

Evaluation of adhesions after laparoscopic myomectomy using the Harmonic Ace and the auto-crosslinked hyaluronan gel vs Ringer's lactate solution

P. Litta¹, N. Pluchino², L. Freschi², S. Borgato¹, S. Angioni³

¹Department of Women's and Children's Health, Obstetrics and Gynecology Clinic, University of Padua, Padua

²Division of Obstetrics and Gynecology, University of Pisa, Pisa

³Division of Obstetrics and Gynecology, University of Cagliari, Cagliari (Italy)

Summary

Objective: To evaluate the efficacy of a crosslinked hyaluronic acid (HA) for the prevention of postsurgical adhesions after laparoscopic myomectomy using the Harmonic Ace. **Materials and Methods:** Women 23-42 years of age who wished to conceive underwent laparoscopic myomectomy. As adhesion preventing agents, crosslinked HA gel was applied on the myometrial scar at the end of the surgery in Group A, whereas in Group B a Ringer's lactate solution was used in a prospective, observational study. Second-look mini-laparoscopy was performed 45-60 days after surgery and the adhesions were assessed according to a site-specific modified scoring. **Results:** The incidence of postoperative adhesions was the same in both groups, but anatomically significant adhesions and site-specific modified score was significantly reduced in Group A compared to Group B control group (31.8% vs 54.6% and 1.05 ± 1 vs 2.27 ± 2.5 , respectively). **Conclusion:** The use of auto-cross-linked HA gel confirms a protection on adhesion formation on myometrial wounds, although the degree of this effect appears to be weak. The absence of adnexa adhesions using the HA and a different uterine incision appear remarkable, although a larger number of patients is required to confirm the present findings

Key words: Myomectomy; Adhesions; Hyaluronan gel.

Introduction

Adhesion formation is a common sequela of pelvic surgery and may cause several complications, such as bowel obstruction [1], chronic pelvic pain [2], and infertility [3-5]. Adhesiolysis increases pregnancy rate from 38% to 52% [6, 7] and reduces pain in 60%-90% of cases of chronic pelvic pain [8, 9].

In addition to a careful surgical technique, to a reduction of surgery time, of blood loss, and the risk of infection, a number of approaches have been proposed to prevent intraperitoneal adhesions. However, despite microsurgical techniques and the adoption of laparoscopic approaches, the problem of adhesions persists [10]. Therefore, other prophylactic measures have to be sought [10, 11].

Among the adhesion preventive agents developed in the last decades, hyaluronan (or hyaluronic acid - HA) based products have been frequently used in different application forms. Hyaluronan-based agents seem to prevent adhesions not only by producing a temporary barrier to fibrin-bridge formation but also through their biological actions. Indeed sodium hyaluronate has been reported to increase the proliferation rate of human peritoneal mesothelial cells, enhancing peritoneal tissue repair [12].

Uterine fibroids represent the most common pelvic tumor of the female reproductive system and myomec-

tomy is traditionally the primary treatment in women with symptomatic fibroids who wish to retain their reproductive potential [13-15].

The accomplishment of myomectomy through laparoscopy has often been questioned due to the excessive blood loss and due to the increase of the operating time owing to hemostasis, which requires a meticulous time-consuming technique [16, 17].

The Harmonic Ace is an ultrasonic surgical instrument that enhances the blade's ability to cut and coagulate blood vessels. The present authors previously demonstrated that the use of the Harmonic Ace for laparoscopic myomectomy is associated with lower operating time and intraoperative blood loss in comparison with conventional electrosurgery [18].

In this regard, the objective of the present study was to prospectively assess adhesion formation following laparoscopic myomectomy using the Harmonic Ace and an auto-crosslinked HA gel vs Ringer's lactate.

Materials and Methods

Between February 2008 and 2010, 50 fertile women desiring pregnancy, underwent single laparoscopic myomectomy and were enrolled in the present study. Patients were divided into two groups (A and B) of 25 women each. At the end of the surgical procedure, group A patients received an application of auto-crosslinked HA gel (five ml) on the injured uterine surface, while in the control Group B Ringer's lactate solution was used.

The type of gel used is sterile, transparent, and highly viscous gel, obtained by condensation of HA through an auto-crosslink-

Revised manuscript accepted for publication November 15, 2013

Table 1. — Clinical parameters compared between Group A (HA) and Group B (Ringer's lactate).

Patients	Group A 22	Group B 22	p
Age (years)	33.6 ± 5.1	33.0 ± 3.9	NS
Operating time (min.)	77.1 ± 43.7	70.5 ± 31.3	NS
Estimated blood loss (cc)	114.0 ± 105.8	105.0 ± 87.0	NS
Size (cm)	7.2 ± 1.0	7.2 ± 1.1	NS
Classification according to Munro			
Subserous (type 5) – n. (%)	14 (63.6%)	8 (36.4%)	NS
Intramural (type 4) – n. (%)	12 (54.5%)	10 (45.5%)	NS
Location			
Anterior wall - n. (%)	5 (22.7%)	13 (59.1%)	NS
Posterior wall - n. (%)	4 (18.2)	7 (31.8%)	NS
Fundus uteri - n. (%)	10 (45.5%)	5 (22.7%)	NS

Table 2. — Adhesions score.

Adhesions	< 1/3	1/3 - 2/3	2/3
Uterus anterior wall			
Filmy	1*	2	3
Dense	2	4	6
Uterus posterior wall			
Filmy	1*	2	3
Dense	2	4	6

Site-specific modified scoring.

*0-1 is assigned when either no adhesions or anatomically non-significant adhesions were found.

Table 3. — Description of site-specific uterine adhesions (Group A vs Group B, p < 0.05).

Treatment	Score								Average
	0	1	2	3	4	5	6	9	
Group A (22 pts)	8	7	4	3	–	–	–	–	1.05 ± 1
Group B (22 pts)	8	2	3	4	2	–	2	1	2.27 ± 2.5

ing process and is indicated for laparoscopic and hysteroscopic surgical procedures.

Ringer's lactate solution is a sterile, non-pyrogenic solution for fluid and electrolyte replenishment and it contains sodium lactate in addition to calcium chloride, sodium chloride, and potassium chloride.

The age, characteristics of the myoma including the Classification according to Munro [19], location, and size were reported. The weight of the myomas was calculated postoperatively. Surgical outcome measures included surgical time "skin-to-skin" in minutes and estimated blood loss (calculated by subtracting irrigation volume from the total volume of fluid suctioned). The uteri morphology was evaluated by ultrasonography.

The sample inclusion criteria were the following: nulligravida associated with pregnancy planning, single myoma of size more than five cm and the largest nine cm, negative pregnancy test, absence of adnexal pathologies or endometriosis, absence of previous abdominal/pelvic surgical treatment, chronic pelvic pain, negative case history of immunosuppressive or cytostatic treatments, absence of pathology such as diabetes, coagulation hepatic, or autoimmune diseases. Informed consent was obtained for all the procedures.

The same surgeon carried out all the operations. Surgical procedure consisted in four-ports approach: one port for the laparoscope and three ancillary ports (one 12-mm and two five-mm ports, respectively, from left to right). Myomectomy was per-

Table 4. — Adhesions after laparoscopic myomectomy according to the number of patients (Group A vs Group B, p = 0.05).

	Post-surgical adhesions			
	0-1		≥ 2	
	No.	%	No.	%
Group A	15/22	68.2	7/22	31.8
Group B	10/22	45.4	12/22	54.6

Table 5. — Histological detection of fibrosis (Group A vs Group B, p < 0.01).

Fibrosis	0/+	+++ / +++	Tot. fields	% fields
Group A	47	33	80	41
Group B	37	63	100	63

Table 6. — Histological detection of inflammation (Group A vs Group B, p < 0.01).

Inflammation	0/+	+++ / +++	Tot. fields	% fields
Group A	73	7	80	8
Group B	45	55	100	55

Table 7. — Histological detection of vessels (Group A vs Group B, p < 0.01).

Vessels	0/+	+++ / +++	Tot. fields	% fields
Group A	59	21	80	26
Group B	34	66	100	66

formed by using a five-mm Harmonic Ace. The technique consisted of transverse incision of the perimetrium, highlighting pseudocapsule of myoma, traction with myoma-drill promoting myoma enucleation, and contemporary section of connectival bridges. Removal of myomas was performed using Steinert electrical (10-15 mm) morcellator. Suturing was always done in double layer (subserous-intramural myomas), intracorporeal single stitches were placed using 0 PDS thread (adsorbable, monofilament polydioxanone). The intraperitoneal cavity was accurately explored and irrigated in order to remove any myoma remnants and blood [18].

The second-look operations were performed in postoperative days 45 to 60 and consisted in a diagnostic minilaparoscopy (five-mm umbilical optic and two three-mm ancillary trocars) performed under general anaesthesia using a laryngeal mask airway in association with chromosalpingoscopy in order to assess tubal patency and function. The description of the type of adhesions and the assessment of their severity took into account whether they were: *de novo adhesions* (with the exclusion of uterine surgical wounds) or *adhesions formed on myometrial scars*.

Adhesions were assessed according to the classification given by the American Fertility Society (AFS). Adhesions formed on the uterine scar sites were assessed using site-specific modified scoring [20-22].

The absence or presence of (filmy) adhesions which were minimally related with the myometrial scar (< 1/3 of its length) were considered anatomically non-significant and were assigned, respectively, a score of 0-1, whereas anatomically significant adhesions were assigned a score of ≥ 2 [23-25] (Table 1). The adhesions at the second-look laparoscopy were sent out for histological analysis. The specimens were stained with haematoxylin-eosin and the assessment was based on the



Fig. 1A

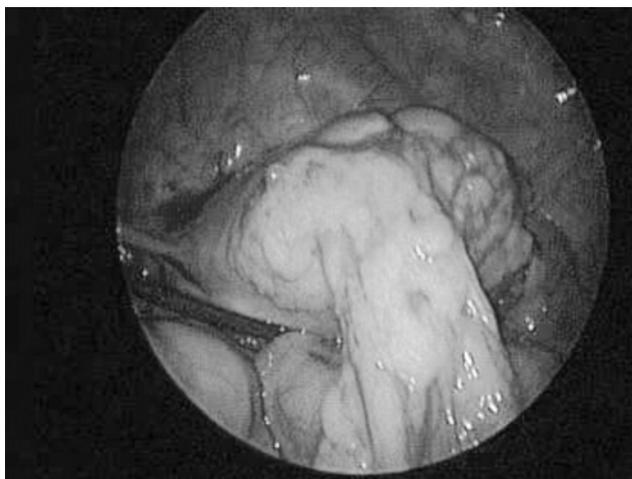


Fig. 1B

Figure 1. — A) Laparoscopic view at the end of myomectomy (Patient n° 29 Group B). B) Laparoscopic view during second-look surgery (Patient n° 29 Group B).

absence (0/+) or presence (++/+++) of fibrosis, inflammation, and vascularization. Fibrosis was coded when more than 50% of the field was filled with collagenous fibres and fibroblasts, inflammation when the field contained more than 20 leukocytes and vascularization when the field contained more than five vessels.

Ethical approval was obtained from the Local Ethical Committee, and informed consent was obtained from patients before enrolment.

Results

The study was successfully conducted in 44 patients. One patient was excluded from the analysis because of pelvic adhesions found during myomectomy, whereas five patients refused second-look laparoscopy (10% drop-out rate).

Patient, fibroid, and surgical procedure characteristics are shown in Table 1. During the postoperative period, no allergic reactions were noted or adverse effect were assessed following the administration of HA.

The second-look operation took place after 44.7 ± 23.7 days, (48.2 ± 24.9 days for Group A and 41.2 ± 22.4 days for Group B).

The authors did not find any adherence involving the adnexa or involving extrauterine organs both in Groups A and B, with the exclusion of omental tissue, although they did not result statistically significant. On the contrary, anatomically significant adhesions (score ≥ 2) developed in seven patients receiving HA and 12 receiving no treatment. Similarly, the average site-specific modified score of adhesions was 1.05 ± 1 in Group A and 2.27 ± 2.5 in Group B.

Adhesions were more frequent in case of larger myomas (7.2 ± 1.0 cm), regardless of presence of HA ($p < 0.001$, Figures 1A-B).

The histological analysis of adhesion tissues performed in Group B revealed higher incidence of fields containing fibrosis, leukocytes, and vessels than in Group A ($p < 0.01$, Tables 6, 7, and 8).

Discussion

Myomectomy is a treatment procedure intended to preserve fertility in cases of uterine myomas. Any postoperative adhesion of the uterus, the adnexa or bowel may reduce fertility or increase post-operative pain.

The present study confirmed that laparoscopic myomectomy is associated with the development of uterine postsurgical adhesions, although their incidence is affected by the use of HA. In particular, the present series confirmed previous analysis, whereas the incidence of post-surgical adhesions after laparoscopic myomectomy varies from 29% and 64% [26, 27] and is consistently lower than with traditional surgery where it has been reported to be 90% [28, 29].

With the exclusion of sites of the uterine surgical wound, the present authors did not evidence any new adhesion formation involving the bowel or between the uterine adnexa. Interestingly, this finding appears to be unrelated with the use of HA. On the contrary, a previous series evidenced at least 8.9% of patients developed *de novo* adhesions of the uterine adnexa, although only the diameter of the largest myoma enucleated was identified as a factor influencing the development of these adhesions [30]. Dubuisson *et al.* reported 12% incidence of adhesions of the uterine adnexa, although enucleation of posterior myomas increased this risk [27].

Traditionally, the surgical technique of laparoscopic myomectomy is borrowed by laparotomy and it is performed by vertically incising the perimetrium using a monopolar or CO₂ laser. In the present series, the perimetrium was always incised transversally, even in case of posterior myomas and the Harmonic scalpel was used to incise and to enucleate the myoma. Although the number of posterior myomas is limited (only ten in this series), the absence of *de-novo* adnexa adhesions appears to be remarkable and, to date, no studies, evaluating whether the type of perimetrium incision might influence the rate of adhesions after laparoscopic myomectomy, are available.

Surgical perioperative strategies have a great impact on

the frequency of development of postoperative adhesions. The present authors previously found that the use of the Harmonic Ace in myomectomy is associated with shorter global operative time and less intraoperative blood loss than epinephrine with electrosurgery [18]. Indeed, at least theoretically, the ultrasound Ace might confer some advantages in the surgical strategy to reduce formation of post-surgical adhesions, although the rate adhesions of the present series resulted in the same range of values available in other studies where conventional electrosurgery was used.

In addition the present findings support the efficacy of HA in reducing the rate and severity of post-surgical adhesions. Although the number of adhesions resulted the same between the two groups, the rate of anatomically significant adhesions for myomectomy site was lower in patients treated with HA. This finding was also confirmed by the histological evaluation of a lower grade of fibrosis, inflammation, and vessels in the sample tissue removed from adhesions of women receiving HA.

No complications or adverse events were reported after 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.

The gel utilized 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 and unmodified HA, and may also have positive biological effects on healing, as would native HA [31, 32].

The safety and efficacy of this auto-crosslinked HA gel in adhesion prevention in different gynaecological surgery settings has also been investigated by other authors [12]. The present series confirms previous findings and the effects of the gel are not modified by the choice of a different surgical technique and by the use of the Harmonic Ace.

In conclusion, although laparoscopic surgery is less invasive, it is still associated with post-surgical adhesion formation with potential critical consequence on fertility preservation. The use of auto-crosslinked HA gel confirms a protection on adhesion formation on myometrial wounds, although the degree of this effect appears to be weak. The absence of adnexa adhesions using the harmonic scalpel and a modified uterine incision appear remarkable, although a larger number of patients is necessary to confirm the present findings.

References

- [1] Ivarsson M.L., Holmadhl L., Frazen G.: "Cost of bowel obstruction resulting from adhesions". *Eur. J. Surg.*, 1997, 163, 697.
- [2] Peters A.A., van Dorst E., Jellis B., van Zuuren E., Hermans J., Trimbois J.B.: "A randomized clinical trial to compare two different approaches in women with chronic pelvic pain". *Obstet. Gynecol.*, 1991, 77, 740.
- [3] Ellis H., Moran B.J., Thompson J.N., Parker M.C., Wilson M.S., Menzies D., et al.: "Adhesion-related hospital readmission after abdominal and pelvic surgery: a retrospective cohort study". *Lancet* 1999, 353, 1476.
- [4] Monk B.J., Berman M.L., Montz F.J.: "Adhesions after extensive gynecologic surgery: clinical significance, etiology and prevention". *Am. J. Obstet. Gynecol.*, 1994, 170, 1396.
- [5] Al-Jaroudi D., Tulandi T.: "Adhesions prevention in gynecologic surgery". *Obstet. Gynecol. Survey*, 2004, 59, 360.
- [6] Di Zerega G.S.: "Biochemical events in peritoneal tissue repair". *Eur. J. Sur. Suppl.*, 1997, 577, 10.
- [7] Tulandi T., Murray C., Guralnick M.: "Adhesion formation and reproductive outcome after myomectomy and second-look laparoscopy". *Obstet. Gynecol.*, 1993, 82, 213.
- [8] Duffy D.M., DiZerega G.S.: "Adhesion controversies: pelvic pain as cause of adhesions cristalloids in perverting them". *J. Reprod. M.*, 1996, 41, 19.
- [9] Di Zerega G.S., Roth R., Johns D.B.: "Quantitation of peritoneal adhesions and correlation with clinical outcomes". *Infertil. Reprod. Med. Clin. N. Am.*, 2003, 14, 431.
- [10] Pados G., Venetis C.A., Almaloglou K., Tarlatzis B.C.: "Prevention of intra-peritoneal adhesions in gynaecological surgery: theory and evidence". *Reprod. Biomed. Online*, 2010, 21, 290.
- [11] Nappi C., Di Spiezio Sardo A., Greco E., Guida M., Bettocchi S., Bifulco G.: "Prevention of adhesions in gynaecological endoscopy". *Hum. Reprod. Update*, 2007, 13, 379.
- [12] Mais V., Bracco G.L., Litta P., Gargiulo T., Melis G.B.: "Reduction of postoperative adhesions with an auto-crosslinked hyaluronan gel in gynaecological laparoscopic surgery: a blinded, controlled, randomized, multicentre study". *Hum. Reprod.*, 2006, 21, 1248.
- [13] Ciavattini A., Tsiroglou D., Piccioni M., Lugnani F., Litta P., Felicciotti F., Tranquilli A.L.: "Laparoscopic cryomyolysis: an alternative to myomectomy in women with symptomatic fibroids". *Surg. Endosc.*, 2004, 18, 1785.
- [14] Ciavattini A., Tsiroglou D., Litta P., Vichi M., Tranquilli A.L.: "Pregnancy outcome after laparoscopic cryomyolysis of uterine myomas: report of nine cases". *J. Minim. Invasive Gynecol.*, 2006, 13, 141.
- [15] Ciavattini A., Tsiroglou D., Litta P., Frizzo H., Tranquilli A.L.: "Ultra-minilaparotomy myomectomy: a minimally invasive surgical approach for the treatment of large uterine myomas". *Gynecol. Obstet. Invest.*, 2009, 68, 127.
- [16] Dubuisson J.B., Fauconnier A., Babaki-Fard K., Chapron C.: "Laparoscopic myomectomy: a current view". *Hum. Reprod. Update*, 2000, 6, 588.
- [17] Hurst B.S., Matthews M.L., Marshburn P.B.: "Laparoscopic myomectomy for symptomatic uterine myomas". *Fertil. Steril.*, 2005, 83, 1.
- [18] Litta P., Fantinato S., Calonaci F., Cosmi E., Filippeschi M., Zerbetto I. et al.: "A randomized controlled study comparing harmonic versus electrosurgery in laparoscopic myomectomy". *Fertil. Steril.*, 2010, 94, 1882.
- [19] Munro M.G., Critchley H.O.D., Broder M.S., Fraser I.S.: "Figo classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nonpregnant women of reproductive age". *Int. J. Gynecol. Obstet.*, 2011, 113, 3.
- [20] The American Fertility Society: "The American fertility Society classifications of adnexal adhesions, distal tubal occlusion, tubal occlusion secondary to tubal ligation, tubal pregnancies, Mullerian anomalies and intrauterine adhesions". *Fertil. Steril.*, 1988, 49, 944.
- [21] The Surgical Membrane Study Group: "Prophylaxis of pelvic sidewall adhesions with Gore Tex surgical membrane: a multicenter clinical investigation". *Fertil. Steril.*, 1992, 57, 921.
- [22] Burns J., Skinner K., Colt M.J. et al.: "A hyaluronate gel for prevention of postsurgical adhesions: evaluation in two animal species". *Fertil. Steril.*, 1996, 66, 814.
- [23] De Iaco P.A., Stefanetti M., Pressato D., Piana S., Donà M., Pavesio A., Bovicelli L.: "A novel hyaluronan-based gel in laparoscopic adhesion prevention: preclinical evaluation in an animal model". *Fertil. Steril.*, 1998, 69, 318.
- [24] Koçak I., Unlü C., Akçan Y., Yakin K.: "Reduction of adhesion formation with cross-linked hyaluronic acid after peritoneal surgery in rats". *Fertil. Steril.*, 1999, 72, 873.

- [25] Johns D.B., Keyport G.M., Hoehler F., diZerega G.S.: "Intergel adhesion prevention study group. Reduction of postsurgical adhesion with Intergel adhesion prevention solution: a multicenter study of safety and efficacy after conservative gynecologic surgery". *Fertil. Steril.*, 2001, 76, 595.
- [26] Takeuchi H., Kinoshita K.: "Evaluation of adhesion formation after laparoscopic myomectomy by systematic second-look micro-laparoscopy". *J. Am. Assoc. Gynecol. Laparosc.*, 2002, 9, 442.
- [27] Dubuisson J.B., Fauconnier A., Chapron C., Kreiker G., Nörgaard C.: "Second look after laparoscopic myomectomy". *Hum. Reprod.*, 1998, 13, 2102.
- [28] Myomectomy Adhesion Multicenter Study Group (MAMSG): "An expanded polytetrafluoroethylene barrier (Gore-Tex Surgical Membrane) reduces post-miomectomy adhesion formation". *Fertil. Steril.*, 1995, 63, 491.
- [29] Gutt C.N., Oniu T., Schemmer P.: "Fewer adhesions induced by laparoscopic surgery?". *Surg. Endosc.*, 2004, 18, 898.
- [30] Takeuchi H., Kitade M., Kikuchi I., Shimanuki H., Kumakiri J., Takeda S.: "Influencing factors of adhesion development and the efficacy of adhesion-preventing agents in patients undergoing laparoscopic myomectomy as evaluated by a second-look laparoscopy". *Fertil. Steril.*, 2008, 89, 1247.
- [31] Mais V., Ajossa S., Piras B., Guerriero S., Marongiu D., Melis G.B.: "Prevention of de novo adhesion formation after laparoscopic myomectomy: a randomized trial to evaluate the effectiveness of an oxidized regenerated cellulose absorbable barrier". *Hum. Reprod.*, 1995, 10, 3133.
- [32] Pellicano M., Bramante S., Cirillo D., Palomba S., Bifulco G., Zullo F., Nappi C.: "Effectiveness of autocrosslinked hyaluronic acid gel after laparoscopic myomectomy in infertile patients: a prospective, randomized, controlled study". *Fertil. Steril.*, 2003, 80, 441.

Address reprint requests to:
P. LITTA, M.D.
Via Giustiniani, 3
35128 Padova (Italy)
e-mail: pietro.litta@unipd.it