

# Effectiveness of autocrosslinked hyaluronic acid gel after laparoscopic myomectomy in infertile patients: a prospective, randomized, controlled study

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**Objective:** To assess the efficacy of autocrosslinked hyaluronic gel in postsurgical adhesion prevention after laparoscopic myomectomy.

**Design:** Prospective, randomized, controlled study.

**Setting:** University of Naples "Federico II".

**Patient(s):** Thirty-six infertile women with symptomatic myomas were randomly divided into two groups of 18 patients each.

**Intervention(s):** Laparoscopic myomectomy with subserous sutures or interrupted figure 8 sutures, with (group A) or without (group B) application of autocrosslinked hyaluronic acid (HA) gel.

**Main Outcome Measure(s):** Rate of postsurgical adhesions at 60–90 days of follow-up.

**Result(s):** The rate of subjects who developed postoperative adhesions was significantly lower in group A in comparison with group B (27.8% vs. 77.8%). In both groups, the rate of adhesions was significantly higher in patients treated with interrupted figure 8 sutures than with subserous sutures.

**Conclusion(s):** Autocrosslinked HA gel is a promising resorbable agent barrier for the reduction of postoperative adhesions after laparoscopic myomectomy. Moreover, the type of suture is a factor influencing the postsurgical adhesion formation. (Fertil Steril® 2003;80:441–4. ©2003 by American Society for Reproductive Medicine.)

**Key Words:** Laparoscopic myomectomy, infertile patients, adhesions, autocrosslinked hyaluronic acid gel

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Uterine fibroids represent the most common pelvic tumor of the female reproductive system and a challenging problem for young infertile women (1). Patients who want to preserve their fertility should be treated with conservative surgery. In this field, although still controversial (2), laparoscopic myomectomy is becoming increasingly more common for the treatment of symptomatic intramural fibroids, probably because laparoscopic surgeons are becoming more proficient in intracorporeal suturing.

An important concern regarding laparoscopic myomectomy is postoperative adhesion formation (3) and the development of such complications as intestinal obstruction, infertility, and chronic pelvic pain. According to some

authors (4), laparoscopic myomectomy could reduce the risk of postoperative adhesions as compared with laparotomy.

Several methods and physical barriers interposed between adjacent injured surfaces have been used to prevent abdominal adhesions after both laparoscopy and laparotomy. An oxidized regenerated cellulose absorbable barrier (5), a hydrophilic polyethylene glycol-based adhesion barrier (6), and a 4% icodextrin solution (7) were recently used with discordant results.

Recent experimental preclinical studies have shown that hyaluronic acid (HA) reduces adhesion formation after abdominopelvic surgery (8). Moreover, HA has been modified by obtaining an autocrosslinked HA gel (9–10) that seems particularly suitable to prevent ad-

hesion formation because of its higher adhesiveness and more prolonged residence time on the injured surface than unmodified HA (11).

The aim of this prospective, randomized, controlled study was [1] to assess the efficacy of the autocrosslinked HA gel in postsurgical adhesion prevention after laparoscopic myomectomy and [2] to compare two types of uterine sutures in terms of postoperative adhesions.

## MATERIALS AND METHODS

From June 2001 to March 2002, 36 infertile women with symptomatic uterine fibroids who referred to the Department of Obstetrics and Gynecology at the University of Naples "Federico II" were included in this randomized trial. The study was approved by the institutional review board and written informed consent was obtained from each patient. Inclusion criteria were described elsewhere (12).

The enrolled patients were preoperatively randomized and allocated to one of the two groups according to a computer-generated random list of 18 women each (groups A and B). Both groups underwent laparoscopic myomectomy. At the end of the surgical procedure, group A patients received an application of autocrosslinked HA gel (5 mL) on the injured uterine surface. Group B was the control group.

Laparoscopic myomectomy was performed by use of a 10-mm scope (Karl Storz, Tuttlingen, Germany) with two or three ancillary ports. The first step was always the infiltration of the fibroid base with up to 20 mL of octapressin (Por-8; Sandoz, Basel, Switzerland) 5 IU in 1 mL diluted 1:50 followed by a longitudinal, possibly close to the midline, unipolar incision. After the identification of the cleavage plane, the fibroid was enucleated by means of adequate traction with a myoma drill or a strong grasper and counter-traction maneuvers with Manhes forceps (12).

The myometrial edges were reapproximated in one or two layers according to the depth of the uterine wound by means of Vicryl CT polyglactin 2-0 (Ethicon SpA, Pratica di Mare, Rome, Italy). Sutures were made with intracorporeal knots. In each group, patients were alternatively treated with subserous sutures (groups A1 and B1) or with interrupted figure 8 sutures (groups A2 and B2).

The fibroids were removed with a 15 or 20 mm Steiner (Karl Storz) automatic morcellator. At the end of surgery, autocrosslinked HA gel (Hyalobarrier gel, Baxter, Pisa, Italy) was easily applied to the surfaces so that all injured areas were completely covered.

The entire operating time and the size and localization of myomas were recorded. In all cases, operative samples were submitted for pathological examination.

Postsurgical adhesions were evaluated 60–90 days after laparoscopic myomectomy. The surgical procedures for the follow-up evaluation consisted of traditional laparoscopy

TABLE 1

Patient characteristics.

Characteristic	Group A (n = 18)	Group B (n = 18)
Age (y ± SD)	28.8 ± 4.1	30.7 ± 2.6
Weight (kg; mean ± SD)	64.4 ± 4.6	62.8 ± 4.4
Diameter of fibroids (cm; mean ± SD)	6.9 ± 1.2	6.1 ± 1.5
No. of fibroids (mean ± SD)	2.1 ± 0.4	1.9 ± 0.5
Localization of fibroids (mean ± SD)		
Anterior face	1.2 ± 0.3	1.3 ± 0.4
Posterior face	1.4 ± 0.3	1.3 ± 0.2

Note: There were no significant differences between groups.

Pellicano. Crosslinked hyaluronic gel in laparoscopic myomectomy. *Fertil Steril* 2003.

under general anesthesia or minilaparoscopy under conscious sedation. The same surgeon performed second-look laparoscopy and evaluated the adhesion score according to the ASRM adhesion score system.

Minilaparoscopy was performed in a day surgery setting using a 3.5-mm lens optic endoscope (Wolf, Tuttlingen, Germany) with a 0° lens. Immediately before surgery, 0.5 mg of atropine and 0.25 mg of fentanyl were administered, followed by a slow i.v. injection of 2.5 mg of midazolam (Ipnovel, Roche, Italy). After cleansing of the abdomen, 10 mL of 1% mepivacaine was injected slowly beneath the umbilicus, gradually deeper down to the peritoneum. After the subumbilical skin incision, a minitrocar was pushed directly into the peritoneum and the 3.5-mm miniendoscope was inserted, insufflating approximately 2 L of CO<sub>2</sub>. Two lateral ancillary sites were anesthetized by administering 10 mL of 1% mepivacaine gradually deeper down to the peritoneum. The patient was put briefly in a steep Trendelenburg position to bring back the bowel; angle of this position was then reduced (13).

Statistical significance of between-group comparisons was assessed by a  $\chi^2$  test for proportions. The Student's *t*-test for unpaired data was used for comparison between groups when appropriate. The operating time was compared using the Wilcoxon rank-sum test. In all analyses, statistical significance was assessed at the 5% level.

## RESULTS

The 36 patients included in the study were aged 24–36 years (means ± SD, 29.2 ± 2.7), with a weight range of 55.4–79.6 kg (63.6 ± 4.7), a myoma diameter range of 4–10 cm (6.5 ± 1.4), and a number range of myomas per patient of 1–4 (2 ± 0.3).

There were no significant differences between the two groups for age, weight, diameter, or number of myomas for

**TABLE 2**

Rate of postsurgical adhesions between groups treated (group A) and untreated (group B) with autocrosslinked hyaluronic acid gel for suture technique.

	Group A (n = 18)			Group B (n = 18)		
	Figure 8 sutures (n = 9)	Subserous sutures (n = 9)	Total no. of patients (n = 18)	Figure 8 sutures (n = 9)	Subserous sutures (n = 9)	Total no. of patients (n = 18)
Adhesion formation (%)	4 (44.4) <sup>a</sup>	1 (11) <sup>a,b</sup>	5 (27.8) <sup>f</sup>	8 (89) <sup>c,d</sup>	6 (66.7) <sup>c,e</sup>	14 (77.8) <sup>f</sup>
No adhesion formation (%)	5 (55.6)	8 (89) <sup>b</sup>	13 (72.2)	1 (11) <sup>d</sup>	3 (33.3) <sup>e</sup>	4 (22.2)

<sup>a</sup>  $P < .01$ .

<sup>b</sup>  $P < .001$ .

<sup>c</sup>  $P < .05$ .

<sup>d</sup>  $P < .001$ .

<sup>e</sup>  $P < .01$ .

<sup>f</sup>  $P < .01$ .

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their localization on the anterior or posterior uterine face (Table 1). The operating time was similar in the two groups.

At follow-up, a significantly ( $P < .01$ ) lower rate of postsurgical adhesions was observed in group A (five out of 18 patients) in comparison with group B (14 out of 18 women) (27.8% vs. 77.8%) (Table 2).

The rate of adhesions was significantly ( $P < .05$ ) higher in patients treated with interrupted figure 8 sutures (groups A2 and B2) than in subjects treated with subserous sutures (groups A1 and B1) (Table 2). This difference was significant in both groups (Table 2). Four out of 9 patients in group A (44.4%) and eight out of nine patients in group B (89%) who were treated with interrupted figure 8 sutures developed postoperative adhesions, while one out of nine in group A (11%) and six out of nine patients in group B (66.7%) who were treated with subserous sutures developed postoperative adhesions.

We did not observe significant differences between myomectomies performed on the anterior or posterior face of the uterus (Table 3).

No complications or side effects were reported after the first laparoscopy or after second-look surgery. Two patients developed a slight postoperative fever ( $< 38.5^{\circ}\text{C}$ ) after laparoscopic myomectomy. The applied gel did not have any side effects.

## DISCUSSION

Surgical procedures on the uterus and laparoscopic myomectomy are the most common causes of adhesion formation (3). According to some investigators, laparoscopic removal of uterine myomas is associated with a lower

adhesion rate in comparison with laparotomy (4, 14). Several methods have been used to prevent abdominal adhesions after laparoscopy and laparotomy as have pharmacological agents (antiinflammatories, antioxidants, anticoagulants, and fibrinolytics) (15–18) and physical barriers interposed between adjacent injured surfaces to avoid direct contact (5–7), including HA, a natural component of the extracellular matrix, the vitreous humor, and the synovial fluid of the joint. Because the anti-adhesive effects depend on the molecular weight as well as the concentration of the preparation (19), HA has been modified with numerous molecules obtaining ferric hyaluronate (20), a hyaluronic-carboxymethylcellulose membrane (21), and an autocrosslinked HA gel (9, 10). The autocrosslinked HA gel has been developed to increase the viscosity and the residence time of the gel upon application (11) and to easily cover all vertical lesions that are frequently

**TABLE 3**

Incidence of adhesion formation with regard to the localization of the main myoma.

	Anterior myomas (n = 17)	Posterior myomas (n = 19)
Adhesion formation (%)	8 (47)	11 (57.8)
No adhesion formation (%)	9 (53)	8 (42.2)

Note: There were no significant differences between groups.

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found during laparoscopic surgery. This substance has been reported to significantly reduce the incidence and severity of adhesions in numerous preclinical studies (8, 10, 22).

The objective of this prospective study has been to evaluate the efficacy of autocrosslinked HA gel in the prevention of postsurgical adhesions after laparoscopic myomectomy and to study the influence of different kinds of laparoscopic sutures.

Our data show a clinical efficacy of autocrosslinked HA gel in terms of prevention of postoperative adhesions after laparoscopic surgery. These results are similar to those reported after the use of other methods (5, 20, 21). Despite their efficacy, ferric and sodium hyaluronate have been associated with some side effects. Sodium hyaluronate plus carboxymethylcellulose and ferric sodium hyaluronate have been associated with a higher rate of peritonitis in treated animals (23). Moreover, ferric hyaluronate should not be used in the presence of bleeding or infection, while sodium hyaluronate plus carboxymethylcellulose has been associated with an increased rate of local tumor growth in animals (24). Another study (25) showed that sodium hyaluronate enhances tumor metastatic potential in vitro and in vivo, which suggests that the use of sodium hyaluronate to prevent adhesions in colorectal cancer surgery may also potentiate intraperitoneal tumor growth. Autocrosslinked HA gel is a physiologic substance of all animal species. For this reason, it produces no side effects or allergic reactions and no patients reported inflammatory or allergic reactions to autocrosslinked HA gel in our study.

The material or diameter of sutures might induce an inflammatory reaction, as might the extent of postsurgical adhesion formation (26). Suture diameter was found to affect only the extent of formation, while the knot configuration did not influence the adhesion formation in any respect (26). On the contrary, we found that the knot configuration is able to induce a different postsurgical adhesion formation rate. Subserous sutures are associated with a significantly lower adhesion rate. However, we did not observe significant differences between myomectomies performed on the anterior or posterior face of the uterus.

In conclusion, autocrosslinked HA gel is a promising resorbable agent barrier for the reduction of postoperative adhesions after laparoscopic myomectomy. We consider this substance especially useful in infertile patients. Moreover, the type of suture is a factor influencing the postsurgical adhesion formation. We suggest that subserous sutures on uterine surfaces always be used.

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