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A Randomized, Multi-Center, Clinical Trial to Assess the Efficacy and Safety of Alginate Carboxymethylcellulose Hyaluronic Acid Compared to Carboxymethylcellulose Hyaluronic Acid to Prevent Postoperative Intrauterine Adhesion

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ABSTRACT **Study Objective:** To estimate the efficacy of alginate carboxymethylcellulose hyaluronic acid (ACH) gel to prevent intrauterine adhesions after hysteroscopic surgery in comparison with carboxymethylcellulose hyaluronic acid (CH) gel, which is known as an effective adhesion inhibitor.

Design: Randomized, multicenter, single-blind, clinical trial (Canadian Task Force classification I).

Setting: Tertiary university hospital.

Patients: One hundred eighty-seven patients with a surgically treatable intrauterine lesion (myomas, polyps, septa, intrauterine adhesion, dysfunctional uterine bleeding).

Interventions: Patients were randomized to 2 groups: hysteroscopic surgery plus intrauterine application of ACH or CH.

Measurements and Results: The rate of adhesion formation and the adhesion severity score with type and extent were calculated 4 weeks after surgery. The ACH group had results that were comparable to the CH group in terms of the development of intrauterine adhesions at 4 weeks follow-up. The adhesion severities were not different between the 2 groups. In a subgroup without baseline intrauterine adhesion, the ACH group showed a lower intrauterine adhesion rate than the CH group ($p = .016$).

Conclusions: ACH had a comparable efficacy to CH in terms of the adhesion rate and severity. In the case of no baseline intrauterine adhesion, intrauterine application of ACH after hysteroscopic surgery had a lower rate of intrauterine adhesion than application of CH. Journal of Minimally Invasive Gynecology (2012) 19, 731–736 © 2012 AAGL. All rights reserved.

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Intrauterine adhesion is a complication of hysteroscopic surgery. The incidence of intrauterine adhesion has been reported to be 0.3% in adult women with an intrauterine device, 7% in women with secondary amenorrhea, and 21.5% in women with a history of postpartum curettage [1,2]. Intrauterine adhesion may cause infertility, recurrent abortion, irregular uterine bleeding, and pelvic pain [3,4]. Surgeons may use several methods to prevent adhesion; these include surgical techniques, such as gentle tissue handling; prevention of infection; antiinflammatory agents; peritoneal instillates; and surgical adhesion barriers [5]. Among the methods, adhesion barriers that use biodegradable biomaterials with complete elimination have been widely used because of their limited biotoxicity.

Hyaluronic acid is 25 000 disaccharide repeats in length and a major component in vitreous body, synovial fluid, cartilage, skin, and umbilical cord. Because of its biocompatibility, moisture capacity, and viscoelasticity, hyaluronic acid has been used as artificial tears in drug delivery systems, and tissue restoration materials, and it plays a role in inflammation, granulation, and reepithelialization for wound healing [6,7]. It has been verified that hyaluronic acid has an antiadhesive effect after hysteroscopic surgeries [8,9]. Carboxymethylcellulose is a high–molecular weight polysaccharide that has a concentration and volume that are inversely correlated with its antiadhesive effect; it has also been demonstrated as an effective antiadhesive agent [10,11]. The combination of carboxymethylcellulose and hyaluronic acid (CH) has had a preventive effect on the formation of adhesion in a various surgical fields [12–14].

Alginate has been used as a wound dressing agent; its calcium or sodium form has hemostatic and antimicrobial effects, and it has been shown to prevent adhesion formation in animal studies [15–17]. Therefore the combination of CH and alginate (ACH) is expected to be at least equal to individual CH or alginate as an antiadhesive agent. This study was aimed at estimating the efficacy and noninferiority of ACH gel to prevent intrauterine adhesions after hysteroscopic surgery in comparison with CH gel, which is known as an effective adhesion inhibitor.

Materials and Methods

This study was approved by each Institutional Review Board of all 12 study hospitals. The outcome measure for sample size power calculation was the adhesion rate of CH gel, and the anticipated treatment-specific proportion was 13%. The power calculation indicated that 158 participants, with 79 in each group, were needed to perform the study to achieve a power of 80% and an alpha error of 2.5%. The calculation for the noninferiority was based on the formula: $n = f(\alpha, \beta) \times [\pi_s \times (100-\pi_s) + \pi_e \times (100-\pi_e)]/(\pi_s-\pi_e-d)^2$ where π_s and π_e are the true percent "success" in the CH and ACH gel treatment group, respectively [18]. The value for $f(\alpha, \beta) = [\Phi^{-1}(\alpha) + \Phi^{-1}(\beta)]^2$, with Φ^{-1} as the cumulative distribution function of a standardized normal deviate.

All patients with submucosal myoma, endometrial polyp, uterine septa, intrauterine adhesion, and dysfunctional uterine bleeding at diagnostic hysteroscopy were invited to participate in the study. The study was designed with statistically even distribution of the operative indications including preoperative intrauterine adhesion into 2 groups. A total of 187 women were enrolled in the study from May 2010 to January 2011. The flow chart for patients is shown in Fig. 1.

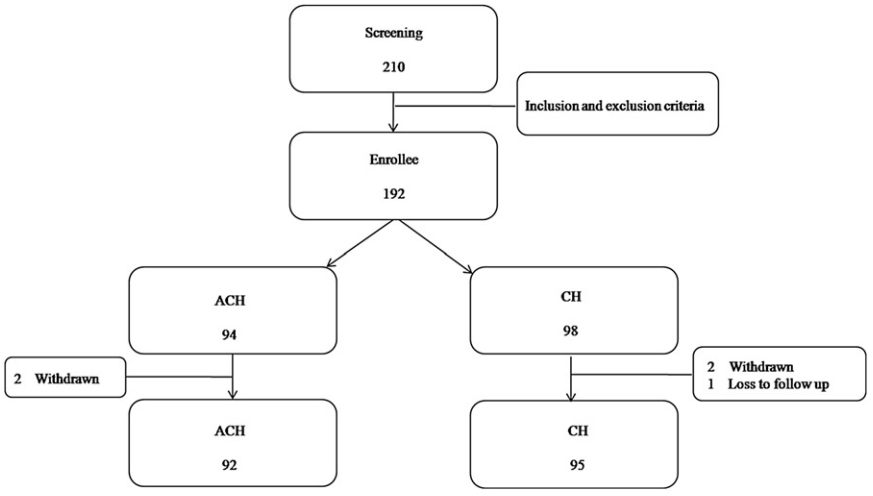
The inclusion criteria were as follow: age 20 years or more, women who agreed with the study and signed the consent form, and women who could be on a form of contraception during the study period. The exclusion criteria were women who planned to use an intrauterine device for contraception during the study period; hormone therapy after hysteroscopic surgery; a local or systemic infection; cancer; heavy uterine bleeding; abnormal hepatic, renal, or hemostatic function; anticoagulants or systemic steroid treatment within a week before the study; immunosuppression or autoimmune diseases; allergies to the study materials; women who were pregnant or who planned pregnancy during the study period; and women who the investigators decided not to enroll in the study. Two weeks before surgery, their demographic features, such as age, height, weight, and vital signs, were evaluated with a preoperative laboratory examination (Visit 1).

On operation day, after a diagnostic 5-mm hysteroscopy, the enrolled patients were randomized into 2 groups: ACH versus CH (Visit 2). The randomization was preprogrammed by a statistician using SAS (version 9.1; SAS Institute Inc., Cary, NC), and a predesigned scratch-off label was used in the operation room. At this time, the investigating surgeon learned of the assignment.

Patients were allocated into 1 of 2 groups with stratified block randomization to be evenly distributed in each operative indication such as submucosal myoma, endometrial polyp, uterine septa, intrauterine adhesion, and dysfunctional uterine bleeding. The study design followed Consolidated Standards of Reporting Trials guidelines (www.CONSORT-statement.

Fig. 1

Flow chart of the study.



org). The overview of the study design is shown in Fig. 2. After hysteroscopic surgery with a 12-mm resectoscope, the study gel 10 mL was applied by use of a syringe with a long plastic tip into the uterine cavity in both groups. Prophylactic antibiotics with cefotiam 1 g (Fontiam; Hanmi Pharmaceutical Co., Ltd., Siheung, Korea) were administered 1 hour before surgery.

One week after the operation, laboratory tests for safety were performed (Visit 3). Hysteroscopic photographs were obtained by an investigator at each hospital who used a 5-mm diagnostic scope 4 weeks after surgery (Visit 4). The rate of adhesion formation and the adhesion severity score, including the type and extent of adhesion, were evaluated by an independent investigator, as well as the investigators of study hospitals. This study was single-blind to the independent investigator for outcome measures. The independent investigator scored the intrauterine adhesion using photographs taken by the investigators at study hospitals. For the masking process, the photographs without any information of the patients were sent to the independent investigator. The criteria for evaluating intrauterine adhesion were as follows as a previous scoring system [19]: 1 for filmy, 2 for filmy and dense, and 4 for dense adhesion in terms of the type of adhesion; 1 for less than one third, 2 for between one third and two thirds, and 4 for more than two thirds in terms of the extent of adhesion. The evaluations of each visit are presented in Table 1. Statistical analysis was performed with the use of SAS (SAS Institute Inc.). Continuous variables were analyzed with Student's *t*-test or Wilcoxon's rank-sum test, and χ^2 or Fisher's exact tests were used for the analysis of categorical variables. Repeated measures analysis of variance was used to compare laboratory data and vital signs before and after surgery. The intrauterine adhesion rates among study hospitals were compared by use of the Cochran-Mantel-Henszel test [20,21]. If the upper limit of the 95% confidence interval of the difference of adhesion rate at 28 days after operation (Adhesion rate in ACH−Adhesion rate in CH) was less than 15%, it was

Fig. 2

Overview of study design.

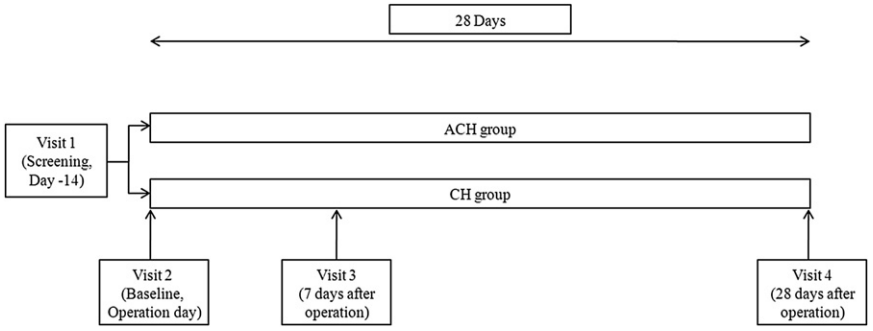


Table 1

Evaluation schedule for study patients

- Screening
  - Visit 1 (Day-14)
    - Consent form
    - Demographics
    - Vital signs
    - Height/weight
    - Physical examination
    - Medical and surgical histories
    - History of concomitant medication
    - Laboratory tests
    - Serum beta-hCG
    - Inclusion/exclusion criteria
- Baseline
  - Visit 2 (Day 0)
    - Randomization of patients
    - Hysteroscopy and intrauterine application of ACH or CH
    - Vital signs
    - Physical examination
    - Inclusion/exclusion criteria
    - History of concomitant medication
    - Adverse events
- Observation
  - Visit 3 (Day 7)
    - Vital signs
    - Physical examination
    - History of concomitant medication
    - Laboratory tests
    - Adverse events
  - Visit 4 (Day 28)
    - Vital signs
    - Physical examination
    - History of concomitant medication
    - Serum beta-hCG
    - Intrauterine adhesion
    - Adverse events

considered to verify the noninferiority of ACH compared with CH.

Results

There were no differences in the demographic data and operative indications between the 2 groups (Table 2). There were no enrolled patients with uterine septum during the study period. The ACH group had results comparable to the CH group in terms of the development of intrauterine adhesions at 4 weeks follow-up, because the upper limit of the 95% confidence interval of the difference of adhesion rate between the 2 groups (Adhesion rate in ACH−Adhesion rate in CH) was 1.39%, which was lower than 15% of the limitation value for noninferiority (Table 3). There were no differences in the intrauterine adhesion rate according to gel type used (ACH versus CH) among study hospitals (Cochran-Mantel-Henszel test, data not shown). The adhesion severity, with the scores of adhesion type and extent,

Table 2

Characteristics of study patients in both groups

	ACH (n = 92)	CH (n = 95)	p
Age (year)	41.4 ± 8.6, 39.6−43.2	40.3 ± 9.5, 38.4−42.2	.442
Height (cm)	159.5 ± 4.9, 158.5−160.5	159.0 ± 5.2, 157.9−160.1	.486
Weight (kg)	56.8 ± 8.5, 55.0−58.6	56.9 ± 8.0, 55.3−58.5	.894
Parity	1.3 ± 0.6, 1.2−1.4	1.8 ± 0.5, 1.7−1.9	.228
Indication for operation*			
Submucosal myoma	24 (26.1%)	15 (15.8%)	.083
Endometrial polyp	56 (60.9%)	57 (60.0%)	.903
Intrauterine adhesion	16 (17.4%)	19 (20.0%)	.648
Dysfunctional uterine bleeding	9 (9.8%)	15 (15.8%)	.22

* There were no patients with uterine septum during the study period. Data are presented as mean ± standard deviation (95% confidence interval). Student's *t*-test or Wilcoxon's rank-sum test for continuous variables and Chi-square test for categorical variables. $p < .05$, statistically significant.

was not different between the 2 groups. In a subgroup without preoperative intrauterine adhesion, the ACH group showed a lower intrauterine adhesion rate than the CH group ($p = .016$). In terms of adverse events, there were 2 patients with diarrhea and general itching sensation, respectively, in the ACH group and 1 patient with lower back pain in CH group; however, the events were mild and showed spontaneous recovery, and there was no definite relationship between them and the study gels. There were no severe adverse events related to drugs in both groups. The laboratory results and vital signs were not different between the 2 groups; there was also no difference in laboratory results and vital signs before and after hysteroscopic operation and intrauterine drug instillation (data not shown).

Discussion

This is the first study to investigate the efficacy and safety of ACH for the prevention of the formation of intrauterine adhesion after operative hysteroscopy. There have been some data on the intrauterine adhesion rate in the absence of any mechanical or pharmacologic effort to prophylactically prevent the occurrence after resective hysteroscopic surgery. Taskin et al [22] showed that the rate of postsurgical intrauterine adhesions 14–30 days after resection of myomas was 30.0%–42.9%. In another study by Guida et al [8], the adhesion rate for all patients was 26.15% (33.3% for myomas, 18.2% for polyps, and 37.5% for septa). These relatively high postsurgical adhesion rates give a rationale for the preventive effort even in initial resective hysteroscopy. Two randomized controlled trials [8,9] have already shown that there is an advantage to using a hyaluronan-based pharmacologic agent over nothing in the prevention of intrauterine adhesions after hysteroscopic

Table 3

Postoperative intrauterine adhesion rate and scores and subgroup analyses according to operative indication in both groups 28 days after hysteroscopic surgery

	ACH (n = 92)	CH (n = 95)	Difference in adhesion rate (95% CI) or p
Postoperative intrauterine adhesion	8 (9.1%)	15 (17.9%)	−8.77 (−18.92, 1.39)
With endometrial polyp	1/56 (1.8%)	5/57 (8.8%)	.113
Without endometrial polyp	7/36 (19.4%)	11/38 (29.0%)	.285
With preoperative intrauterine adhesion	7/16 (43.8%)	8/19 (42.1%)	.858
Without preoperative intrauterine adhesion	1/76 (1.3%)	8/76 (10.5%)	.016
Adhesion score			
Type of adhesion	2.8 ± 1.4	1.9 ± 1.4	.215
Filmy	2 (25.0%)	10 (66.7%)	
Filmy and dense	2 (25.0%)	1 (6.7%)	
Dense	4 (50.0%)	4 (26.7%)	
Extent of adhesion	1.1 ± 0.4	1.0 ± 0.0	.201
<3/1	7 (87.5%)	15 (100.0%)	
1/3–2/3	1 (12.5%)	0 (0.0%)	
>2/3	0 (0.0%)	0 (0.0%)	

CI, confidence interval. Data are presented as mean ± standard deviation. Student's *t* test or Wilcoxon's rank-sum test for continuous variables, and χ^2 or Fisher's exact tests are used for categorical variables. The $p < .05$ is statistically significant.

surgery. In a study with 92 women with irregular menses and intrauterine adhesions, the group of adhesiolysis plus intrauterine application of auto-cross-linked hyaluronic acid gel had a significant decrease in intrauterine adhesions at 3 months follow-up compared with the control group of adhesiolysis only [9]. The other study with 132 patients with a single surgically remediable intrauterine lesion (myomas, polyps and uterine septa) concluded that the auto-cross-linked hyaluronic acid gel reduces the incidence and severity of de-novo formation of intrauterine adhesions after hysteroscopic surgery [8]. Even though there was no control group of placebo only in our study, our study design and results would be supported by these 2 prior studies.

A variety of methods have been developed to reduce postoperative intrauterine adhesion after hysteroscopic surgery. The Practice Committee of the American Society of Reproductive Medicine has reviewed the methods for control and prevention of peritoneal adhesions in gynecologic surgery; these methods include surgical techniques such as gentle tissue handling, minimal desiccation, meticulous hemostasis, the use of fine suture materials, and prevention of infection; adjuncts to surgical techniques, such as antiinflammatory agents and peritoneal instillates with dextran or crystalloid solution; and surgical adhesion barriers such as polyethylene glycol (Spraygel; Confluent Surgical, Waltham, MA), fibrin glue (Tissucol; Baxter International, Deerfield, IL), hyaluronic acid film (Seprafilm; Genzyme, Cambridge, MA), and oxidized regenerated cellulose (Interceed; Gynecare, Sommerville, NJ) [5].

Hyaluronic acid with carboxycellulose is a well-known antiadhesive material with long-lasting action for about 7 days that is used to separate abutting tissue surfaces [23]. Recently it has been reported that the carboxycellulose hyaluronate gel type, the control material in this study, has a beneficial effect on reduction of pericardial adhesion formation in rabbits [14] and antiadhesive effectiveness in a laminectomy model in rats [13]. In addition, a bioresorbable membrane by use of carboxycellulose hyaluronate, such as Seprafilm, has been widely used as an antiadhesive agent, despite the fact that its use is limited in special circumstances such as uterine myomectomy [5,24].

This study showed that ACH was not inferior in its antiadhesive effect compared with CH. Instead, ACH was more beneficial than CH in women with hysteroscopic indications, including endometrial polyp, submucosal myoma, and dysfunctional uterine bleeding other than intrauterine adhesion. This means that alginate may have a role in the antiadhesive effect. Alginate is known to have an antimicrobial effect and increases the efficacy of hemostasis, which may affect the reduction of tissue adhesion [25]. A recent study also demonstrated the antiadhesive effects of alginate flake experimentally both ex vivo and in vivo by use of moist pig skin and a rat intraabdominal adhesion model [16]. In their study, the alginate flakes were superior to a CH film in terms of the antisolubility and attachment stability ex vivo, as well as the antiadhesive efficacy in vivo. The adhesion scores observed in the alginate flake and cellulose film groups were almost the same.

A few randomized studies have reported the potential benefits of auto-cross-linked hyaluronan gel without any additives that is a fully biocompatible cross-linked derivative of hyaluronic acid; this gel has prolonged in vivo residence time and improved mechanical properties with respect to native hyaluronan for use in various surgical applications [8,9,26]. The intrauterine adhesion rates in 2 recent randomized controlled trials for hysteroscopic application were 14.0% (6/43) and 10.4% (7/67), respectively [8,9]. Although it could be difficult to directly compare the antiadhesive efficacy between ACH and auto-cross-linked hyaluronan gels, ACH could be an appropriate option to

prevent postsurgical intrauterine adhesion (intrauterine adhesion rate, 9.1% [8/88] in our study).

This study is clinically meaningful, because intrauterine ACH application after hysteroscopic surgery could be an option for physicians who are concerned about future fertility, menstrual irregularity, pain, and other issues that pertain to their patients. Nonetheless, this study has the following limitations. First, our results could be more reliable with data on the hysteroscopic use of CH, which was the control material in this study. However, we cautiously believed that data on the efficacy of CH to prevent postoperative adhesion in various models of different animal species could be scientifically acceptable for a comparative human study such as this one. Second, a control group without the application of any materials would present clearer data as previously mentioned. Third, a scoring of the patients with preoperative intrauterine adhesion in Visit 2 and comparison between preoperative and postoperative scores could show a general adhesion-preventive efficacy of study gels. Hereafter, further comparative randomized trials with a variety of antiadhesive agents in different surgeries may confirm the efficacy and safety of ACH.

In conclusion, ACH had a comparable efficacy to CH in terms of adhesion rate and severity. In the case of no prior intrauterine adhesion, intrauterine application of ACH after hysteroscopic surgery resulted in lower de novo intrauterine adhesion compared with CH.

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