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Reduction of postoperative adhesions with an auto-crosslinked hyaluronan gel in gynaecological laparoscopic surgery: a blinded, controlled, randomized, multicentre study

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BACKGROUND: Following myomectomy, postoperative adhesions occur in many patients with adverse effects on fertility. This study investigated the applicability, safety and efficacy of an auto-crosslinked hyaluronan gel in preventing adhesion formation after laparoscopic myomectomy. METHODS: Fifty-two patients aged 22–42 years, undergoing surgery at four centres, were randomly allocated to receive either the gel or no adhesion prevention. The incidence and severity of postoperative adhesions were assessed laparoscopically after 12–14 weeks in a blinded, scored fashion. The primary efficacy variable was the presence/absence of postoperative adhesions at second-look. RESULTS: A nonsignificantly higher proportion of patients receiving the gel were free from adhesions (13 of 21; 62%) compared with control patients (9 of 22; 41%), with a statistically significant difference between the severity of uterine adhesions at baseline and at second-look (0.3 ± 0.9 versus 0.8 ± 1.0, $P < 0.05$). In subjects undergoing myomectomy without concomitant surgery, the proportion of adhesion-free patients was 8 of 12 (67%) and 4 of 11 (36%) (not significant) in the gel and control groups, respectively, with a significant difference in the mean severity scores ($P < 0.05$). In subjects without uterine adhesions before myomectomy, 12 of 18 (67%) and 8 of 20 (40%) patients in the gel and control groups, respectively were adhesion-free (not significant), with a significant difference in the severity of uterine adhesions ($P = 0.05$). CONCLUSIONS: Our results suggest that the auto-crosslinked hyaluronan gel may have a favourable safety profile and efficacious antiadhesive action following laparoscopic myomectomy.

Key words: adhesions/hyaluronic acid/laparoscopy/myomectomy/prevention

Introduction

Formation of postoperative adhesions occurs in up to one-half of the patients undergoing laparoscopic myomectomy, leading to infertility, chronic pelvic pain and bowel obstruction, in addition to difficulties in reoperation (Dubuisson *et al*., 2000; Fauconnier *et al*., 2000; Miller, 2000). Thus, although the current strategy for reducing the formation of postoperative adhesions generally consists in improving surgical technique (minimizing invasiveness, surgical trauma, bleeding and ischaemia), the prevention of adhesions using additional, more effective tools would be of tremendous benefit.

Several alternative strategies have been proposed with the aim of reducing the incidence of postoperative adhesions. Pharmacological agents, including steroids, antihistamines and heparin, have been used without any clearly demonstrated advantage (Watson *et al*., 2000). The first effective commercially available adhesion-prevention barriers were membranes such as Interceed (Gynecare, Somerville, NJ, USA) or Seprafilm (Genzyme, Cambridge, MA, USA), but however, these are problematic to use via laparoscopy (Mais *et al*., 1995; Diamond, 1996; diZerega, 1996; Pelosi and Pelosi, 2002). More recently, the efficacies of an icodextrin solution, a sprayable gel system, and a viscoelastic gel have been investigated as instillates, and gels are easier to deliver during laparoscopic gynaecological surgery (diZerega *et al*., 2002; Mettler *et al*., 2003; Mettler *et al*., 2004; Lundorff *et al*., 2005). To date, no adhesion-prevention strategy has been found to be consistently effective for the reduction of postsurgical adhesions following laparoscopic myomectomy (Koh and Janik, 2003).

Hyaluronan (HA) is a naturally occurring component of the extracellular matrix and peritoneal fluid that has received much attention because of its possible application as an adhesion-prevention adjuvant in a variety of surgical procedures. Indeed, several authors in different experimental and clinical settings have proposed that deposition of HA around surgically treated tissues reduces postoperative adhesion formation (Amiel *et al*., 1989; Hagberg and Gerdin, 1992; Burns *et al*., 1995; Chen and Abatangelo, 1999). Moreover, native HA has a high degree of biocompatibility and a favourable safety profile (Laurent and Fraser, 1992).

A highly viscous gel of HA derivatives obtained through an auto-crosslinking process that does not introduce foreign bridge molecules, namely Hyalobarrier®, has recently been developed. The auto-crosslinked polymer is an inter and intramolecular ester of HA in which a proportion of the carboxyl groups are esterified with hydroxyl groups belonging to the same and/or different molecules of the polysaccharide, thus forming a mixture of lactones and intermolecular ester bonds. The level of crosslinking can be varied by modulating the reaction conditions. The absence of foreign bridge molecules ensures the release of native HA only during degradation, while the auto-crosslinking process improves the viscoelastic properties of the gel compared with unmodified HA solutions of the same molecular weight (Balazs *et al*., 1991; Mensitieri *et al*., 1996; Renier *et al*., 2005).

Preclinical trials in animal models have shown that Hyalobarrier® gel reduces the incidence and severity of postoperative adhesions (De Iaco *et al*., 1998; Belluco *et al*., 2001; De Iaco *et al*., 2001; Pucciarelli *et al*., 2003). Moreover, preliminary clinical studies in hysteroscopic surgery as well as laparotomic and laparoscopic myomectomy have suggested that Hyalobarrier® gel may reduce the incidence and severity of postoperative adhesions in pelvic surgery (Acunzo *et al*., 2003; De Iaco *et al*., 2003; Pellicano *et al*., 2003; Carta *et al*., 2004; Guida *et al*., 2004) with improvement in the pregnancy rate in infertile patients who were submitted to laparoscopic myomectomy (Pellicano *et al*., 2005).

To further explore the feasibility, safety and efficacy of applying Hyalobarrier® gel following laparoscopic myomectomy to prevent adhesion formation, we performed a randomized, controlled, multicentre and observer-blind study. Second-look laparoscopy was performed 12–14 weeks after the initial surgery. In each centre, the presence, location and severity of adhesions at second-look laparoscopy were blindly assessed.

Materials and methods

Hyalobarrier® GEL × ENDO is a sterile, transparent and highly viscous gel, obtained by condensation of HA through an auto-crosslinking process and is indicated for laparoscopic and hysteroscopic surgical procedures (Fidia Advanced Biopolymers, Abano Terme, Padova, Italy).

Four centres in Italy were involved in the study: (i) Department of Surgery, Maternal–Fetal Medicine and Imaging, Division of Gynaecology, Obstetrics and Pathophysiology of Human Reproduction, University of Cagliari; (ii) Department of Gynaecology, Perinatology and Human Reproduction, University of Florence; (iii) Department of Human Reproductive Sciences, 2nd Gynaecology Clinic, University of Padova; (iv) Department of Obstetrics and Gynaecology, Ospedale Maria Vittoria, Turin. The study was approved by the relevant committee at each study centre. Written informed consent was obtained from each patient. Patients were free to withdraw from the study at any time.

The age of the patients participating in the study ranged from 22 to 42 years and included premenopausal, nonpregnant women requiring laparoscopic myomectomy and expected to undergo a second-look laparoscopy as part of their treatment plan 12–14 weeks after the initial surgery. All women had both the tubes and both the ovaries and single or multiple (1–3) subserous and/or intramural myomas. To avoid the risk of conversion to an open procedure, only women having the size of the largest myoma ranging from 20 to 50 mm were enrolled on the basis of preoperative ultrasound evaluation (Mais *et al*., 1996). Exclusion criteria were history of diabetes, hepatic disorders, renal disorders, severe cardiopathies and malignancies; previous administration of anti-adhesive measures; presence of pelvic or abdominal infection; concurrent treatment with oral steroids; immunosuppressive or cytostatic treatments; suspected or confirmed pregnancy and presence of coagulation disorders or insufficient intraoperative haemostasis.

Patient enrolment

Patients were enrolled at an initial visit to determine compliance with the inclusion and exclusion criteria. During this visit, each patient was provided with an informed consent form detailing the purpose and procedures of the study. After informed consent was obtained, the following baseline examination was performed within 7 days before the date of surgery: demographics, clinical history including previous surgery, previous and concomitant medication history, physical examination, pregnancy test and laboratory tests including blood count (red blood cell count, haematocrit, haemoglobin, white blood cell count and platelets), serum chemistries (sodium, potassium, creatinine, glucose, total bilirubin, AST and ALT) and coagulation test (antithrombin, prothrombin time international normalized ratio (PT-INR) and activated partial thromboplastin time (aPTT).

Randomization

Patients were randomly allocated intraoperatively to receive either the study device (Hyalobarrier® gel group) or surgery alone without adhesion prevention (controls), using the numbered, sealed envelope technique (Mais *et al*., 1995). A computer generated 1 : 1 random allocation sequence within balanced blocks of four was concealed in numbered, sealed envelopes until interventions were assigned. At each study centre, patients were assigned the next available study number, and the envelope seal was broken in the operating theatre at the conclusion of laparoscopic myomectomy after the suturing of uterine defects and before the removal of laparoscopic ports. The investigator who generated the allocation sequence (V.M.) was not involved in either the patient enrolment or the assignment of the study groups.

Laparoscopic myomectomy

All surgical procedures were performed by the same surgeon at each study centre. A pneumoperitoneum was established with CO_2 insufflation through a Veress needle. A 10 mm port was inserted through the umbilicus to carry the laparoscope, which was connected via a television camera to video monitoring equipment. Additional ports were inserted to carry the surgical instruments. After a visual exploration of the pelvic organs and upper abdomen, which was carried out to evaluate the possible presence of pre-existing adhesions, an incision was made through the uterine wall and the pseudocapsule of the leiomyoma(s). The technique of incision and the number and the sites of hysterotomic incisions were recorded. The tumour masses were

removed and their size and position within the uterus (intramural or subserous) recorded. The incidence, severity and extent of any pre-existing adhesions were also recorded. The Operative Laparoscopy Study Group scoring system was used to describe the severity of adhesions at 12 sites (Operative Laparoscopy Study Group, 1991). Blood vessels at the operative sites were coagulated to achieve complete haemostasis. All uterine defects were closed by sutures. Saline or Ringer lactate solutions were used as the irrigant during surgery and removed by suction with the patients in a reverse Trendelenburg position before their assignment to the study groups.

Application of study device

In the Hyalobarrier® gel group, a 1–2 mm thick layer of gel was applied to coat all uterine incisions and suture materials. Hyalobarrier® GEL × ENDO is available as individually packaged, single-use, prefilled, sterile syringes, each containing 10 ml of gel with individually packaged, sterile, 30 cm cannulae designed to be utilized through a 5 mm laparoscopic port. One to three prefilled 10 ml syringes can be injected through the same cannula.

For evaluation of feasibility, both the amount of gel (number of used syringes) required to coat all incisions and suture materials and the time (min) required to apply the gel were recorded.

In controls, no adhesion treatment was applied following the conclusion of the surgical procedure.

Postoperative safety assessment

The following evaluations were performed on the day of surgery and one day after surgery: physical examination, vital signs, adverse experience recording, blood count, serum chemistries and coagulation test were repeated before second-look laparoscopy. Complications and duration of the hospital stay after surgery were recorded for each patient.

Second-look laparoscopy

A second-look laparoscopy was performed at 12–14 weeks after laparoscopic myomectomy to assess the incidence, severity and extent of adhesions. The surgeon performing the second-look laparoscopy was unaware of the assignment of the patients to the different study groups. The Operative Laparoscopy Study Group scoring system was used to describe the severity of adhesions at 12 sites (Operative Laparoscopy Study Group, 1991). These included uterus, ovaries (right and left), Fallopian tubes (right and left), omentum, cul-de-sac, pelvic side-wall (right and left), large bowel (right and left) and the small bowel. At each of these sites, adhesions were given the following scores: 0, no adhesion; 1, filmy and avascular; 2, dense and/or vascular and 3, cohesive. Scores from all potential adhesion sites were averaged to yield a total adhesion score.

The number of patients with adhesions at second-look observed in the Hyalobarrier® gel group was compared with those observed in controls receiving surgery alone.

Statistical analysis

This study was an exploratory trial and so the sample size was not derived from statistical considerations. Descriptive statistics and inferential methods were used to analyse data. The analysis provided statistics between groups, using the nonparametrical test of hypothesis with the significance level set at 5%.

The primary efficacy variable, namely the presence/absence of postoperative adhesions at second-look procedure, was compared using Fisher's exact test. An estimate of relative risk (RR) was also carried out. The RR is the ratio of the incidences of adhesions in the two groups and is a measure of how much the treatment with Hyalobarrier® gel influences the risk of postoperative adhesions. If the RR is <1, then the probability of the specific outcome is greater in the second group compared with the first (i.e. the first group has a lower risk of postoperative adhesions).

The secondary endpoints, the number and proportion of sites with adhesions, calculated by dividing the number of sites with adhesions by the number of sites recorded (n = 12), the total adhesion scores and the uterine adhesion scores were compared between groups using the Wilcoxon-Mann–Whitney U-test. A median test was applied to compare the medians of the two study arms.

Multivariate analysis was performed, and the linear regression model was applied to the total adhesion score at second-look, using the baseline score, the treatment group and the concomitant surgeries as co-variates. Linear regression model was also applied to the total adhesion score and to the uterine adhesion score at the second-look, using type of fibromas, the sites of uterine incisions and the number of uterine incisions as explicative factors.

Results

Among 60 cases who were screened and considered eligible for entry in the study, informed consent was obtained from 52 patients (mean age 34 years, range 22–42 years). All 52 patients were submitted to laparoscopic myomectomy and were randomly allocated intraoperatively to receive either the study device (Hyalobarrier® gel group, n = 26) or surgery alone without adhesion prevention (controls, n = 26) (Figure 1). Of these 52 patients, five patients in the Hyalobarrier® gel group and four in the control group were lost to follow-up because they declined to undergo second-look laparoscopy at the scheduled time (12–14 weeks after laparoscopic myomectomy) for personal reasons such as working or family needs. Thus, 43 patients completed the study and underwent second-look laparoscopy, 21 in the Hyalobarrier® gel group and 22 in the control group. The first patient was enrolled on 5 March 2002, and the last patient ended the study on 4 March 2004.

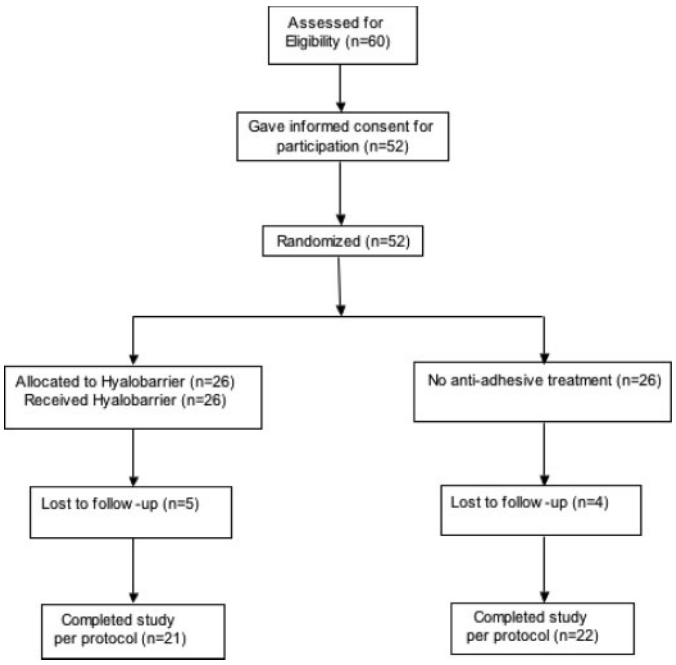

Figure 1. Flow chart indicating major events in the randomized clinical trial.

The demographic and myoma characteristics at baseline were homogenous between the two groups as summarized in Table I. A total of 20 patients underwent concomitant surgery (diagnostic hysteroscopy, pelvic adhesiolysis, ovarian drilling, ovarian cyst removal, paratubal cyst removal, endometriosis excision, uterine septum hysteroscopic removal, hysteropexy or bowel adhesiolysis). Five patients already had uterine adhesions at baseline. The technique of incision and the number and the sites of hysterotomic incisions were comparable between the two groups (Table I).

In 16 patients of the Hyalobarrier® gel group (76%), only one syringe (10 ml) of gel was used, whereas in the other five patients, two syringes (20 ml) were used. The mean application time of the product was 2 ± 1 min.

No complications or adverse events were reported in either group, and no clinically meaningful differences in haematological parameters were observed between the two groups after surgery or at second-look. Only three patients had nausea (two in the Hyalobarrier® gel group and one in the control group). One patient in the Hyalobarrier® gel group had vomiting. None of the patients needed transfusion. The duration of the hospital stay after surgery was 2.3 ± 1.1 days in the Hyalobarrier® gel group and 2.0 ± 1.0 days in the controls. There were no significant differences in the mean follow-up time between the two groups (91 ± 28 days in the Hyalobarrier® gel group and 78 ± 37 days in the controls).

At second-look laparoscopy, a higher number of adhesion-free patients was found in the Hyalobarrier® gel group (13 of 21, 62%) compared with the controls (9 of 22, 41%), although this difference did not reach statistical significance (Table II). There were 8 of 21 (38%) patients with adhesions in the Hyalobarrier® gel group compared with 13 of 22 (59%) in the control group (not significant). Therefore, patients treated with Hyalobarrier® gel appeared to have a lower risk of forming postoperative adhesions with respect to controls [RR = 0.64 (0.38/0.59), $P = 0.17$]; however, this observation did not reach statistical significance.

The mean total adhesion score at second-look was similar for both the groups, with a median total adhesion score value of 0 for the Hyalobarrier® gel group and 2 for the controls ($P = 0.08$) (Table II). The uterine score at second-look was 0.6 ± 0.9 for Hyalobarrier® gel group and 0.9 ± 1.0 for the control group ($P = 0.08$), with median values 0 and 1, respectively ($P = 0.09$). The difference between uterine adhesion score at baseline and at second-look was significantly lower in the Hyalobarrier® gel group compared with the control group (0.3 ± 0.9 versus 0.8 ± 1.0, $P = 0.03$) (Table II).

Because women undergoing myomectomy in a routine surgical setting represent a rather heterogeneous group of subjects, as shown by the characteristics of patients enrolled in the present study, the efficacy of study device was also evaluated on subgroups of patients to investigate the possible effects of factors such as associated pathologies with concomitant surgery or presence of uterine adhesions before myomectomy.

The subgroup of patients who were submitted to myomectomy alone without concomitant surgery included 23 patients (12 treated with Hyalobarrier® gel and 11 controls; Table III).

Table I. Demographic and surgical characteristics of patients completing the study with a second-look laparoscopy

	Hyalobarrier (n = 21)[a]	Control (n = 22)
Age (years)	33 ± 5	34 ± 5
Number of myomas	1.8 ± 0.9	1.7 ± 0.9
Subserous	1.0 ± 1.1	1.0 ± 0.8
Intramural	0.8 ± 0.8	0.7 ± 0.7
Size of largest myoma (mm)	42.8 ± 11.9	45.0 ± 10.6
Uterine adhesions (n)	3	2
Concomitant surgery (n)	9	11
Incision technique (n)		
Cold blade	4	4
Ultrasonic	8	12
Monopolar	4	2
Bipolar	0	2
Not recorded	5	2
Number of hysterotomic incisions	1.6 ± 0.9	1.8 ± 0.9
Anterior	0.6 ± 0.7	0.5 ± 0.6
Fundic	0.5 ± 0.6	0.7 ± 0.6
Posterior	0.5 ± 0.6	0.5 ± 0.8

[a]Values are mean ± SD.

Table II. Incidence and severity of adhesions at second-look

	Hyalobarrier (n = 21)	Control (n = 22)	P
Adhesion-free patients	13/21 (62%)	9/22 (41%)	NS
Patients with adhesions	8/21 (38%)	13/22 (59%)	
Number of sites with adhesions	1.4 ± 2.3	1.4 ± 1.5	NS
Proportion of sites with adhesions (Number of sites with adhesions/12)	0.1 ± 0.2	0.1 ± 0.1	—
Total score at baseline			
Mean ± SD	1.4 ± 2.4	1.7 ± 2.5	NS
Median	0	0	NS
Total score at second-look			
Mean ± SD	2.1 ± 3.9	2.1 ± 2.2	NS
Median	0	2	NS (0.08)
Uterine score at baseline			
Mean ± SD	0.2 ± 0.7	0.1 ± 0.5	NS
Median	0	0	NS
Uterine score at second-look			
Mean ± SD	0.6 ± 0.9	0.9 ± 1.0	NS (0.08)
Median	0	1	NS (0.09)
Uterine score second-look versus baseline			
Mean ± SD	0.3 ± 0.9	0.8 ± 1.0	0.03
Median	0	1	0.02

NS, not significant.

Table III. Incidence and severity of adhesions at second-look in a subgroup of patients who underwent myomectomy without concomitant surgery (n = 23)

	Hyalobarrier (n = 12)	Control (n = 11)	P
Adhesion-free patients	8/12 (67%)	4/11 (36%)	NS
Patients with adhesions	4/12 (33%)	7/11 (64%)	
Total score at second-look			
Mean ± SD	1.5 ± 3.2	2.7 ± 2.4	0.04
Median	0	2	0.03
Uterine score at second-look			
Mean ± SD	0.5 ± 0.9	1.4 ± 1.1	0.02
Median	0	1	0.02
Uterine score second-look versus baseline			
Mean ± SD	0.5 ± 0.9	1.2 ± 1.0	0.03
Median	0	1	0.03

NS, not significant.

Table IV. Incidence and severity of adhesions at second-look in a subgroup of patients without uterine adhesions at baseline (n = 38)

	Hyalobarrier (n = 18)	Control (n = 20)	P
Uterine adhesion-free patients	12/18 (67%)	8/20 (40%)	NS
Patients with uterine adhesions	6/18 (33%)	12/20 (60%)	
Uterine score at second-look			
Mean ± SD	0.5 ± 0.9	0.9 ± 0.9	0.05

NS, not significant.

In this subgroup, 67% of patients were adhesion-free in the Hyalobarrier® gel group compared with 36% of controls (not significant), with a significant difference between the mean total and uterine scores of adhesions at second-look ($P < 0.05$) (Table III).

The subgroup of patients without uterine adhesions at baseline (n = 38) was also considered and included; 18 cases treated with Hyalobarrier® gel and 20 controls (Table IV). In this set of patients, 67% of patients were uterine adhesion-free in the Hyalobarrier® gel group compared with 40% of controls, with a significant difference (P = 0.05) between the uterine mean scores of adhesions at second-look (Table IV). Thus, Hyalobarrier® gel appeared to decrease the adhesion score and thereby decrease the severity of postsurgical adhesions following laparoscopic myomectomy.

As for multivariate analysis, linear regression demonstrated that the total adhesion score at second-look significantly depends on the total adhesion score at baseline ($\beta = 0.6$, $P < 0.01$). Women with both intramural and subserous fibromas had a total adhesion score higher than women with only intramural or subserous fibromas ($P < 0.01$); patients with posterior incisions had a total adhesion score higher than patients with anterior incisions ($P = 0.02$); patients with more than one incision had a total adhesion score higher than the others ($P < 0.01$). The uterine adhesion score of women with intramural fibromas was higher than the score of the other patients ($P < 0.01$); patients with posterior incisions had a uterine adhesion score higher than patients with anterior incisions ($P = 0.01$); patients with more than two incisions had a uterine adhesion score higher than the others ($P = 0.01$).

Discussion

To our knowledge, this is the first multicentre, observer-blind, randomized, controlled study performed to evaluate the feasibility, safety and efficacy of applying a highly viscous gel of Hyalobarrier® following laparoscopic myomectomy to prevent adhesion formation. In each centre, the presence, location and severity of adhesions at second-look laparoscopy were assessed by a surgeon who was unaware of the treatment received after laparoscopic myomectomy. A previous study on the same issue has been recently published by a single centre in Italy (Pellicano *et al*., 2003; Pellicano *et al*., 2005).

In this multicentre study, the application of Hyalobarrier® did not significantly prolong operating times because the mean application time of the product was 2 min. These results demonstrate the feasibility of applying Hyalobarrier® gel following laparoscopic myomectomy and confirm that gels are easier to deliver during laparoscopic surgery (diZerega *et al*., 2002; Mettler *et al*., 2003; Mettler *et al*., 2004; Lundorff *et al*., 2005) compared with membrane barriers, which are problematic to use via laparoscopy (Mais *et al*., 1995; Diamond, 1996; diZerega, 1996; Pelosi and Pelosi, 2002).

No complications or adverse events were reported after Hyalobarrier® gel administration, and no clinically meaningful differences in haematological parameters were observed between the patients treated with the gel and the controls either after surgery or at second-look procedure. Therefore, no safety considerations were raised in any case.

Compared with controls, the proportion of patients with adhesions at second-look laparoscopy appeared lower in the Hyalobarrier® group, although this difference did not reach statistical significance. The lack of statistical significance could be due to the small series of patients and/or to the fact that the enrolled population was not clinically homogeneous, owing to the broad inclusion criteria. While the former factor could be overcome in larger trials, one objective difficulty was encountered in the present study in recruiting an adequate number of patients scheduled to submit to laparoscopic myomectomy alone without concomitant surgery for associated pathologies. In fact, the patients enrolled in the present study adequately represent the spectrum of patients in a routine clinical setting. Therefore, we focused our attention on the severity (i.e. the score) of uterine adhesions as a marker of the efficacy of Hyalobarrier® gel. Indeed, the gel was applied only to uterine incisions and sutures; the difference between uterine adhesion score at baseline and at second-look was significantly lower in the gel group. Moreover, to circumvent the problem of the heterogeneous study population, efficacy was also analysed in two subgroups of patients, namely those who were submitted to myomectomy alone without concomitant surgery and those without uterine adhesions before laparoscopic myomectomy. In both the subgroups, a difference was observed in the mean adhesion scores, which was significantly lower in the Hyalobarrier® gel group compared with the controls. This suggests that the application of Hyalobarrier® gel may significantly reduce the severity of postoperative adhesions following laparoscopic myomectomy.

Similar results have been obtained in a previous study on the clinical efficacy of auto-crosslinked HA gel in the prevention of postoperative adhesions after laparoscopic myomectomy, recently published by Pellicano *et al*. (2003). The authors evaluated the adhesion score according to a different adhesion score system (American Fertility Society, 1988) from the one used in the present multicentre clinical trial (Operative Laparoscopy Study Group, 1991) and concluded that the rate of postsurgical adhesions was significantly lower in treated patients than in the controls (Pellicano *et al*., 2003). However, the rate of postsurgical adhesions was also significantly dependent on the kinds of laparoscopic sutures that were used to close uterine defects, both in treated patients and in controls (Pellicano *et al*., 2003).

The formation of postmyomectomy adhesions is not trivial from a clinical standpoint as adhesions may have adverse

effects on fertility (Fauconnier *et al*., 2000) and cause a wide variety of patient discomforts (Tulandi *et al*., 1993; Dubuisson *et al*., 2000; Miller, 2000). The formation of postmyomectomy adhesions depends on several factors such as previous adhesions, location of fibromas, location and number of uterine incisions, as previously shown by Dubuisson *et al*. (1998) and confirmed by the multivariate analysis performed in this study. Several approaches have been attempted to reduce the incidence of postoperative adhesions, including mechanical barriers and pharmacological agents, although to date no device has been found that provides consistent efficacy (Koh and Janik, 2003). Hyalobarrier® gel is a reabsorbable adhesion-prevention gel barrier formed of auto-crosslinked HA, which is a natural component of the extracellular matrix and synovial fluid. It is highly biocompatible, possesses increased *in situ* residency time compared with native, unmodified HA and may also have positive biological effects on healing, as would native HA (Hagberg, 1992; Laurent and Fraser, 1992; Zhong *et al*., 1994). Therefore, the high viscosity of Hyalobarrier® gel may allow the reduction of adhesion formation by providing a physical barrier that limits the contact among injured peritoneal sites for a protracted period, without introducing foreign molecules in the peritoneal cavity (Renier *et al*., 2005).

The safety and efficacy of this auto-crosslinked HA gel in adhesion prevention in different gynaecological surgery settings has been investigated by other authors (Acunzo *et al*., 2003; De Iaco *et al*., 2003; Carta *et al*., 2004; Guida *et al*., 2004). In two studies, the gel was shown to significantly reduce the incidence and severity of *de-novo* intrauterine adhesion formation after hysteroscopic surgery (De Iaco *et al*., 2003; Guida *et al*., 2004). Similar results were reported in patients who submitted to hysteroscopic adhesiolysis (Acunzo *et al*., 2003). Finally, one study examined the effectiveness of the gel applied after myomectomy performed via laparotomy (Carta *et al*., 2004). In all these studies, the auto-crosslinked HA gel demonstrated to be safe and efficacious in reducing postoperative adhesion formation. Additionally, its ease of use has been extensively demonstrated (Acunzo *et al*., 2003; De Iaco *et al*., 2003; Pellicano *et al*., 2003; Carta *et al*., 2004; Guida *et al*., 2004; Pellicano *et al*., 2005).

In summary, Hyalobarrier® gel is a biodegradable barrier that appears to have efficacious antiadhesive action. This easy-to-use device also requires minimal application time and has a positive safety profile.

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