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New Crosslinked Hyaluronan Gel, Intrauterine Device, or Both for the Prevention of Intrauterine Adhesions

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ABSTRACT

Background and Objectives: To compare the efficacy of 3 different techniques for prevention of adhesion reformation after hysteroscopic adhesiolysis in patients with moderate-to-severe intrauterine adhesions. Short-term assisted reproductive outcomes were also compared.

Study Design: Total of 72 cases were randomized to Lippes loop intrauterine device (IUD) only, IUD plus a new crosslinked hyaluronan (NCH) gel, or NCH gel only following hysteroscopic adhesiolysis. All cases received hormonal therapy and a second hysteroscopy was carried out. Endometrial thickness values were measured using transvaginal ultrasonography and American Fertility Society adhesion scores were noted during first and second hysteroscopy in all groups. Reproductive outcomes were also compared for those who received in vitro fertilization treatment.

Results: Transvaginal ultrasonography revealed significantly better endometrial thickness in the IUD+NCH (7.5 mm) and NCH-only groups (6.5 mm) than the IUD-only group (5 mm) ($P < .001$). All groups revealed enhanced but comparable American Fertility Society adhesion scores on second-look hysteroscopy. A total of 37 patients received in vitro fertilization treatment after surgical management of adhesions. Ongoing pregnancy rates after in vitro fertilization were 27%, 40%, and 36% in IUD, IUD+NCH, and NCH groups, respectively. However, the difference between the groups did not reach statistically significant difference.

Conclusion: All interventions are of similar efficacy in the prevention of adhesion reformation after hysteroscopic adhesiolysis for moderate to severe intrauterine adhesions. However, better endometrial thickness values were observed in those who received NCH gel either alone or in combination with IUD. Assisted reproductive outcomes of both groups were comparable for ongoing pregnancy rates.

Key Words: Adhesion, Asherman, Gel, Hysteroscopy, IVF.

INTRODUCTION

Intrauterine adhesion (IUA) formation is one of the most challenging issues in gynecology practice resulting in infertility, recurrent miscarriages, or menstrual abnormalities.[1] It occurs in 1.5% to 3% of infertile women and in up to 40% of women after recurrent dilatation and curettage (D/C) for miscarriage.[1] Moderate-to-severe intrauterine adhesions (IUAs) may greatly impact the fertility potential of affected women. Trauma to the basal layer of the endometrium is regarded as the primary initiating factor for adhesion formation.

Hysteroscopy has been the most effective method for diagnosis and treatment. It does not only offer magnification but also allows direct view of the adhesions; therefore, allowing for a precise and safe treatment. Despite favorable outcomes, adhesion recurrence is one of the most challenging issues complicating nearly one fourth of the cases, which can hinder reproductive outcomes.[2] In order to prevent recurrences, several measures have been suggested.[3] Advancements in technology, especially in the field of antiadhesive gels, have recently gained attention. A new cross-linked hyaluronan (NCH) gel has been used postoperatively in an attempt to decrease intra-abdominal and intrauterine adhesion formation. Two recent randomized controlled trials revealed enhanced adhesion scores either following laparoscopy[4] or hysteroscopy.[5]

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One of the commonly used adhesion re-formation prevention strategies is the placement of an intrauterine device (IUD) after hysteroscopic adhesiolysis.[6] Historically, all women with moderate-to-severe IUAs routinely have received a Lippes loop IUD after hysteroscopic adhesiolysis in our clinic.

Therefore, we hypothesized that NCH alone or in combination with an IUD may provide better adhesion prevention compared to IUD alone. Our primary objective was to compare the adhesion scores according to American Fertility Society (AFS) adhesion scoring system[7]. (**Figure 1**) at the time of the second-look hysteroscopy after the initial hysteroscopic adhesiolysis in three groups which were IUD alone, NCH alone, and combination of NCH with IUD. Our secondary objectives were to compare endometrial thickness and in vitro fertilization (IVF) outcomes in the same groups.

MATERIALS AND METHODS

This prospective study had a quasi-randomized, open-labeled design, and was conducted at our clinic between January 2015 and March 2018. The Ethics Committee approved the study protocol (99950669/256) and all participants were required to provide a signed informed consent. Participants with moderate-to-severe adhesions were consecutively assigned to IUD only, NCH only, or NCH+IUD groups at the end of the initial hysteroscopic adhesiolysis. All hysteroscopy procedures were performed by the investigator (R.P.). Inclusion criteria were 1) women aged 18 to 40 years, 2) moderate-to-severe intrauterine adhesion (AFS score ≥ 5), 3) no previous history of adhesiolysis, 4) a signed written consent prior to the initial hysteroscopy, 5) consent to have a second-look hysteroscopy, and 6) desired future fertility. Exclusion criteria were 1) minimal adhesion (AFS score < 5), 2) previous hysteroscopic adhesiolysis, 3) known or suspected intolerance or hypersensitivity to the hyaluronan gel or its derivatives or IUD, 4) genital tract malformations, and 5) acute infection. Endometrial thickness was measured using transvaginal ultrasonography (Voluson 730 Pro, GE Medical GmbH, Austria) in all women both before and after hysteroscopic interventions.

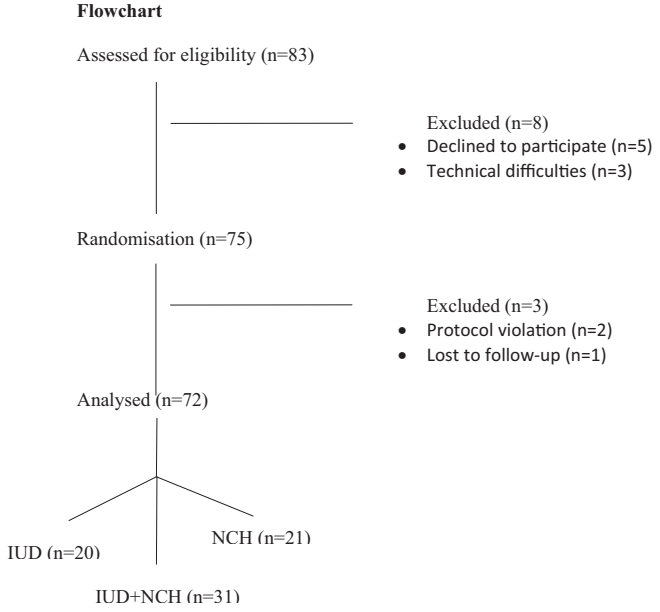

Figure 1. The American Fertility Society classification of intrauterine adhesions, 1988.[7]

Surgical Procedure

Uterine cavity was assessed using AFS adhesion scoring system (**Figure 1**) at the beginning of the procedure. A 5-F rigid hysteroscope that was equipped with hysteroscopic scissors (Karl Storz GmbH, Tuttlingen, Germany) was introduced into the uterine cavity under direct visualization. Normal saline was used as the distention medium. The adhesiolysis was initiated inferiorly and carried cephalad to the fundus using sharp dissection with the hysteroscopic scissors until the uterine cavity was normalized.

NCH Gel and/or IUD Application

At the end of the hysteroscopy procedure, 5 mL of the NCH gel (MateRegen gel, BioRegen Biomedical Ltd Inc., Changzhou, China) was injected into the uterine cavity through a 15-cm sterile delivery cannula in women assigned to the NCH gel groups. A Lippes loop IUD was inserted into the uterine cavity using a carrier cannula under transabdominal ultrasound guidance in women assigned to the IUD groups. In the NCH+IUD group, following the placement of the IUD, the NCH gel was injected into the cavity through its delivery cannula.

Followup

In all women, hormone therapy was initiated on the day of the operation, which consisted of estradiol valerate at a dose of 6 mg daily for 21 days, with the addition of medroxyprogesterone acetate at a dose of 10 mg daily for the last 7 days of estrogen therapy. After the withdrawal bleeding, hormone therapy was repeated for another cycle. Eight to 12 weeks after the initial surgery, women underwent a second-look hysteroscopy to determine the

reoccurrence of IUAs. After the assessment of the adhesion score, adhesiolysis was also carried out with hysteroscopic scissors if necessary. In women who received an IUD, a 5-F hysteroscope was inserted under direct visualization with guidance of IUD loops, and adhesiolysis was carried out beginning from the adjacent areas of the IUD.

In vitro fertilization (IVF) treatment was offered to those who were unable to conceive despite unprotective intercourse for 6 months. All women who proceeded with IVF received one to two blastocysts in a fresh cycle managed with antagonist protocol. Frozen-thaw embryo transfers, preimplantation genetic screening cycles, males with azoospermia, and cases with diminished ovarian reserve were excluded from the final data.

Statistical Analysis

Data analyses were performed by using SPSS for Windows, version 22.0 (SPSS Inc., Chicago, Illinois, USA). The normal distribution of continuous variables was determined by Kolmogorov Smirnov test. Levene test was used for the evaluation of homogeneity of variances. Unless specified otherwise, continuous data were described as mean ± SD for normally distributed data, and median (minimum–maximum value) for skewed distributions. Categorical data were described as number of cases (%). One-way ANOVA was used to compare more than two groups for normally distributed data, and Kruskal Wallis test was applied for comparisons of the skewed data. Post-hoc analyses were performed using the least significant difference (LSD) or Conover nonparametric multiple comparison tests. Paired groups were analyzed by Wilcoxon Signed-Ranks test. A box plot graph was used for variables that were not normally distributed. Nominal data were analyzed by Pearson's χ^2 or Fisher's exact test, where applicable. A P value less than .05 was considered statistically significant.

RESULTS

Between January 2015 and March 2018, a total of 83 women were initially recruited. Among them, 5 women

Table 1.
Demographic Data and Basal Findings of the Groups

	IUD (n:20)	IUD+NCH (n:31)	NCH (n:21)	*P*
Age*	31.75 ± 4.80	32.19 ± 5.13	31.05 ± 4.72	NS
Gravida (mean ± SD)	1.1 ± 0.8	1.7 ± 0.9	1.3 ± 0.8	NS
Live births†, n (%)	1 (5.0)	2 (6.5)	3 (14.3)	NS
BMI‡ (median, min–max)	25 (19–31)	26 (19–32)	26 (8–31)	NS
Abortions‡ (median, min–max)	1 (0–3)	1 (0–4)	1 (0–3)	NS
Amenorrhea†, n (%)	11 (55.0)	17 (54.8)	13 (61.9)	NS
Oligomenorrhea†, n (%)	6 (30.0)	12 (38.7)	8 (38.1)	NS
Previous D/C, n (%)	15 (75)	24 (77)	18 (85)	NS
Mean D/C number‡ (median, min–max)	1 (0–2)	1 (0–4)	1 (0–3)	NS
Infection†, n (%)	2 (10.0)	3 (9.7)	2 (9.5)	NS
End Echo in mm (before)‡ (median, min–max)	4 (3–5)	3.5 (3–6)	4 (3–6)	NS
AFS score (before)‡ (median, min–max)	8 (5–12)[b]	8 (5–12)	8 (5–12)[b]	**.044**

AFS, American Fertility Society; BMI, Body mass index; D/C, Dilatation and Curettage; IUD, Intra uterine device; NCH, Cross linked hyaluronan; NS, Not significant.

Data are expressed as mean ± standard deviation or median (minimum–maximum) for continuous variables and number (percentage) for categorical variables.

*One-way Anova test.

†Chi-square; least significant difference (LSD) or conover-Inman test were performed for the binary comparisons among the groups and the *P* value was set at .05.

‡Kruskal wallis test.

Significant differences were found between (**a**) HS RIA vs HS ACP RIA, (**b**) HS RIA vs HS ACP, and (**c**) HS ACP RIA vs HSP ACP.

subsequently declined participation, and 3 cases were excluded due to technical difficulties (inability to reach the endometrial cavity) with the NCH gel or IUD insertion. Due to the protocol violation (n = 2) and loss of followup (n = 1), 72 women were left in the data analysis. Twenty women were in group I (IUD alone), 31 in group II (IUD+NCH) and 21 in group III (NCH alone). The baseline characteristics including age, gravidity, live births, and Body Mass Index (BMI) did not differ between the three groups. More than half of all women experienced amenorrhea before surgery. Majority of the women in all three groups had a history of at least one D/C. Initial endometrial thickness measurements and median AFS scores of the groups were comparable. Baseline data are shown in **Table 1**.

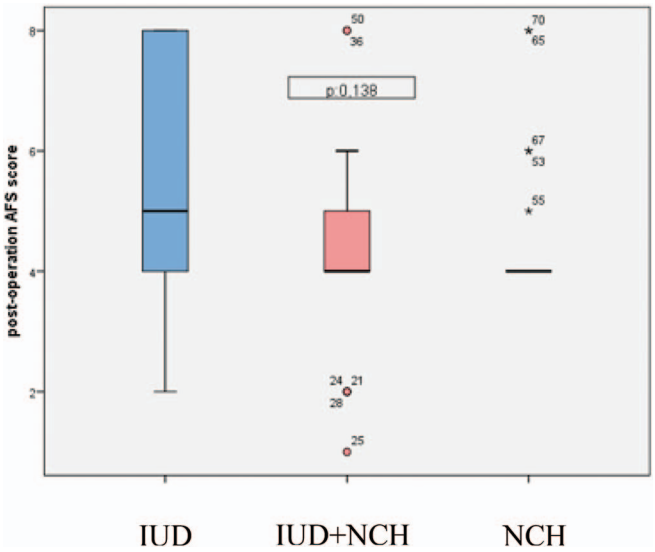

Figure 2. American Fertility Society scores following second hysteroscopy of the groups.

The mean interval between the initial and second surgery was 9 weeks in all groups. Endometrial thickness were significantly higher in group II and III than group I ($P <$ .001) prior to the second-look hysteroscopy. The AFS scores of all groups were comparable at the time of the second hysteroscopy. All groups revealed enhanced but comparable adhesion scores (P = .1) (**Figure 2**). Outcomes following the second hysteroscopy are shown in **Table 2**. However, all three intervention groups revealed significantly enhanced endometrial thickness values and AFS scores after the initial hysteroscopy ($P <$ .01) (**Table 3**) (**Figure 3**). IVF treatment was offered to those who failed to conceive within a year following the second hysteroscopy. A total of 41 women received IVF treatment in our clinic. Of those, 4 cases were excluded due to cycle cancellation and 37 were included in the analysis. Ongoing pregnancy rates were 27% (3/11), 40% (6/15), and 36% (4/11) in IUD, IUD+NCH, and NCH groups, respectively. However, the differences between the groups were not statistically significant.

DISCUSSION

In our study, all three interventions were of similar efficacy in the prevention of adhesion reformation after the hysteroscopic adhesiolysis for moderate to severe IUAs. However, better endometrial thickness values were ob-

Table 2.
Main Outcomes and ART Results of the Study Groups

	IUD (n:20)	IUD+NCH (n:31)	NCH (n:21)	*P*
Interval (weeks)*	9 (8–12)	9 (9–12)	9 (9–12)	NS
End. Echo in mm (after)*	5 (3–8)[a,b]	7.5 (4–9)[a]	6.5 (3–8)[b]	**<.001**
AFS score (after)*	5 (2–8)	4 (1–8)	4 (4–8)	NS
ART admissions (IVF/ICSI)[t]	11/20	15/31	11/21	NS
Positive hCG[†]	4/11 (36%)	6/15 (40%)	5/11 (45%)	NS
Ongoing pregnancy[†]	3/11 (27%)	6/15 (40%)	4/11 (36%)	NS

AFS, American Fertility Society; ART, Assisted Reproductive Technics; hCG, Human chorionic gonadotropin; ICSI, Intracytoplasmic sperm injection; IUD, Intra-uterine device; IVF, Invitro fertilization; NCH, New cross linked hyaluronan; NS, Not significant.

Data are expressed as median (minimum–maximum) for continuous variables and number (percentage) for categorical variables.

*Kruskal wallis test.

[†]Chi-square; least significant difference (LSD) or conover-Inman test were performed for the binary comparisons among the groups and the *P* value was set at .05.

Significant differences were found between (**a**) HS RIA vs HS ACP RIA, (**b**) HS RIA vs HS ACP, and (**c**) HS ACP RIA vs HSP ACP.

Table 3.
Endometrial Echo Measurements and AFS Scores of the Groups

	Before	After	*P*
IUD			
Echo	4 (3–5)	5 (3–8)	**.005**
AFS score	8 (5–12)	5 (2–8)	**.001**
IUD+NCH			
Echo	3,5 (3–6)	7,5 (4–9)	**<.001**
AFS score	8 (5–12)	4 (1–8)	**<.001**
NCH			
Echo	4 (3–6)	6,5 (3–8)	**<.001**
AFS score	8 (5–12)	4 (4–8)	**<.001**

AFS, American Fertility Society; IUD, Intrauterine device; NCH, New cross linked hyaluronan.

Continuous variables are expressed as either the median (minimum–maximum) and variables were compared with an Wilcoxon Signed-Ranks test.

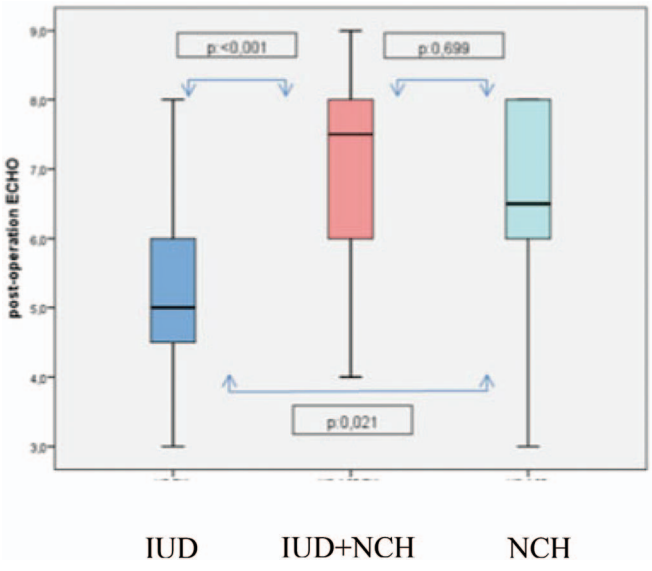

Figure 3. Endometrial thickness measurements following second hysteroscopy of the groups.

served in those who received NCH gel either alone or in combination with Lippes loop IUD.

The rate of IUA reformation after surgery remains as high as up to 24%.[2] To date, many interventions have been suggested to prevent recurrences including early second look, barrier methods such as IUDs, and hormonal therapy.[3,6,8] We have previously documented the efficacy of IUD-guided adhesiolysis in a randomized controlled trial with favorable live birth rates.[6] Particularly, Lippes loop IUD appears to enlarge the cavity most effectively and creates bits of healthy endometrium, which helps with the adhesiolysis. Moreover, additional studies also showed favorable reproductive outcomes with Lippes IUD use.[10,11] A recent American Association of Gynecologic Laparoscopists/European Society of Gynecologic Endoscopy (AAGL/ESGE) practice guideline commented in favor of Lippes loop IUD for secondary prevention.[12] In our practice, with its peculiar trapezoidal shape, the Lippes loop has been the method of choice for a long while, albeit it is no longer available in the global market.

In the last decade, antiadhesive gels mostly derived from hyaluronon have been adopted in gynecology practice to prevent both intraperitoneal and intrauterine adhesions.[13–15] Although it has distinctive functions such as reducing inflammation and improving peritoneal re-epithelialization, hyaluranon may not be suitable for endometrial surfaces due to short half-life.[16] To overcome this shortcoming, crosslinking modification has been adopted to improve in vivo persistence by increasing material viscosity and delaying degradation.[17] To date, several randomized controlled trials (RCTs) revealed promising results both in primary and secondary prevention of IUAs when compared to patients treated with hysteroscopic surgery alone.[18] Recently, a large multicenter RCT demonstrated that NCH gel application following D/C has significantly reduced adhesion reformation when compared to D/C alone.[5] In our study, mild IUAs were excluded as all cases were moderate or severe and most of them had at least one D/C procedure. This may explain our failure to find a significant decline in AFS scores in women who received the NCH gel.

Favorable results with NCH either alone or along with IUD in the literature could be attributed to optimal mechanical distention of uterine walls and/or facilitation of the biologic processes to restore the functioning of the endometrium. A recent AAGL/ESGE guideline recommended semisolid barriers, particularly auto-cross-linked hyaluranon to reduce adhesion recurrence.[13]

The differences in ongoing pregnancy rates following IVF were not significantly different in our study. Thus, all interventions seem to have similar effects on the endometrium in women who required fertility treatments. However, further studies are needed to determine whether NCH application further enhances endometrial receptivity.

The limitations of our study include a quasi-randomized design. Moreover, we lack spontaneous pregnancy rates in women who did not undergo IVF. On the other hand, a

single surgeon (R.P.) performed all hysteroscopies and scorings. Hence, reproductive outcomes were provided from a single center, which may minimize the intercenter variability.

To conclude, all interventions are of similar efficacy in the prevention of adhesion reformation after hysteroscopic adhesiolysis for moderate to severe IUAs. Despite the fact that the only outcome that improved significantly was endometrial thickness in women who received the NCH gel, further studies are needed to assess efficacy of the NCH gel in prevention of intrauterine adhesion reformation.

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