).

At initial surgery, 37 Adept- and 35 LRS-treated infertility patients had moderate/severe AFS category scores; 16 (43%) fewer patients had moderate/severe AFS category scores at second surgery with Adept compared with five (14%) fewer with LRS.

AFS score—infertility patients with endometriosis: One hundred seventeen patients in the study had a diagnosis of infertility and confirmed endometriosis at first surgery (Adept, 56 patients; LRS, 61 patients). At the time of second-look laparoscopy, 54% of patients treated with Adept had a reduction in AFS score compared with only 25% of patients treated with LRS ($P=.003$) (Fig. 6).

AFS score—infertility patients with pelvic pain: Ninety-three patients had a diagnosis of infertility with pelvic pain at initial surgery (Adept, 45 patients; LRS, 48 patients). At the second laparoscopy, 51% of patients treated with Adept had a reduction in AFS score compared with 23% of LRS-treated patients ($P=.006$) (Fig. 7).

Severity and Extent

Extent and severity of adhesions were examined at each of the 23 anatomical sites. The mean (\pm SD) percent reduction in ex-

tent and severity of adhesions per patient between baseline and follow-up for Adept and LRS was 26.9 ± 51.4 versus 21.8 ± 48.5 ($P=.240$) and 24.2 ± 45.2 versus 21.5 ± 41.0 ($P=.415$), respectively. Overall, the extent and severity of adhesion reductions were 77% and 73% in the Adept group compared with 70% ($P=.084$) and 70% ($P=.446$) in the LRS group.

Adhesion Burden

The study showed that the absolute decrease in adhesion incidence provided by Adept and LRS became greater in proportion to the number of sites lyzed at initial surgery (Fig. 8). The higher the initial number of sites lyzed, the greater the reduction in adhesion incidence with Adept compared with LRS. For instance, in those patients with 11 or more adhesions lyzed at initial surgery, the mean reduction in incidence of adhesions with Adept was 4.38 ± 3.70 versus 2.95 ± 3.35 for LRS patients.

Endometriosis

The majority of patients had surgical treatment of endometriosis at first laparoscopy: 241, compared with 161 who did not. From a mean of 3.01 sites at first look, 2.95 were treated ($n = 402$), which equals 1,210 sites with endometriosis at baseline, 1,182 (98%) of which were treated.

Figure 9 shows the clinical success for all patients according to endometriosis severity, which is defined as the number of anatomical sites with treated endometriosis: 0, 1–3, 4–6, and >6 sites.

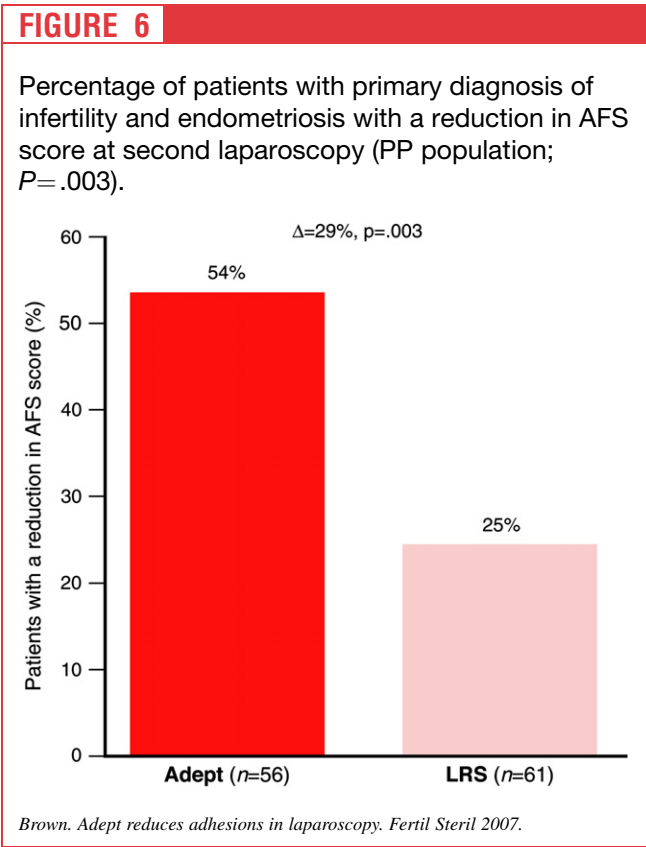
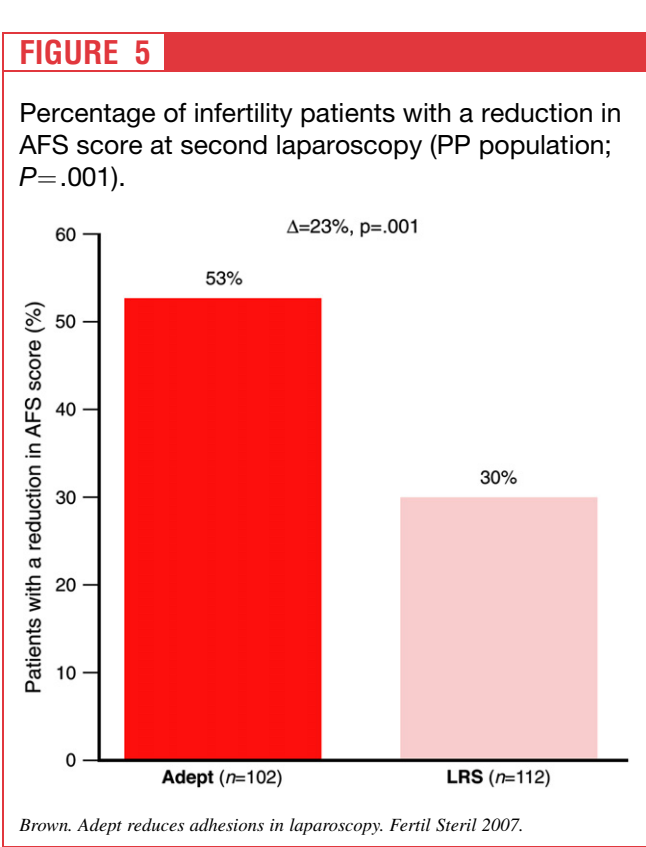
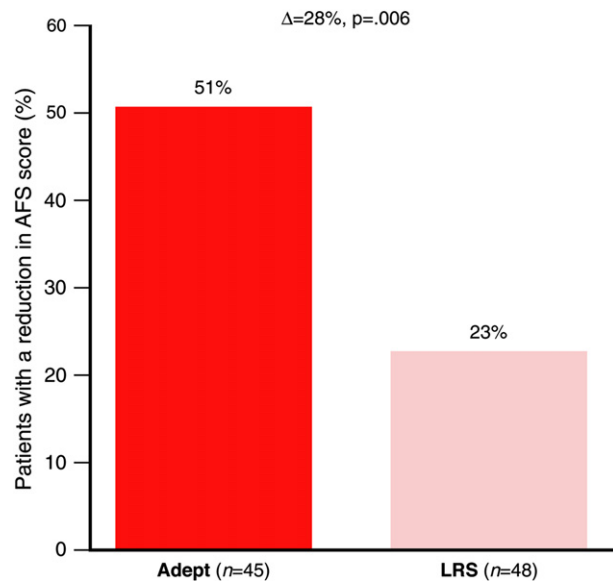


FIGURE 7

Percentage of patients with primary diagnosis of infertility and pelvic pain with a reduction in AFS score at second laparoscopy (PP population; $P=.006$).



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For patients with treated endometriosis, the benefits of Adept over LRS increased with increasing disease, with 39% of those with severe endometriosis showing clinical success for Adept compared with 15% for LRS ($P=.036$).

However, there was also a benefit for patients with no treated endometriosis, where 20% more Adept patients than LRS patients achieved clinical success ($P=.009$).

Pain

Assessment of subjective patient VAS scores for pelvic pain before and after treatment showed that 83% ($n = 118$) of Adept patients and 82% ($n = 108$) of LRS patients with a primary diagnosis of pelvic pain had a clinically significant reduction in their VAS scores from baseline (35.8 ± 32.8 mm with Adept and 30.8 ± 30.2 mm with LRS).

Visceral and Abdominal Wall Adhesions

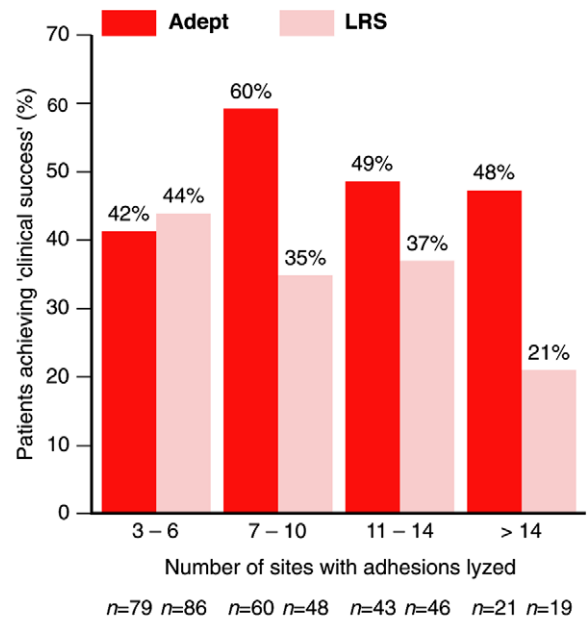
A significantly greater reduction occurred in the number of visceral sites with adhesions in the Adept group (1.5 ± 2.6) compared with patients treated with LRS (1.1 ± 2.2 ; $P=.046$). A similar effect was also reported for adhesions to the abdominal wall, but the difference between treatments did not reach significance (1.2 ± 1.6 vs. 0.9 ± 1.6 ; $P=.184$).

Overall Efficacy

Odds ratio analyses of all primary and secondary parameters for individual patients showed that, overall, patients treated

FIGURE 8

Clinical success in patients with increased adhesion burden (PP population).



**Clinical Success defined as the percentage of patients in whom the number of sites with adhesions decreased by at least 3 or 30% of the number of sites lysed

Brown. Adept reduces adhesions in laparoscopy. *Fertil Steril* 2007.

with Adept had more favorable outcomes than those receiving LRS (Fig. 10). In patients with infertility and in the subgroups with diagnoses of endometriosis or pain, the parameters of clinical success and AFS score also showed more favorable outcomes with Adept compared with LRS (Fig. 11).

Safety

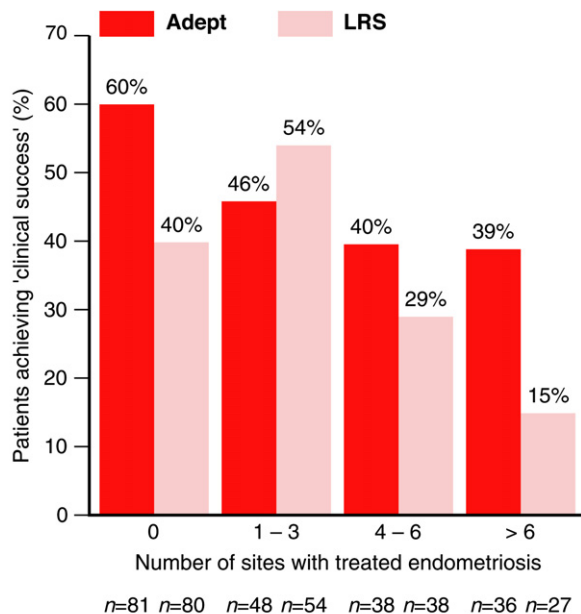
Adverse events The frequency of adverse events and the number of patients who reported them were similar in both treatment groups (Table 2). The majority of events were recorded as mild or moderate and not considered related to Adept or LRS. The most common adverse events reported after the initial laparoscopy were postprocedural pain (Adept, 83%; LRS, 87%), headache (Adept, 34%; LRS, 32%), and nausea (Adept, 16%; LRS, 17%), all of which are commonly experienced postsurgery (Table 2).

Postoperative infections were reported in 1% of Adept patients and 3% of LRS cases. Some other adverse events were reported with a higher frequency in one of the treatment groups, but most of these were relatively low incidence and were not statistically significant between groups, with the following exceptions:

- Diarrhea was reported by three (1%) Adept patients and 13 (6%) LRS patients ($P=.01$).

FIGURE 9

Clinical success in patients with endometriosis according to number of sites treated for endometriosis (PP population).



*'Clinical Success' defined as the percentage of patients in whom the number of sites with adhesions decreased by at least 3 or 30% of the number of sites lysed

Brown. Adept reduces adhesions in laparoscopy. *Fertil Steril* 2007.

- Dizziness was reported by one (0.4%) Adept patient and eight (4%) LRS patients ($P=.02$).
- Labial/vulval swelling was reported by 13 (6%) Adept and one (0.4%) LRS patient ($P=.002$).

The labial/vulval swelling was rated mostly mild or moderate. In 77% of the Adept cases, it resolved by expectant management within a week. None required surgical treatment.

Adverse events reported as serious occurred in 19 patients (eight Adept patients, 25 events; 11 LRS patients, 19 events). The type and incidence of SAEs were similar in both treatment groups, and in general they were due to postoperative complications and were not related to the study device (Table 2). Overall, three patients (one Adept, two LRS) reported SAEs considered by the investigator to be probably or possibly related to treatment: in the Adept patient, the events were pelvic pain, chest pain, shoulder pain, abdominal pain, nausea, dysuria, and urinary frequency; and in the LRS patients, events were decreased urinary output and elevated creatinine in one patient and severe abdominal pain, nausea, vomiting, and lower back pain in the other. Only one withdrawal was due to an SAE (bowel perforation), which occurred in an LRS patient, and there were no deaths during the study.

Laboratory tests Laboratory values were compared with normal values and compared within patient from baseline.

There were no clinically meaningful changes in laboratory test results in either treatment group, and most values remained within the reference ranges throughout the study.

DISCUSSION

This pivotal study assessed the safety and efficacy of Adept in reducing postsurgical adhesion formation after gynecologic laparoscopic surgery that included adhesiolysis. It was the first double-blind as well as the largest clinical study of an adhesion reduction device. Possible bias on the part of the clinical investigators has existed in previous studies designed to test the effectiveness of an adhesion reduction device. In contrast, in this study, investigator bias was unlikely because of the similarity in appearance of Adept and LRS, so that the clinical investigators were not able to tell them apart. As a result, this study was the first double-blind study of an adhesion reduction device where investigator bias was minimized.

The study protocol included endpoints defined in consultation with the FDA. The primary endpoint was the measure of clinical success in reducing adhesions. Clinical success was defined for a patient as a reduction of at least three or 30% of the number of preexisting sites with adhesions between initial surgery and the follow-up laparoscopy. Because the FDA-specified endpoint of clinical success was unique to this study, a number of other endpoints were specified by the protocol and agreed with by the FDA. Importantly, these endpoints demonstrated an outcome improvement in patients who received Adept compared with patients who received LRS.

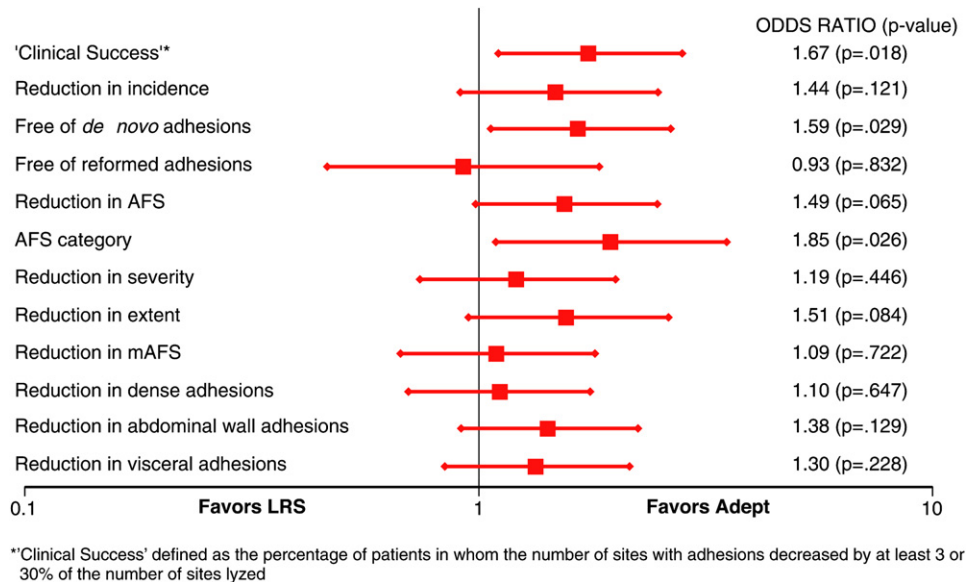
This study demonstrated that use of Adept as an irrigant and postoperative instillate reduces adhesions after laparoscopic gynecologic adhesiolysis. Furthermore, use of Adept as an irrigant and postoperative instillate in laparoscopic gynecologic adhesiolysis reduces adhesions more than LRS used in the same way.

Adhesion scoring systems have been developed to provide a more direct correlation between adhesion formation and clinical outcomes (40, 41). The AFS score used here is a classification of adnexal adhesions based on extent and severity of adhesions involving the Fallopian tube and ovary. An AFS score of 10 or less is predictive of a good prognosis for pregnancy (60%); a score of 20 or more is predictive of a poor prognosis for pregnancy (<20% chance) (42). Similar observations have been made regarding pelvic pain (43). Of the various systems that have been developed, the AFS adnexal adhesion score is the most widely used in gynecologic surgery. Since commencement of this study, the FDA has recommended AFS adnexal adhesion classification as a primary outcome measure in studies of anti-adhesion agents (44).

In the infertility subgroup, a significantly greater percentage of Adept patients had a reduction in AFS score than did LRS patients. This finding has important implications for the treatment of adhesion-related infertility and for the development of adnexal adhesions after surgery that may lead to infertility.

FIGURE 10

Odds ratio plot with 95% confidence interval (95.2% for clinical success) for each of the study parameters (PP population).



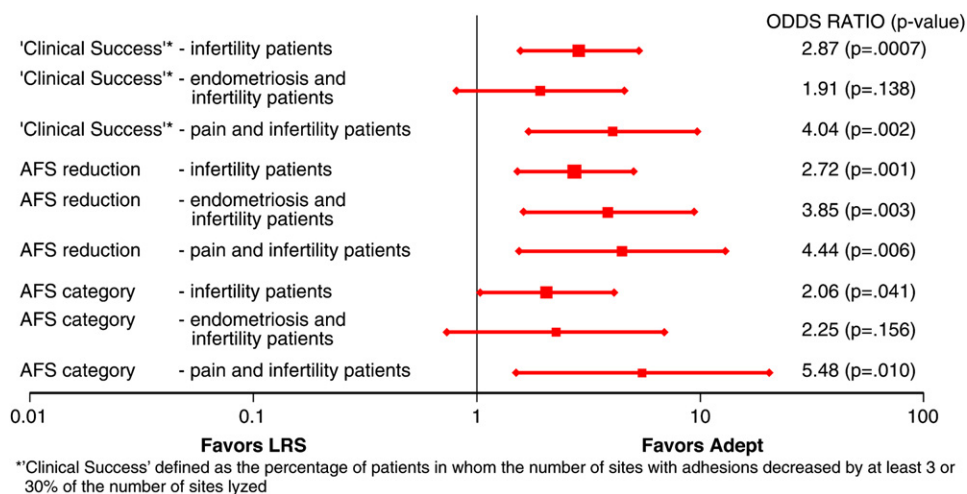
Brown. Adept reduces adhesions in laparoscopy. *Fertil Steril* 2007.

While both Adept- and LRS-treated patients had a reduction in AFS score from their baseline score, the Adept patients had a greater reduction in AFS score of 2.5–3.0 units beyond that of LRS patients. A reduction of three units is considered clinically significant as it can place a patient in a better prognostic category (minimal, mild) for pregnancy than would have occurred otherwise (moderate, severe) (42). In

this study, nearly half the Adept-treated infertility patients with moderate/severe AFS adnexal adhesion scores at initial surgery demonstrated improvements to minimal and mild in their AFS category at second-look laparoscopy. These data suggest that infertility patients undergoing surgery and treated with Adept may have a better prognosis for pregnancy.

FIGURE 11

Odds ratio plot with 95% confidence interval (95.2% for success) for clinical success and AFS scores in infertility patients (PP population).



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TABLE 2

Frequency of adverse events in both treatment groups—ITT population.

Adverse event	Adept		LRS	
	No. of subjects reporting	No. of reports	No. of subjects reporting	No. of reports
Overall adverse events	221	1,065	218	1,047
Between first and second laparoscopy	221	1,009	217	985
Related adverse events	55	84	38	48
Adverse events recorded as serious	8	25	11	19
Serious adverse events (SAEs)	44	77	36	57
Most frequent adverse events between surgeries (>10% patients):				
Post-procedural pain	189 (83.3%)	203	194 (87.4%)	213
Headache	77 (33.9%)	126	72 (32.4%)	125
Nausea	37 (16.3%)	39	37 (16.7%)	41
Post-procedural discharge	31 (13.7%)	31	28 (12.6%)	28
Dysmenorrhea	29 (12.8%)	31	24 (10.8%)	32
Constipation	24 (10.6%)	26	22 (9.9%)	23

Note: Adept, n = 227; LRS n = 222.

Brown. Adept reduces adhesions in laparoscopy. *Fertil Steril* 2007.

Pelvic adhesions are the leading cause of infertility in ovulating women, and adhesiolysis is the surgical treatment option (41). Patients with a primary diagnosis of infertility had a significant reduction in AFS score with Adept compared with LRS. However, more important are the individual patient differences. Significantly more of the Adept-treated patients (53%) had a reduction in AFS score at second look compared with those treated with LRS (30%). A logistic regression analysis of this 23% gross difference in the number of patients who had a reduction in AFS score as a result of their infertility surgery is significant ($P=.001$).

Although many clinical conditions can lead to adhesion formation, endometriosis is considered the most clinically challenging because adhesions that form are typically more severe and widespread throughout the pelvis (19). Recent work by Parker et al. has demonstrated that most patients undergoing radical surgical excision of endometriosis with concurrent adhesiolysis for pelvic pain will develop adhesions, including reformation of adhesions at surgery sites and the formation of de novo adhesions (45). Formation and reformation of adhesions may be due to inflammatory cytokines that are shown to be present in the pelvic cavity of women with endometriosis (19). As a result, demonstration of adhesion reduction in patients with endometriosis provides a marked challenge to an adhesion reduction device. Logistic regression analysis of the patients with a reduction in AFS score was significant for the Adept group compared with the LRS group ($P=.003$).

The relative benefit of an adhesion reduction device is best shown where there is a high preexisting adhesion burden, as the greater the number of adhesions lysed at initial surgery

the greater the rate of adhesion reformation (mean, 85%) (4, 46). The study showed that the greater the number of sites lysed at initial surgery, the greater the reduction of adhesions was with Adept as compared with LRS at second laparoscopy. These results demonstrate the greater effect of Adept as an adhesion reduction agent.

The significant reduction in visceral and abdominal wall adhesions is of clinical importance because these sites are associated with subsequent complications including small bowel obstruction (4) and pelvic pain (47, 48). This is of increased importance for patients who may have to undergo further abdominal surgery, not only because adhesions prolong subsequent surgeries (10), but because the site of these adhesions increases the risk of inadvertent enterotomy at subsequent surgery (11, 12, 49). Indeed tissue damage to underlying structures and particularly bowel or other visceral damage at adhesiolysis is one of the commonest causes of successful surgical negligence suits (17, 50).

The recognized parameters for measuring adhesions include measurement of incidence; sites of adhesion; type, extent, and tenacity/severity; and adhesion scores (AFS) (40). The odds ratio analyses for improvements in these parameters in individual patients consistently showed improvements with Adept compared with LRS. These findings were further strengthened with odds ratio analyses of clinical success, reduction in AFS score, and AFS score shift to a less severe category for the infertility patients.

The improvements seen in the LRS-treated group were contrary to expectations from the literature (32). A meta-analysis of studies with lower volume use (200–500 mL)

(32) of LRS, saline, and Hartmann's crystalloid solutions does not show a reduction of adhesions. This finding can be predicted, as crystalloids at this volume are absorbed from the peritoneal cavity at the rate of 30-50 mL/hour. At this rate there is likely to be little crystalloid solution remaining in the pelvis after 24 hours (27-29). A recent study examining absorption of 2 L of crystalloid solutions suggested that approximately 500 mL remained 24 hours later (35).

The explanation for the adhesion reduction seen with LRS in this study is probably related to the meticulous irrigation during surgery, the best surgical technique employed, and a hydroflotation effect from using larger volumes than in previous studies (i.e., 1 L) (26). Previous studies have shown adhesion reduction with regular intraoperative irrigation of tissues with PBS or coating with a 0.4% sodium hyaluronate solution (51).

From a safety perspective, the study demonstrated that both treatments were well tolerated, with a similar number of adverse events reported in the Adept and LRS treatment groups. The instillation of Adept solution was not associated with postoperative complications, such as peritonitis.

There was a 6% incidence of labial enlargement (including vaginal and vulval swelling and vaginal fullness) reported in the Adept patients compared with a 0.4% incidence among the LRS cases. Vulval edema is accepted as an unpleasant but nonserious and usually self-limiting problem associated with the use of intraperitoneal fluids for irrigation and instillation, particularly in laparoscopic surgery (52, 53). The edema probably results from fluid entering the Canal of Nuck or other fascial defects or planes. The fluid is typically reabsorbed spontaneously within a few days, and this process is facilitated by bed rest and does not usually require drainage. Vulval edema occurs in association with LRS and Adept because they are fluids rather than because of any specific properties of either LRS or Adept (52).

The safety of Adept use in routine surgery has been extensively monitored and well established through the ARIEL Registry in Europe (54, 55). The ease of use and acceptability and the safety of the Adept solution in routine gynecologic and general surgery were recorded in 4,620 patients in six European countries, with 2,882 undergoing gynecologic surgery (2,069 laparoscopy, 813 laparotomy). ARIEL showed that Adept was well tolerated, well accepted by patients, and considered easy to use by participating surgeons.

A number of adhesion reduction agents have been developed for use in abdominopelvic surgery in recent years; however, with the exception of Adept, none of the devices currently available have been approved for use in laparoscopic surgery by the FDA. All other adhesion reduction devices approved in the United States are solely for use in laparotomy and are limited in their effectiveness because of handling issues and site specificity (18). Therefore, an effective, broad-coverage, adhesion reduction agent like Adept that is easy to apply during laparoscopic procedures would be of major clinical benefit. As well as potentially reducing

the morbidity and mortality associated with adhesions, Adept use should make any further reoperative surgery easier and safer and reduce the considerable cost burden on health systems (9-12, 14, 15).

Recommendations recently developed in gynecological surgery advise that surgeons consider the use of adhesion reduction agents as part of an adhesion prevention strategy (18, 56, 57). To date, adhesion reduction agents have played a limited role in adhesion reduction strategies. This study, the first randomized, double-blind trial of an anti-adhesion agent, supports the safe and effective use of Adept as a routine prophylactic adhesion reduction agent.

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