ellipse 19(1): 15–18 (2003)

Hyaluronan derivative gel (HYALOBARRIER® gel) in intrauterine adhesion (IUA) prevention after operative hysteroscopy

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■ **Abstract:**

Objective: To evaluate the effectiveness of an autocrosslinked hyaluronan derivative in the form of a gel (HYALOBARRIER® gel) in IUA prevention after hysteroscopic surgery.

Design: Prospective, randomized trial at a single center.

Setting: University Hospital.

Patients: Sixty women aged between 18–65 years old undergoing hysteroscopic surgery were included in the study. After surgery, the patients were randomly assigned to treatment with HYALOBARRIER® gel or surgical procedure alone.

Main Outcome Measures: Nine weeks after surgery, a second look office hysteroscopy was performed and the adhesions were blindly evaluated according to the modified American Society for Reproductive Medicine (ASRM) intrauterine adhesions classification.

Results: At the end of the study, a total of 40 patients were evaluated and intrauterine adhesions were seen in 12 patients (30.0%). Thirteen out of 18 patients (72.2%) in the treated group and 15 out of 22 (68.2%) in the control group were free from synechiae. Severe adhesions (Stage II) were present in 5.6% of the treated group and 22.7% of the control group. The safety profile of HYALOBARRIER® gel treated patients was comparable to that of the control group.

Conclusion: This study showed that in presence of bleeding, ACP gel reduces severe IUA formation.

■ **Keywords:** Intrauterine adhesions – hysteroscopy – synechiolysis

Intordution

Intrauterine adhesions (IUA), defined as scar tissue inside the uterine cavity, remain a clinical problem. IUA are formed when the internal walls of the uterus adhere to each other causing partial or total (Asherman's Syndrome) obliteration of the cavity.

The most important causes of IUA are previous traumas to the uterine cavity associated to infection, as it may occur following D&C to treat spontaneous abortion or abnormal uterine bleeding [1, 7]. Less commonly, endometrial tuberculosis or the prolonged use of an intrauterine device (IUD) may also lead to the development of intrauterine adhesions. The hysterosalpingography (HSG) and hysteroscopy are common methods used to diagnose intrauterine adhesions. The most frequent symptoms related to the presence of intrauterine adhesions are hypomenorrhea, amenorrhea, dysmenorrhea, infertility or recurrent miscarriage. Consequently, the surgical removal of IUA with hysteroscopic guidance is generally recommended.

Earlier strategies for the prevention of adhesions have included the intrauterine insertion of a Foley catheter, the intraoperative insertion of an IUD (Intra-Uterine Device), or postoperative estroprogestin administration [4, 6].

A new category of adhesion prevention methods are represented by barrier systems that, by separating raw surfaces, avoid the formation of fibrin bridges and subsequent adhesion formation. Such systems include synthetic and natural-based polymer barriers, including hyaluronan-based devices that have been reported to be effective in the prevention of adhesions in abdomino-pelvic settings [5, 9]. Recently, the use of a hyaluronan-based antiadhesive membrane (Seprafilm®) has been described as an intrauterine adhesion prevention system after hysteroscopic surgery [10]. This study reports the results of a blind randomized, clinical trial conducted to assess the safety and the effectiveness of antiadhesion HYALOBARRIER® gel, a cross-linked hyaluronan derivative gel, after hysteroscopic surgery.

Materials and methods

Materials

Hyalobarrier® gel was purchased from Fidia Advanced Biopolymers S.r.l. (Abano Terme, Italy). It is a highly viscous injectable, transparent, sterile, biocompatible and biodegradable gel, obtained by the cross-linking reaction of highly purified Hyaluronan (HA). HA is a naturally occurring polysaccharide, ubiquitously found in many connective tissues and organs.

Study population

Women were eligible for inclusion if they were undergoing endometrial ablation or hysteroscopic removal of submucosal fibroids, endometrial polyps, septatae uterus or intrauterine synechiae. The study protocol was reviewed and approved by the Institutional Review Board for human experimentation of the University of Bologna. Sixty patients aged from 18 to 65 years old were enrolled in the study and written, informed consent was obtained from each patient.

Hysteroscopy

All patients were admitted to the hospital the evening before surgery; surgical procedures were done under general anesthesia in the endoscopic operating room. No antibiotic prophylaxis was administered.

An 8 mm hysteroscopic resectoscope (Storz, Tuttlingen, Germany) with electrosurgical tips was used. In all cases, sorbitol-mannitol (Clear-Flex®, Baxter S.A., Lessines, Belgium) was used as distention media; and fluid intake and output were continuously monitored (Hysteromat, Storz). After dilating the uterine cervix, the resectoscope was inserted in the uterine cavity. Under direct vision, using a monopolar probe, the polyps, fibroids, synechiae, or the entire endometrial lining were completely resected. An adequate hemostasis was obtained with monopolar electrocautery.

After completion of the surgical procedure, the patients who met the inclusion criteria were randomly assigned either to the treatment with HYALOBARRIER® gel or to the control group, according to a computer-generated randomization schedule. The gel was applied by means of a 20 cm long cannula with a diameter of 5 mm in order to cover the entire uterine cavity. An average volume of 10.5 ± 5.5 ml of Hyalobarrier® gel (range 5–20) was applied in the uterine cavity. No adhesion prophylaxis measures were used in the control group. The patients were monitored for vital signs intraoperatively and postoperatively in the following 24 hours before discharge.

Second look hysteroscopy and follow-up

Second look hysteroscopy was undertaken nine weeks after the initial procedure by a blinded investigator after insertion in the uterine cavity of a 5 mm hysteroscope (Storz) with CO_2 distention media. After visualization of the uterine cavity, intrauterine synechiae were evaluated applying the American Society for Reproductive Medicine (ASRM) modified scoring system (Tab. 1) [2]. All diagnostic procedures were recorded.

Comparison of adhesion scores between the groups was performed using the Wilcoxon Mann-Whitney Test. The presence/absence and extent of adhesions were also separately evaluated by the Chi-square Test and Student's t-Test. All tests were performed using an I type error alpha 0.05.

Tab. 1: American Fertility Society, classification of intrauterine adhesions, modified

Extent of cavity involved	< 1/3	1/3–2/3	> 2/3
	1	2	4
Type of adhesions	Filmy	Filmy & Dense	Dense
	1	2	4
Stage I (mild)	1–4		
Stage II (severe)	5–8		

Safety evaluation was based on the type and severity of any adverse events recorded throughout the study.

Results

No Adverse events such as vaginal bleeding, headache, nausea, vomiting or pelvic pain were recorded. A total of 40 patients attended the postoperative diagnostic hysteroscopy, 18 and 22 in the Hyalobarrier® gel and control groups respectively. The two groups were comparable in terms of age, weight, height, and baseline conditions.

The incidence of adhesion-free patients was 72.2% and 68.2% in HYALOBARRIER® gel treatment and control groups respectively. Analysis of the extent of the adhesions showed that in the gel treated group, 16.7% of the patients had adhesions in less than 1/3and 11% in between 1/3 and 2/3 of the uterine cavity, while none hadadhesions in more than 2/3 of the uterine cavity. In the control group, 13.6% of the patients had adhesions in less than 1/3 of the uterine cavity, 13% had adhesions in between 1/3 and 2/3 and 4.6% had adhesions in more than 2/3 of the uterine cavity. Dense adhesions were found in 5.6% and 22% in the HYALOBARRIER® gel and control groups respectively. After statistical analysis, no significant difference were seen, although more severe adhesions were seen in the control group (stage II, 22%) than in the HYALOBARRIER® gel treatment group (stage II, 5.6%). Data are summarized in figures 1, 2, and 3.

Conclusion

Intrauterine adhesions, which tend to form in 25–30% of patients after hysteroscopic surgery, can be considered as one of the causes of infertility, recurrent pregnancy loss, dysmenorrhea, hypomenorrhea or amenorrhea [8]. There are various methods for the prevention of IUA: In the past, the intrauterine insertion of a Foley catheter and the insertion of an IUD to prevent adhesion reformation have been reported. Pharmacological therapies have also been

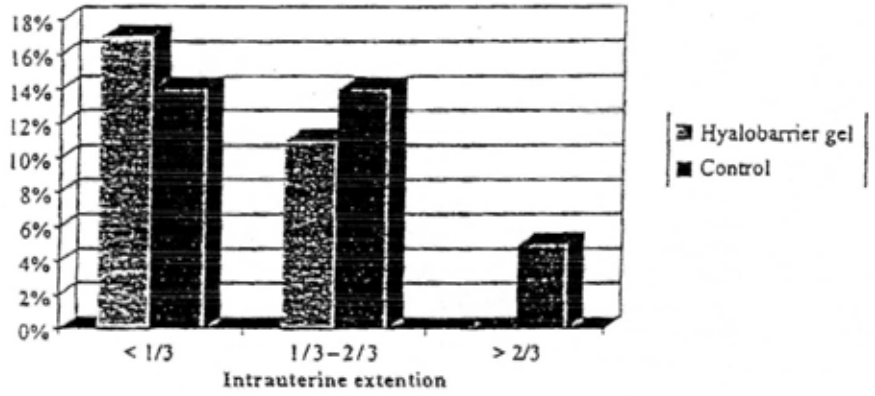

Fig. 1: Extension of IUA in the intrauterine cavity

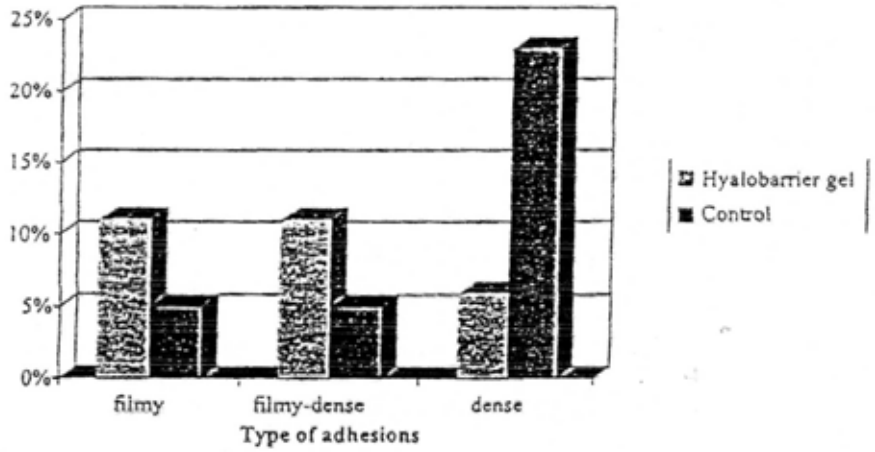

Fig. 2: Type of adhesions

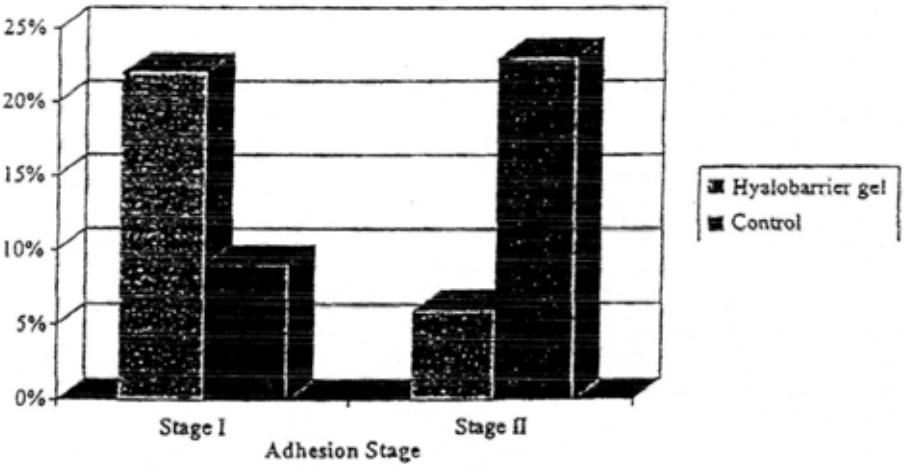

Fig. 3: Adhesion Stage

proposed, but postoperative estroprogestins or danazol administration proved inadequate methods of adhesion prevention. One of the most widely used postoperative therapies to prevent adhesions in abdominal and pelvic surgery is the placement of physical barriers (absorbable or not absorbable) between adjacent injured surfaces of the organs or abdominal wall until peritoneal wound healing has occurred. HYALOBARRIER®, a hyaluronan cross-linked derivative in the form of a highly viscous gel has been reported to prevent adhesions in experimental abdominal and gynecological surgery [3, 5]. The use of this device, introduced in the uterine cavity at the end of hysteroscopic surgery, does not seem to increase the incidence of adhesion-free patients. Nevertheless, the adhesions observed after HYALOBARRIER® gel administration involved smaller areas of the cavity (stage II in 22.7% and 5.6% in the control and treated groups, respectively) and were less severe (dense adhesion in 22.7% and 5.6% in the untreated and treated groups, respectively).

In conclusion, the authors recognize that the data reported lack statistical significance given the small sample size of the population evaluated. Despite this, newly induced synechiae were less severe in the HYALOBARRIER® gel-treated patients, thus reducing the risk of pregnancy morbidity and improving the outcomes of hysteroscopic surgery.

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