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Original Article

New Crosslinked Hyaluronan Gel for the Prevention of Intrauterine Adhesions after Dilation and Curettage in Patients with Delayed Miscarriage: A Prospective, Multicenter, Randomized, Controlled Trial

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ABSTRACT **Study Objectives:** To evaluate the efficacy of a new crosslinked hyaluronan (NCH) gel in reducing the formation of intrauterine adhesions (IUAs) after dilation and curettage (D&C).

Design: Randomized controlled trial (Canadian Task Force classification I).

Settings: Six hospitals for maternal and child healthcare in China.

Patients: A total of 300 patients were randomized to undergo D&C for delayed miscarriage without previous history of D&C. Twenty-six patients (9%) were lost to follow-up and were excluded from the analysis.

Interventions: Women were randomly assigned to D&C alone (control group; n = 150) or D&C plus NCH gel application (NCH gel group; n = 150) with 1:1 allocation.

Measurements and Main Results: All patients were evaluated using the American Fertility Society classification of IUAs during follow-up diagnostic hysteroscopy, scheduled at 3 months after D&C procedure. The primary endpoint was the number of women with IUAs at 3 months, and the secondary endpoints were adhesion scores and severity of IUAs. Postoperative efficacy data were available for 274 women (137 in each group). Intrauterine adhesion formations were observed in 13 of the 137 women (9.5%) in the NCH gel group and in 33 of the 137 women (24.1%) in the control group (p = .0012; relative risk [RR], 0.3939; 95% confidence interval [CI], 0.2107–0.7153), a difference of 14.6% (95% CI, 5.92%–23.28%) between the 2 groups. The extent of intrauterine cavity involved, type of adhesion and menstrual pattern, and cumulative adhesion scores were significantly lower in the NCH gel group compared with the control group (p = .0007, .008, .0012, and .0006, respectively). The proportion of women with moderate to severe IUAs was significantly lower in the NCH gel group than that in the control group (1 of 137 [0.7%] vs 16 of 137 [11.7%]; p = .0002; RR, 0.0625; 95% CI, 0.0084–0.4648), a difference of 11.95% (95% CI, 5.39%–16.51%) between the 2 groups.

Conclusions: The current study demonstrates that IUAs are frequently formed after D&C for delayed miscarriage in women without a previous history of D&C procedures, and the application of NCH gel significantly reduces IUA formation. Journal of Minimally Invasive Gynecology (2018) ■■, ■■–■■

Keywords: American Fertility Society classification; Crosslinked hyaluronan gel; Hyaluronic acid gel

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Trauma to a gravid uterine cavity is known to be the main cause of intrauterine adhesions (IUAs), which occur in 1 of 5 women after miscarriage [1–4]. Considering the large number of miscarriages and terminations of pregnancy, with most treated by dilation and curettage (D&C), IUAs are a serious clinical problem and social issue. Approximately 15% to 20% of all clinically confirmed pregnancies end in miscarriage [3], and the annual number of abortions worldwide between 2010 and 2014 was estimated to be as high as 56.3 million [5], which may be the cause of more than 10 million IUAs annually. Although the clinical relevance of mild IUAs is unknown, moderate to severe IUAs are of concern and may have a significant impact on fertility and reproduction. In a systematic review and meta-analysis, 42% of pooled IUAs after miscarriage were found to be moderate to severe [3].

The etiology of IUA formation is multifactorial, making it important to identify preventive measures to avoid formation. A recent randomized controlled trial (RCT) evaluated the incidence of IUA after D&C in patients with a history of previous D&C [6]; however, the incidence of IUA after D&C in patients without previous D&C is not well determined, although this population is the majority experiencing miscarriage or termination of pregnancy [7–9].

Here we report the results of a prospective, multicenter RCT with a large number of patients to evaluate the incidence of IUAs, especially moderate to severe IUAs, after D&C in women without a history of previous D&C. The efficacy of a new crosslinked hyaluronan (NCH) gel (MateRegen; BioRegen Biomedical, Changzhou, China), a sterile, transparent, viscoelastic, and nonpyrogenic gel composed of highly purified crosslinked hyaluronan molecules, was also evaluated for the prevention of IUAs.

Materials and Methods

This prospective study, with a randomized, double-blind, parallel-group, controlled design, was conducted at 6 hospitals for maternal and child healthcare in China. The study protocol was approved by the Ethics Committee at each hospital. All participants were required to provide signed informed consent before participating. This study was registered at ClinicalTrials.gov (NCT03353909).

To minimize deviations in data owing to different types of miscarriage, only those patients with current delayed miscarriage were included in the study cohort. Inclusion criteria included age 18 to 45 years, no history of previous D&C, and undergoing D&C for current delayed miscarriage (gestational age no more than 20 weeks). All participants agreed to use adequate contraception throughout the follow-up period and to attend the follow-up examination according to the study protocol. Exclusion criteria for this study included known/suspected intolerance or hypersensitivity to hyaluronan gel or its derivatives; genital tract malformation; inflammation of the genital tract or pelvic cavity or clinical evidence of cancer in the genital tract; suspected genital tuberculosis; abnormal blood coagulation; history of peripheral vascular disease, alcohol/drug abuse, and/or mental illness; acute or severe infection; and autoimmune disease. Participants could voluntarily withdraw from the study for any reason at any time or be terminated by investigators owing to safety, violations of inclusion/exclusion criteria, and/or pregnancy.

The participants were randomly assigned to either D&C alone (control group) or D&C plus intrauterine NCH gel application (NCH gel group) in a 1:1 ratio. To avoid potential bias from surgeons, participant randomization and grouping were assigned only after the D&C procedure was completed. The study was not blinded to the surgeons, but the patients and the hysteroscopic examiners during follow-up were unaware of the group allocation of the patients under examination.

Surgical Procedure and Gel Application

All D&C procedures were performed by suction curettage under general anesthesia in accordance with procedural standards. In total, ten surgeons with minimum experience of 1000 procedures each performed the D&C procedures. The obtained tissues were sent for pathologic analysis at the discretion of the surgeon or according to local hospital guidelines. At the end of the D&C procedure, a syringe of NCH gel (3 mL) was inserted into the uterine cavity for patients assigned to the NCH gel group through a 15-cm sterile delivery cannula. NCH gel was not applied to the uterine cavity for patients in the control group.

A follow-up hysteroscopic examination was scheduled for 3 months (±7 days) after the D&C procedure at approximately 1 week after cessation of menstruation. Surgeons who performed the follow-up hysteroscopic examination did not participate in the D&C procedure and were not aware of the treatment that the patient received. Patients were also blinded to the treatment they received. A pregnancy test was performed before hysteroscopic examination. For patients with a positive pregnancy test, the hysteroscopic examination was canceled.

Findings on follow-up hysteroscopy were evaluated and recorded according to the American Fertility Society (AFS) classification (Supplementary Table S1) [10]. Hysteroscopic adhesiolysis was performed when adhesions were detected.

A follow-up survey was performed by all patients to record other treatments received, complications, and adverse events related to the D&C procedure and hysteroscopy, including postoperative complications, menstrual pattern, and use of contraception.

Endpoints

In this study, the primary endpoint was the number of women with IUA formation at the 3-month follow-up. Secondary endpoints included the extent of uterine cavity involvement, type of adhesions and menstrual pattern, cumulative adhesion scores, and severity of IUAs according

to the AFS classification [10]. Safety was evaluated based on complications and adverse events possibly related to the NCH gel application were recorded.

Statistical Analysis

The primary hypothesis in this study was that D&C plus NCH gel is superior to D&C alone, based on the primary assumption of an estimated IUA incidence of 30% in the control group and 15% in the NCH gel group. With a 2-tailed .05 significance level and 20% loss rate during follow-up, 300 patients with a 1:1 allocation would yield 80% power to detect this superiority.

All randomized women who started treatment were included in the intent-to-treat analysis. Continuous variables are expressed as mean ± standard deviation (SD) or as median (interquartile range), and categorical variables are expressed as count and percentage. The Student *t* test/Wilcoxon rank-sum nonparametric test and χ^2 test/Fisher exact test were used to check the homogeneity of baseline characteristics. The Wilcoxon rank-sum nonparametric test was used if variables did not follow a normal distribution and results were expressed as median (interquartile range). The Cochran–Mantel–Haenszel χ^2 test with a center effect adjustment was performed to estimate the difference in IUA incidence between the 2 groups. Analysis of covariance with center effect adjustment was performed to estimate the difference in IUA scores between the groups. All analyses were performed using SAS 9.13 (SAS Institute, Cary, NC), and a p value ≤.05 (2-tailed; $\alpha = 0.05$) was considered to indicate statistical significance.

Results

Between July 2016 and February 2017, 300 women were randomized into either the NCH gel group or the control group at 1:1 ratio. The NCH gel was applied in all women assigned to the NCH gel group (n = 150; 100%). Three hundred women constituted the full analysis set, as well as the safety population. A CONSORT flow chart of participants is shown in Figure 1. No women were withdrawn owing to adverse events. Twenty-six women did not undergo follow-up hysteroscopic examination because they did not return within the stipulated period; as a result, postoperative efficacy data were available for 274 women (137 in each group), who constituted the per protocol set.

Only patients who did not undergo previous D&C procedures were included in the study. Table 1 presents the baseline characteristics of the patients who completed the study. Age, gravidity, parity, and gestational age were comparable in the 2 groups (p = .6667, .3795, .3818, and .6728, respectively). One woman in the NCH gel group (transcervical resection of polyps) and 2 women in the control group (cesarean section) had undergone previous uterine surgery (p = .5701).

Blood loss during D&C was comparable in the 2 groups (11.37 ± 8.13 mL in the NCH gel group vs 10.81 ± 10.84 mL in the control group; p = .5743), and no signs of postoperative infection were reported in either group. No serious adverse events were observed during the study period, and there were no prolonged hospitalizations or reoperations owing to adverse events. Furthermore, no adverse events were attributed to the NCH gel treatment.

In each group, 137 of 150 women (91.3%) underwent the scheduled follow-up hysteroscopic examination. IUAs were observed in 13 of 137 patients in the NCH gel group, compared with 33 of 137 in the control group (9.5% vs 24.1%; p = .0012; risk ratio [RR], 0.3939; 95% confidence interval [CI], 0.2107–0.7153), a difference of 14.6% (95% CI, 5.92%–23.28%) (Fig. 2). The number needed to treat to benefit was 6.8 (95% CI, 4.3–19.9).

Adhesion scores are presented in Table 2. The subcategory adhesion scores of uterine cavity involved, type of adhesion, and menstrual pattern were all significantly lower in the NCH gel group compared with the control group (p = .0007, .008, and .0012, respectively). The mean cumulative adhesion score was also significantly lower in the NCH gel group (0.33 ± 0.106 vs 1.07 ± 2.06; p = .0006) (Table 2).

According to the AFS classification, 12 of the 13 IUAs (92.3%) observed in the NCH gel group were identified as mild and 1 IUA was moderate. In contrast, in the control group, 17 of 33 IUAs (51.5%) were mild and 16 (48.5%) were moderate. No patient had severe IUAs. The difference in IUA severity between the 2 groups was statistically significant (p = .0087).

In conclusion, moderate to severe IUAs were observed in 1 of 137 patients (0.7%) in the NCH gel group and in 16 of 137 patients (11.7%) in the control group (p = .0002; RR, 0.0625; 95% CI, 0.0084–0.4648), a difference of 11.95% (95% CI, 5.39%–16.51%). The number needed to treat to benefit was 9.1 (95% CI, 6.1–18.6).

Discussion

D&C procedures have been identified as 1 of the 2 most important risk factors for the development of IUAs, and the number of D&Cs is correlated with the severity of IUAs, which is linked to the risk of recurrent miscarriage [3]. Our present results show that the IUA formation frequently occurs even after only 1 D&C procedure for delayed miscarriage, consistent with data reported in the literature [2,3]. Comparing IUA formation in the current RCT with that found in a recent RCT reported by Hooker et al [6], the incidence of IUAs after more than 1 D&C procedure was higher than that after only 1 D&C procedure (odds ratio, 1.93), and the incidence of IUAs of moderate to severe grades was similar in the 2 circumstances (odds ratio, 1.58). However, the type of miscarriage (delayed or incomplete) experienced by patients enrolled in these 2 studies may affect this comparison [2,3].

Fig. 1

CONSORT flow diagram of participants.

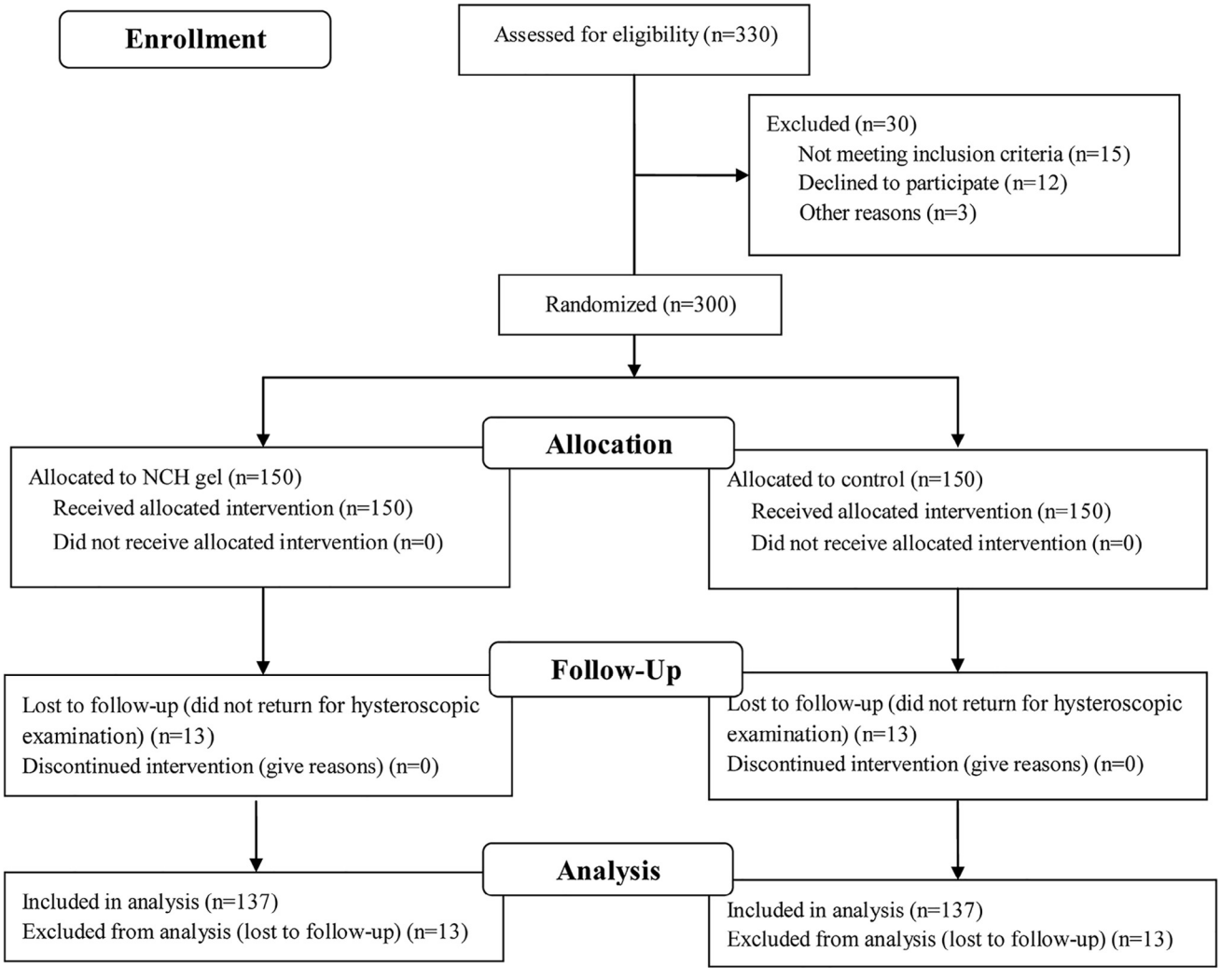
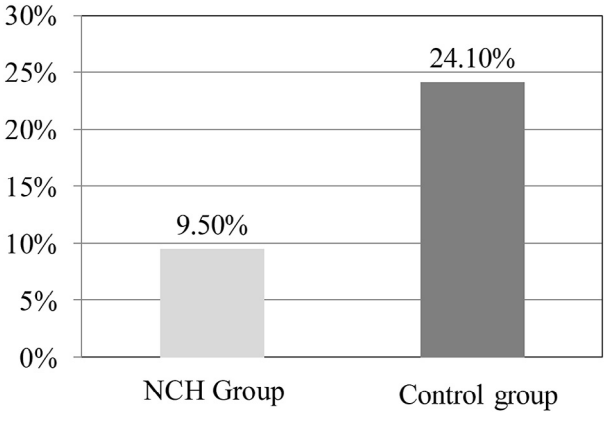


Fig. 2

The incidence of postoperative intrauterine adhesions (IUAs).



Surgical treatment of delayed miscarriage is more likely to result in IUA formation than incomplete miscarriage [2]. With respect to missed miscarriage, the period between fetal demise and D&C increases the likelihood of adhesion formation, possibly owing to fibroblastic activity of the remaining placental tissue [2]. On the other hand, no significant differences were detected in the pooled IUAs in patients with incomplete and delayed miscarriage in a meta-analysis of 1 cross-sectional study and 3 prospective cohort studies [3].

The objectives of IUA prevention are to maintain the normal size and shape of the uterine cavity, normal endometrial function, and fertility. Our present results clearly show that the application of NCH gel after D&C may significantly reduce the formation of IUAs, including moderate to severe IUAs, and it is reasonable to anticipate that NCH gel may have value in improving subsequent fertility and reproduction, as was shown in a preliminary consecutive case study.

Table 1

Baseline patient characteristics

Characteristic	NCH gel group (n = 137)	Control group (n = 137)	p value
Mean age, year ± SD	26.94 ± 4.72	26.84 ± 4.70	.6667
Age range, yr	17–44	19–45	
Gravidity, mean ± SD	1.17 ± 0.43	1.21 ± 0.43	.3795
Gravidity, n			
1	116	109	
2	20	27	
3	0	1	
4	1	0	
Parity, mean ± SD	0.11 ± 0.34	0.14 ± 0.37	.3818
Parity, n			
0	123	118	
1	13	18	
2	1	1	
Gestational age, wk, mean ± SD	9.33 ± 2.09	9.25 ± 2.27	.6728
Previous D&C, n	0	0	1.000
Previous intrauterine surgery, n (%)	1 (0.7%)	2 (1.4%)	.5701

D&C = dilation and curettage; NCH = new crosslinked hyaluronan; SD = standard deviation.

However, a well-designed study is warranted to confirm this expectation.

In human adults, the wound repair process commonly leads to a nonfunctioning mass of fibrotic tissue known as a scar [11–14]. Intrauterine trauma with disruption of the basalis layer may retard endometrial regrowth and lead to fibrotic tissue formation, resulting in endometrial sclerosis (fibrosis) and adhesion formation (the adherence of opposing surfaces by fibrotic tissue) [2]. The insertion of inert materials (e.g., intrauterine contraceptive devices, balloon catheter) may help to maintain the anatomic shape of the uterine cavity and reduce adhesion formation, but is unlikely to restore normal endometrial function.

Hyaluronan has been reported to have distinctive functions in scar-free wound healing by reducing inflammation and improving peritoneal reepithelialization [15]. However, owing to its fluid nature and rapid in vivo degradation, hyaluronan cannot persist sufficiently long to provide mechanical distention of the healing injuries during endometrial regrowth [16]. Therefore, natural hyaluronan is not suitable for adhesion prevention. Crosslinking modification is an effective way to improve in vivo persistence by increasing material viscosity and retarding degradation [17–19]. Therefore, in recent years, novel crosslinked hyaluronan gels have been successfully developed as absorbable adhesion barriers for intrauterine cavities [20,21]. Applied in the uterine cavity, these gels provide mechanical distention of the healing tissue during endometrial regrowth and also promote scar-free healing through the unique physicochemical properties and distinct biological functions of hyaluronan.

Table 2

Patient adhesion scores and severity of IUAs at follow-up hysteroscopic examination

Parameter	NCH gel group	Control group	p value
Adhesion scores, mean ± SD	n = 137	n = 137	
Extent of cavity involved	0.09 ± 0.29	0.32 ± 0.62	.0007
Type of adhesions	0.10 ± 0.33	0.33 ± 0.63	.0008
Menstrual pattern	0.13 ± 0.50	0.42 ± 0.89	.0012
Cumulative	0.33 ± 0.106	1.07 ± 2.06	.0006
Severity of IUAs, n (%)*	n = 13	n = 33	.0087
Stage I (mild)	12 (92.3)	17 (51.5)	
Stage II (moderate)	1 (7.7)	16 (48.5)	
Stage III (severe)	0 (0)	0 (0)	

IUA = intrauterine adhesion; NCH = new crosslinked hyaluronan; SD = standard deviation.
* Severity is based on the cumulative score of the American Fertility Society classification.

This large, multicenter RCT examining the formation and prevention of IUAs after D&C for delayed miscarriage in women without a history of previous D&C has several strengths. The participants and hysteroscopic examiners were blinded to treatment assignment during follow-up. More than 90% of the participants completed the study, and the number of patients lost to follow-up was limited. Potential limitations of this study include the weakened generalizability owing to the all-Chinese population and lack of racial diversity in the study cohort, the short duration (3 months), and the lack of data regarding impacts on fertility and long-term clinical symptoms.

In conclusion, this study demonstrates that IUAs are frequently observed after D&C for delayed miscarriage in women without previous D&C, and that the application of NCH gel in the uterine cavity after D&C significantly reduces incidence and severity of IUAs and potentially facilitates endometrial function, as evidenced by an improved menstrual pattern.

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Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jmig.2018.03.032.

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Supplementary Table 1

The American Fertility Society (AFS) classification of intrauterine adhesion (1988)

Extent of cavity involved	<1/3	1/3–2/3	>2/3
Score	1	2	4
Type of adhesions	Filmy	Filmy and dense	Dense
Score	1	2	4
Menstrual pattern	Normal	Hypomenorrhea	Amenorrhea
Score	0	2	4

Prognostic classification of disease severity: Stage I (mild) cumulative score 1–4; Stage II (moderate) cumulative score 5–8; Stage III (severe) cumulative score 9–12.

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