

Using New-Crosslinked Hyaluronic Acid Gel to Prevent Intrauterine Adhesion After Hysteroscopic Septum Resection: A Prospective, Randomized, Controlled Study

Histeroskopik Septum Rezeksiyonu Sonrası İntrauterin Adezyonu Önlemede Yeni Çapraz Bağlı Hyaluronik Asit Jel: Prospektif, Randomize Kontrollü Çalışma

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ABSTRACT

Objective: A prospective, randomized, controlled study was performed to assess the effect of new-crosslinked hyaluronic acid (NCHA) gel on the reoperation rates of women who underwent hysteroscopic septum resection. **Material and Methods:** A total of 45 infertile women who underwent hysteroscopic septum resection were randomly assigned to two groups as group with new-crosslinked hyaluronic acid (NCHA) gel applied following septum resection (n=23) and group without hyaluronic acid gel (n=22) but Foley catheter insertion into the cavity, groups were assessed 3 months later whether the postoperative uterine cavity was appropriate for embryo implantation and normal pregnancy. Uterine adequacy was determined according to the presence of remnant septum and adhesion formations. **Results:** There was a significant difference between groups in terms of rate of reoperation indicated for remnant septum resection or adhesiolysis of the previously resected septum site (1/23 versus 7/22, P<0.05). **Conclusion:** Our data showed that application of new-crosslinked hyaluronic acid (NCHA) gel following hysteroscopic septum resection is associated with significantly higher rate of surgical success in women with uterine septum.

Keywords: Uterine septum; hysteroscopy; intrauterine adhesion; new-crosslinked hyaluronic acid gel

ÖZET

Amaç: Yeni çapraz bağlı hyaluronik asit jelinin, histeroskopik septum rezeksiyonu uygulanan kadınların reoperasyon oranlarına etkisini değerlendirmek için prospektif, randomize, kontrollü bir çalışma yapıldı. **Gereç ve Yöntemler:** Histeroskopik septum rezeksiyonu uygulanan toplam 45 kısır kadın, septum rezeksiyonu sonrası hyaluronik asit jeli uygulanan (n=23) ve hyaluronik asit jeli olmaksızın Foley kateter uygulanan (n=22) hastalar olmak üzere iki gruba randomize edildi. Gruplar 3 ay sonra postoperatif uterus kavitesinin embriyo implantasyonu ve normal gebelik için uygun olup olmadığı açısından değerlendirildi. Uterin kavite yeterliliği, kalan septum ve adezyon formasyonlarının varlığına göre belirlendi. **Bulgular:** Gruplar arasında rezidüel septum rezeksiyonu ya da daha önce rezekte edilen septum alanının adezyolizisi ile ilişkili reoperasyon oranı açısından gruplar arasında anlamlı fark vardı (1/23'e karşı 7/22, P<0,05). **Sonuç:** Verilerimiz, histeroskopik septum rezeksiyonu sonrası hyaluronik asit jeli uygulamasının, uterus septumlu kadınlarda anlamlı olarak daha yüksek cerrahi başarı oranı ile ilişkili olduğunu göstermiştir.

Anahtar Kelimeler: Uterin septum; histeroskopi; intrauterin adezyon; hyaluronik asit jel

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Intrauterine adhesions are the most commonly encountered chronic complications following operative hysteroscopy.^{1,2} Variable rates have been reported and depend on the complexity of the surgical intervention ranging between 4 to 45%.³ Severity of the condition has been defined according to the ostial visibility and the presence of menstrual bleeding, using AFS or ESGE classification systems.⁴ Complete obliteration of the whole uterine cavity, the Asherman syndrome, is a serious issue presenting with secondary amenorrhea.⁵ Moreover some other severe consequences have been introduced such as placental adhesion anomalies in the following pregnancies.⁶ Hysteroscopy is the most commonly suggested tool to diagnose and treat these complications.⁶

Some anti-adhesive materials have been used to prevent postoperative adhesions.⁷ Hyaluronic acid gel has been studied to prevent intrauterine adhesions and favorable fertility outcomes have been reported by studies on rabbits.⁸⁻¹⁰

Our study was performed to assess the effect of new-crosslinked hyaluronic acid (NCHA) gel on the reoperation rates of women who underwent hysteroscopic septum resection.

MATERIAL AND METHODS

This prospective randomized study was approved by the institutional review board of our hospital, Zeynep Kamil Women and Children's Health, Training and Research Hospital and carried out at the IVF department between January 2016 and March 2017.

A total of 45 infertile women with a diagnosis of uterine septum by prior hysterosalpingography were randomly assigned to two groups by choosing themselves, a closed envelope which contains the selected group written in it and underwent hysteroscopic septum resection (Table 1). Before the surgery, history of the menstrual pattern, previous intrauterine interventions and reproductive history and written consent were obtained from each participant. All women underwent transvaginal sonographic evaluation. We excluded the cases with additional interventions to the septum resection, systemic disorders and cases with any other intracavitary pathology.

Hysteroscopic interventions were performed under general anaesthesia for uterine septum resection. The operation was carried out by one of three reproductive surgeons in the same department with the use of similar techniques.

A 4.5 mm hysteroscope (Storz, Germany) and the loop electrode were used for resection. Following the complete resection of uterine septum, we applied 5 ml new-crosslinked hyaluronic acid (NCHA) gel (MateRegen gel, Bioregen Biomedical Co.) to the patients randomized in the first group (n=23) and in the second group (n=22) we inserted a Foley catheter into the uterine cavity and inflated it with 3 cc of serum physiologic, in the immediate postoperative period.

All patients had prophylactic antibiotherapy (100 mg doxycycline BID) for 5 days and 2 cycles of Estrogen 2 mg BID for 25 days plus 5 mg MPA in the last 10 days, for endometrial regeneration. For women who had an intrauterine Foley catheter inserted, the device was removed after 7 days as an outpatient procedure.

Both groups were assessed by a second-look hysteroscopy planned for each case 3 months later in the early proliferative phase; whether the postoperative uterine cavity was appropriate for embryo implantation and normal pregnancy. During the second look hysteroscopy following overall inspection to document the extent and severity of any intra-uterine adhesions, patients were evaluated for further intervention to resect remnant uterine septum or adhesiolysis, if needed. Uterine adequacy was determined according to the presence of remnant septum or adhesion of the previously resected septum site.

STATISTICAL ANALYSIS

Data were analyzed using SPSS 15.0 for Windows. Fisher's exact test was used to compare rate of necessity of reoperation due to the postoperative intrauterine adhesions. P value <0.05 was accepted to be statistically significant.

RESULTS

We found that there were 7 patients in the Foley catheter group who need reoperation for adhesiolysis of the previously resected septum site vs only 1 in the

TABLE 1: Second look hysteroscopy findings.

	45 infertile women		p
	Hyaluronan (n=23)	Foley Catheter (n=22)	
Post-op Adhesions	1	7	<0.05
Remnant Septum	0	0	NS

new-crosslinked hyaluronic acid (NCHA) gel group. There was any remnant septum in both groups.

The AFS score of post op adhesions are shown on the Table 2. The difference between these two groups, in terms of rate of reoperation was statistically significant (1/23 versus 7/22, p<0.05).

DISCUSSION

In our study, we tried to assess the efficacy of new-cross linked derivative of hyaluronic acid (NCHA) to prevent postoperative adhesion following uterine septum resection. Our data showed that the intrauterine application of new-crosslinked hyaluronic acid (NCHA) gel, just after the surgical intervention, may be superior to the conventional techniques. As previous studies indicated, the major long-term complication that all surgeons try to avoid during resectoscopic surgery is post-operative adhesions.³ Due to the high frequency of intrauterine adhesions after resectoscopic surgery, clinicians look for new approaches to prevent these complications.³ Some measures have been introduced to prevent intrauterine adhesions.¹²⁻¹⁵ In the first studies, auto-cross linked derivative of hyaluronic acid was shown to reduce reformation of intrauterine adhesions after hysteroscopic adhesiolysis.¹⁵ Following recent studies confirmed earlier findings and pointed the safety and

effectiveness of this agent to improve women’s health, reducing the need for re-intervention after hysteroscopic surgery due to post-operative intrauterine adhesion formation.¹⁶

Accumulated data were presented by two recent metaanalyses. In one of the metaanalyses Healey indicated a lack of definitive evidence to conclude that any treatment is effective in preventing posthysteroscopy uterine adhesion formation, the heterogeneity and a high risk of bias to make any definitive conclusion.¹⁷

In the second metaanalyses, Mais showed a lower incidence of postoperative adhesions in patients who received hyaluronan gel compared to patients who underwent standard surgery only, but authors pointed the necessity of further RCTs to assess the efficacy of auto-crosslinked hyaluronan gel.¹⁸

In conclusion, the data of our study showed that the application of new-crosslinked hyaluronic acid (NCHA) gel following hysteroscopic septum resection is associated with significantly higher rate of surgical success in women with uterine septum. Then we strongly recommend the use of it.

TABLE 2: Severity of post-op adhesions.

	Post-op Adhesions-AFS score	
	Hyaluronan (n=23)	Foley Catheter (n=22)
1	3	3
2	-	3
3	-	6
4	-	2
5	-	4
6	-	2
7	-	2

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