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Effectiveness of auto-crosslinked hyaluronic acid gel in the prevention of intrauterine adhesions after hysteroscopic surgery: a prospective, randomized, controlled study

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BACKGROUND: A prospective, randomized, controlled study was performed to assess the efficacy of auto-crosslinked hyaluronic acid (ACP) gel to prevent the development of de-novo intrauterine adhesions following hysteroscopic surgery. METHODS: One hundred and thirty-two patients with a single surgically remediable intrauterine lesion (myomas, polyps and uterine septa, subgroups I–III) completed the study. Patients were randomized to two different groups: group A underwent hysteroscopic surgery plus intrauterine application of ACP gel (10 ml) while group B underwent hysteroscopic surgery alone (control group). The rate of adhesion formation and the adhesion score was calculated for each group and subgroup 3 months after surgery. RESULTS: Group A showed a significant reduction in the development of de-novo intrauterine adhesions at 3 months follow-up in comparison with the control group. Furthermore, the staging of adhesions showed a significant decrease in adhesion severity in patients treated with ACP gel. CONCLUSIONS: ACP gel significantly reduces the incidence and severity of de-novo formation of intrauterine adhesions after hysteroscopic surgery.

Key words: adhesion score/de-novo intrauterine adhesions/hyaluronic acid gel/hysteroscopic surgery

Introduction

Intrauterine adhesions are the major long-term complication of operative hysteroscopy, with frequency dependent on the pathology initially treated (Taskin *et al*., 2000). They may result in infertility, recurrent miscarriages and irregular periods with dysmenorrhea and pelvic pain (Valle and Sciarra, 1988; Menzies, 1993).

Post-operative adhesions are classified as '*de novo*' when they develop at sites that did not have adhesions initially, and as 'reformed' when they redevelop at sites at which adhesiolysis has been performed (Diamond *et al*., 1987).

We recently reported that the intrauterine application of auto-crosslinked hyaluronic acid (ACP) gel following hysteroscopic adhesiolysis significantly reduces the reformation of post-operative intrauterine adhesions. Furthermore, ACP gel has been associated with a reduction of the severity of post-operative adhesions (Acunzo *et al*., 2003).

The aim of this prospective, randomized, controlled study was: (i) to assess the efficacy of ACP gel in the reduction of development of de-novo post-surgical adhesions in women undergoing hysteroscopic surgery for submucous myomas, endometrial polyps and uterine septa; and (ii) to evaluate the characteristics of the adhesions at 3 months follow-up.

Materials and methods

The protocol of the study was approved by our Institutional Review Board and the study was conducted according to the guidelines of the Declaration of Helsinki (1975). The study project was conducted according to Consort RCT guidelines (www.consort-statement.org) and the patient flow chart is set out in Figure 1.

All patients with surgically remediable single lesions at diagnostic hysteroscopy were invited to participate in the study. Between September 2002 and June 2003, 138 women were enrolled in the study.

Inclusion criteria were hysteroscopic diagnosis of submucous myomas or endometrial polyps or uterine septa. Exclusion criteria were: age >50 years, weight >100 kg, menopausal (FSH > 40 mIU/ml, 17β-estradiol <20 pg/ml) or pregnancy (positive β-HCG test), presence of uterovaginal prolapse and severe urinary symptoms, presence of malignancy, or presence of severe intercurrent illness (coagulative disorders, systemic disease, severe cardiopathy). The presence of the association of equal or different intrauterine remediable lesions or the presence of intrauterine adhesions was also considered an exclusion criteria.

Diagnostic hysteroscopy was performed using a 3.5 mm instrument (Gynecare Versascope, Gynecare; Ethicon Inc., Somerville, NJ, USA) using normal saline solution (NaCl, 0.9%) as distension medium. Before hysteroscopy, all patients underwent vaginal examination to ascertain the position and size of the uterus, and a speculum was inserted into the vagina to expose the cervix.

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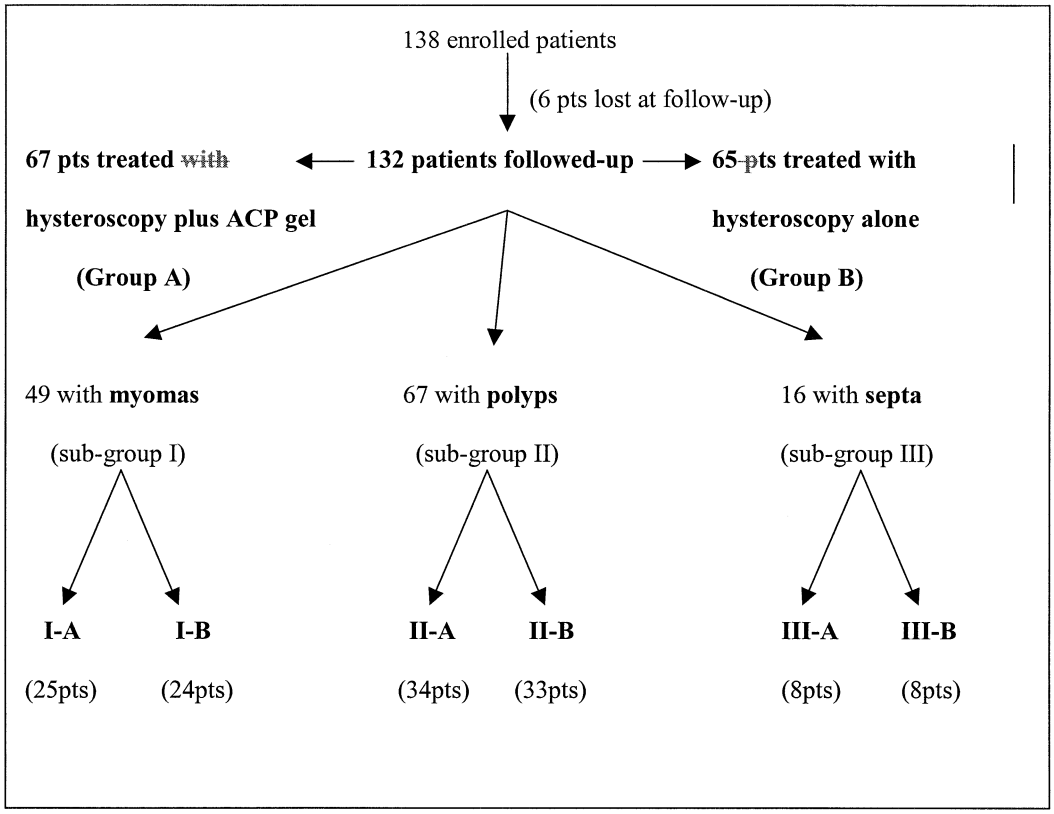

ACP gel= auto-crosslinked hyaluronic acid gel

Group A: patients were treated with hysteroscopy plus ACP gel (10 ml)

Group B: patients underwent hysteroscopy alone (control group)

Figure 1. Patients' enrolment and randomized assignation. Group A: patients were treated with hysteroscopy plus ACP gel (10 ml). Group B: patients underwent hysteroscopy alone (control group).

The type and characteristics of pathologies were recorded on a dedicated schedule.

Before entering the study, the purpose of the protocol was explained clearly to women attending our Hysteroscopic Unit, and a printed explanatory consent form was signed and obtained by all subjects enrolled.

After diagnostic hysteroscopy and after the written consent form was signed, patients from each pathology subgroup (submucous myomas, endometrial polyps, septa) were randomized into two groups, group A (treatment group) (n = 69) and group B (control group) (n = 69), using a computer-generated randomization list (Figure 1).

The treatment group received an intrauterine application of 10 ml of ACP gel (Hyalobarrier Gel; Baxter, Pisa, Italy) under hysteroscopic view after operative histeroscopy. In the control group, hysteroscopic surgery alone was performed.

Operative hysteroscopy was performed by means of a rigid resectoscope (Gynecare Versascope, Gynecare; Ethicon Inc.) with a 30° fore-oblique telescope with different bipolar electrodes and with a bipolar energy source (Versapoint, Gynecare; Ethicon Inc.); normal saline solution (NaCl, 0.9%) was used as the distension medium. Myomectomy was performed by resecting the free side of the myoma by moving the activated bipolar loop from back to front till the exposure of normal myometrium. Polyps were treated by positioning the loop behind the base of pedicle and pushing from back to front. One or several passages of the activated loop were necessary according to the size of lesion being treated. Hysteroscopic metroplasty was performed under laparoscopic control by the use of a modified 0° equatorial loop: uterine septa were cut in the midline portion from the proximal part to the uterine fundus until a normal fundus shape was achieved.

In group A, ACP gel was introduced into the uterine cavity at the end of the procedure through the out-flow channel of the resectocope, whilst the surgeon progressively limited the entrance of the distension medium through the in-flow channel. The procedure was considered complete when, under hysteroscopic view, the gel seemed to have replaced all the liquid medium and the cavity appeared completely filled by the gel from tubal osthia to internal uterine orifice (Acunzo *et al.*, 2003).

Each patient underwent a follow-up diagnostic hysteroscopy 3 months after the surgical procedure, and the adhesion score (American Fertility Society, 1988) was assessed.

Both the initial diagnostic hysteroscopy and the follow-up diagnostic hysteroscopy were performed by the same operator (G.A.). G.A. evaluated the adhesion score for each patient and was blind for patients' randomized allocation, whilst operative hysteroscopies and application of ACP gel were performed by a different operator (M.G.). To avoid any bias related to the surgical treatment, the surgeon was informed about patients' allocation immediately after the surgical removal of the intrauterine lesion.

Table I. Patient characteristics

Characteristic	Group A (ACP gel) (n = 67)	Group B (control) (n = 65)	Significance
Age (years)	37 ± 3.2	36 ± 2.8	NS
Weight (kg)	68 ± 4.2	69 ± 2.3	NS
Uterine size (hysterometry) (cm)	7.5 ± 1.2	7.3 ± 2.2	NS
Parity	2.0 ± 1.3	2.1 ± 0.9	NS

Values are mean ± SD.
NS, not significant.

Table II. Incidence of adhesion formation (at 3 months follow up) in different pathology subgroups in women treated (group A) and untreated (group B) with ACP gel

Pathology (subgroup)	Group A: hysteroscopy plus ACP gel (n = 67)		Group B: hysteroscopy alone (n = 65)	
	All patients	No. patients (%) with adhesions at follow-up	All patients	No. patients (%) with adhesions at follow-up
All patients	67	7 (10.44)*	65	17 (26.15)*
Myomas (I)	25	4 (16.0)*	24	8 (33.33)*
Polyps (II)	34	2 (5.88)*	33	6 (18.18)*
Septa (III)	8	1 (12.5)*	8	3 (37.5)*

*Group A versus group B: $P < 0.05$.
ACP gel, auto-crosslinked hyaluronic acid gel.

Statistical analysis was performed with a commercial software program (Statistica for Windows; Statsoft, Inc., Tulsa, UK). Data distribution was performed using Shapiro–Wilks test. Differences in age, weight and parity, which showed a normal distribution, were compared using the two-tailed Student's t-test for unpaired data. The Wilcoxon sum rank test was used to compare adhesion scores at 3 months between groups A and B, and the χ^2-test was used for proportions. $P < 0.05$ was considered statistically significant.

Results

Between September 2002 and June 2003, 164 patients met the study's inclusion criteria and were invited to participate in the study. Of these, 26 did not participate in the study: 18 refused to undergo operative hysteroscopy and eight refused to participate after the explanation of the study protocol.

The characteristics of the treated patients are reported in Table I. There were no significant differences in age, weight, uterine size and parity between patients in group A and group B.

Six women (two from group A and four from group B) did not attend for follow-up hysteroscopy.

As shown in Figure 1, 49 patients presented submucous myomas (subgroup I); 67 patients presented endometrial polyps (subgroup II); and 16 patients presented uterine septa (subgroup III). There were no significant differences in lesions' size and localization between group A and group B. All submucous myomas were classifiable as G_0–G_1 myomas, according to the international classification of uterine fibroids. Myomas in group A measured 2.9 ± 0.6 cm (mean ± SD; ultrasonographic measurement), while those in group B measured 3.1 ± 0.7 cm.

At 3 months follow-up, a significantly lower rate of post-surgical intrauterine adhesions was observed in group A (seven out of 67 patients) compared with group B (17 out of 65 women) (10.44 versus 26.15%; $P < 0.05$) (Table II). This significance was conserved when adhesion rates were evaluated within pathology subgroups (Table II).

The mean adhesion score was significantly lower in group A in comparison with group B (adhesion score of entire group A versus entire group B, mean ± SD: 2.42 ± 0.78 versus 3.83 ± 0.98; $P < 0.05$). When individual pathology subgroups were compared for the adhesion score, although each treated subgroup (group A) showed a lower score in comparison with the corresponding untreated control subgroup (group B) [mean adhesion score ± SD: subgroup I (myomas): 2.25 ± 0.5 (group A) versus 3.5 ± 1.19 (group B); subgroup II (polyps): 2.0 ± 0.0 (group A) versus 3.5 ± 0.54 (group B); subgroup III (septa): 4.0 ± 0.0 (group A) versus 5.33 ± 1.15 (group B)], we did not represent this difference as statistically significant due to the loss of statistical power. Differences in adhesion score between groups and subgroups at follow-up hysteroscopy are shown in Figure 2. When the intrauterine adhesion staging (American Fertility Society, 1988) was evaluated, patients from group A showed a significant decrease in adhesion severity (85.71% stage I, mild adhesions; 14.29% stage II, moderate adhesions) in comparison with group B (23.53% stage I; 76.47% stage II). No significant difference was detected in localization of adhesions between different groups and subgroups at follow-up. No adverse gel-related effects were detected in group A.

Discussion

The major long-term complication that all surgeons try to avoid during resectoscopic surgery is post-operative adhesions (Taskin *et al.*, 2000). Considering the high frequency of intrauterine adhesions after resectoscopic surgery (Taskin *et al.*,

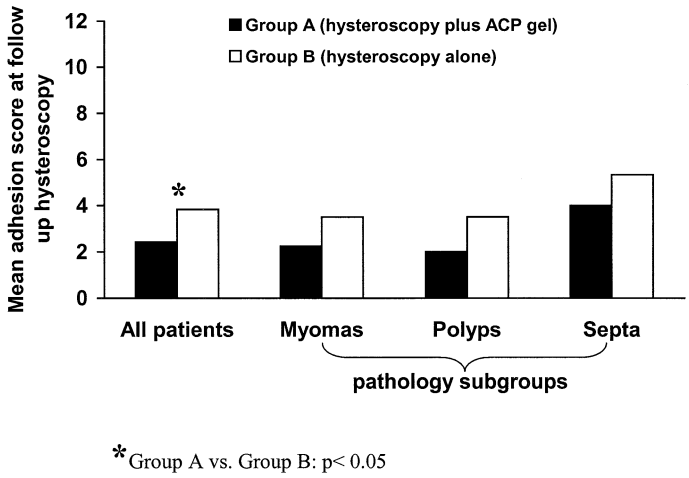

Figure 2. Adhesion score in groups and subgroups of patients at 3 months follow-up according to the American Fertility Society (1988).

2000), it is cost effective and efficacious to develop new strategies for the prevention of de-novo adhesion formation.

Several methods have been used to prevent intrauterine adhesions in the past (Schenker and Margalioth, 1982; Valle and Sciarra, 1988; Risberg, 1997; Farquhar *et al*., 2002; Tsapanos *et al*., 2002; Watson *et al*., 2002; Acunzo *et al*., 2003). We recently reported that an auto-cross linked derivative of hyaluronic acid (ACP gel) significantly reduces the reformation of intrauterine adhesions after hysteroscopic adhesiolysis, and that its use is associated with a reduction of the severity of adhesions (Acunzo *et al*., 2003).

The objective of this prospective study was to evaluate whether ACP gel is also effective in the prevention of post-surgical de-novo adhesions after the most common hysteroscopic surgical procedures (resection of myomas and polyps and metroplasty for uterine septa).

In our experience, high frequencies of post-operative adhesions were observed, especially after resectoscopic myomectomy and metroplasty; hysteroscopic resections of endometrial polyps were associated with a lower incidence of de-novo adhesions.

Our randomized, controlled trial showed a significant reduction in de-novo intrauterine adhesion formation in patients treated with intrauterine application of ACP gel (10 ml) after hysteroscopic surgery in comparison with patients treated with hysteroscopic surgery alone. The difference in adhesion formation was both significant when group A was compared with group B, and when individual pathology subgroups were compared with corresponding controls ($P < 0.05$).

A significant difference was also observed in mean adhesion score between group A and group B. Although not definitive, our data show that ACP gel seems to be able to prevent de-novo formation of intrauterine adhesions, and also seems to reduce the severity of adhesions that do develop.

This new absorbable barrier agent could represent a safe and effective strategy to improve women's health, reducing the need for re-intervention after hysteroscopic surgery due to post-operative intrauterine adhesion formation. However, our results need to be confirmed in larger controlled randomized studies.

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