Efficacy and safety of auto-cross-linked hyaluronic gel to prevent intrauterine adhesion after hysteroscopic electrosurgical resection: a multi-center randomized controlled trial

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Background: The electrothermal effect of hysteroscopic bipolar electrosurgical resection may cause damage to the endometrium, leading to intrauterine adhesion (IUA). Although some studies have demonstrated the efficacy and feasibility of auto-cross-linked hyaluronic (ACP) gel in preventing IUAs, controversy over its use continues. In this randomized controlled multi-center 2-arm parallel trial, we aimed to examine the efficacy and safety of ACP gel in preventing IUA after hysteroscopic electrosurgical resection and facilitate pregnancy in patients.

Methods: Patients from 4 centers in China were randomly assigned (1:1) to receive an intrauterine infusion of ACP gel or nothing after hysteroscopic electrosurgical resection. The randomization assignment was generated by computer and kept in a sealed envelope. A second-look hysteroscopy was performed within 3 months of the surgery.

Results: From June 2018 to May 2021, 200 patients were recruited. Ultimately, 82 patients in both groups were included in the result analysis. The baseline characteristics were comparable. The outcomes were assessed by using per-protocol analysis. The incidence of IUA in the ACP gel group was lower than that in the control group [3.66% *vs.* 10.98%, risk ratio (RR) =0.333, 95% confidence interval (CI): 0.094–1.187, P=0.072], and the planned pregnancy rate was higher than that of the control group (60.98% *vs.* 40.54%, RR =1.504, 95% CI: 0.949–2.384, P=0.071), but the difference was not statistically significant. There was no significant difference in menstruation change. Menstrual volume remained unchanged in most cases (86.59% in ACP gel group *vs.* 89.02% in the control group, RR =0.877, 95% CI: 0.877–1.109, P=0.815). Menstrual volume decreased in 10 women in the ACP gel group and 8 in the control group (12.20% *vs.* 9.76%, RR =1.250, 95% CI: 0.520–3.007, P=0.617). No adverse effects were observed after the ACP administration.

Conclusions: The present study showed that the use of ACP gel appeared to reduce both the tendency of IUA and American Fertility Society (AFS) scores and improve the subsequent pregnancy rate during hysteroscopic electrosurgical resection when treating polyps, fibroids, and uterine septum. ACP might be recommended to prevent IUA after such surgery. Further studies should be conducted with larger numbers of participants.

Trial Registration: Chinese Clinical Trial Registry ChiCTR2100047165.

Keywords: Auto-cross-linked hyaluronic (ACP) gel; intrauterine adhesion (IUA); hysteroscopy; electrosurgical resection; randomized controlled trial

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Introduction

Intrauterine adhesions (IUAs), which were first described by Asherman in 1894 (1), are fibrous adhesive bands causing the partial or complete obliteration of the uterine cavity (2). The main symptoms of IUA include amenorrhea, oligomenorrhoea, infertility, and miscarriage (3). IUA can occur after surgical or infectious trauma to the basalis layer of the endometrium. Other etiological factors include uterine artery embolization and low estrogen status (4).

Hysteroscopy has been considered the most reliable diagnostic and therapeutic method for intrauterine diseases. It provides direct visualization of the uterine cavity and allows simultaneous surgical treatment. However, hysteroscopy may cause IUA when used as a treatment for intrauterine diseases (5). The electrothermal effect of electrosurgical resection may cause extra damage to the endometrium (6). A previous study reported that without preventive measures, new IUAs formed in 88%, 76%, and 40% of women post-operatively after septum, resection, adhesiolysis, and myomectomy, respectively (7).

Several anti-adhesion therapies exist, such as solid barriers (intrauterine contraceptive devices, stents, or balloon catheters), semi-solid barriers (hyaluronic acid or cross-linked hyaluronic gel), tissue barriers (fresh or freeze-dried amnion grafts), and hormonal treatments (4,8-12). Hyaluronic is a viscoelastic, water-soluble glycosaminoglycan that physically supports the endometrial lining and prevents adhesion formation. Its high biocompatibility makes it ideal as a barrier gel for IUA. There is no safety issue with its use in humans, and it has been used to preserve fertilized eggs. However, its fluidity and fast degradation limit its effects in treating IUA.

A cross-linking modification is an effective way to reduce the fluidity and prolong the half-life of the gel. Under this modification, linear hyaluronic molecules are activated and modified into a 3-dimensional web-like structure. The auto-cross-linked hyaluronic (ACP) gel overcomes the shortcomings of the fluidity and fast degradation *in vivo* of linear hyaluronate. ACP can stay in the uterine cavity stably and plays an effective role in isolating the uterine cavity. The product degrades in 7–14 days; however, it can play a physiological role in regulating the damaged endometrium during the critical period of endometrial repair. Several previous studies have demonstrated the efficacy and feasibility of ACP gel in preventing IUAs in animals and humans (13,14); however, controversy over its use continues. A recent randomized controlled trial (RCT) study found that there was no significant difference between the recurrence rate of IUA (31.1% *vs.* 39.8%) or the median American Fertility Society (AFS) score between the ACP gel group and the control group, and concluded that ACP gel did not seem to improve the recurrence rate of IUA after hysteroscopic adhesiolysis (15).

In the present multi-center randomized controlled trial, we aimed to examine the efficacy of ACP gel in preventing adhesion formation after hysteroscopic electrosurgical resection and in facilitating pregnancy in patients. We present the following article in accordance with the CONSORT reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-4988/rc).

Methods

Trial design

This randomized controlled multi-center, 2-arm, parallel trial was approved by the Medical Ethics Committee of the West China Second University Hospital, Sichuan University (No. 2017035). The other hospitals were informed and agreed with this study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Written consent was obtained from all the included participants. Patients from the following 4 centers in China were enrolled: West China Second University Hospital, Affiliated Hospital of North Sichuan Medical College, Deyang People's Hospital, and Meishan Maternal and Child Health Hospital.

Patients who were scheduled to receive hysteroscopic bipolar electrosurgical resection were recruited. To be eligible for inclusion in this study, patients had to meet the following inclusion criteria: (I) be a female aged 18–55 years who had been diagnosed with submucosal myoma, endometrial polyp, or uterine septum; (II) provide informed consent to participate in the study and agree not to take any hormonal treatments within 3 months of the surgery; and (III) show good compliance, and be willing and able to engage in the follow-up and be observed as required.

Patients were excluded from the study if they met any of the following exclusion criteria: (I) were aged >55 years and had a body weight >100 kg; (II) were postmenopausal [follicle-stimulating hormone (FSH) >40 mIU/mL, estradiol <20 pg/mL] or pregnant; (III) had IUAs; and/or (IV) had pelvic inflammation, reproductive tract malignancy, or other severe systemic diseases.

Based on the reported rates of adhesion reformation in the literature, we estimated that the clinically reasonable reduction rate would decrease from 45% in the control group to 20% in the ACP gel group (4,16-19). Adopting a significance level of 5% and a power of 80%, the number of subjects required in each arm to demonstrate significant differences was calculated to be 79. Assuming a withdrawal rate of 20%, the total number of subjects recruited for each group was set at 100.

Randomization

The recruited patients were randomly assigned (1:1) to receive an intrauterine infusion of ACP gel (MateRegen® 3 mL, Bioregen Biomedical Co., Ltd., China) or nothing after hysteroscopic electrosurgical resection. The randomization assignment was generated by computer and kept in a sealed envelope by a statistician, who was not involved in the following treatment or follow-up of the patients. Each recruited patient was assigned an envelope consecutively by the medical staff in the ward according to the time of inclusion. The envelopes were opened by an assistant at the end of the hysteroscopy, and the surgeon used or did not use ACP gel according to the randomization. All the patients received the same observation and nursing after surgery.

Follow-up and data collection

A second-look hysteroscopy was performed within 3 months of the surgery to determine whether postoperative IUAs had occurred. The surgeons who performed the second-look hysteroscopies were not aware of whether the patient belonged to the ACP gel group or the control group. The postoperative conditions of the patients were also recorded, including menstruation and adverse reactions. Patients engaged in pregnancy planning were followed-up at least 10 months after the surgery.

Baseline data, including data on age, uterine cavity disease, history of gestation, history of uterine surgery, and previous menstruation, were collected. Detailed records were also made during the hysteroscopy, including observations on intrauterine lesions (lesion location, size and number of fibroids or polyps, and length and width of septum), the surgical wound area, the presence (or absence) of already existing IUAs, the operation time, the amount of blood loss, and the infusion (or not) of ACP gel.

Outcome measurements

The primary outcome measurement was the rate of IUA, which was confirmed by a second-look hysteroscopy within 3 months of the surgery. If IUA was confirmed, its severity and extent were scored according to the AFS classification (20). The secondary outcomes were menstrual volume change, the pregnancy rate, and adverse reactions.

Statistical analyses

The Kolmogorov-Smirnov test was used to test the data distribution. Numerical data with a skewed distribution are presented as the median [interquartile range (IQR)]. A contingency table analysis and the Chi-square test or Fisher's exact test along with risk ratios (RRs) and 95% confidence intervals (CIs) were used to compare the categorical data. A P value <0.05 in the 2-tailed tests was considered significant. All the statistical analyses were carried out using SPSS 22.0 (SPSS Corp., Chicago, IL, USA).

Results

A total of 200 patients were recruited for this study from June 2018 to May 2021. The patients were randomly divided into 2 groups with 100 in the ACP gel group and 100 in the control group. In total, 33 patients (17 in the ACP gel group and 16 in the control group) dropped out mainly due to the coronavirus disease 2019 (COVID-19) pandemic, which prevented the patients from undergoing a second-look hysteroscopy. Additionally, 3 patients were excluded, 1 of whom was postmenopausal and 2 of whom were treated with intrauterine balloons intraoperatively (1 in the ACP gel group and 1 in the control group). A flow chart of selecting patients in the trial is provided in *Figure 1*. Ultimately, the data of 82 patients in the ACP gel group and 82 patients in the control group were included in the analysis.

The baseline characteristic data, including age, weight, pregnancy rate, parity, surgical blood loss and operation time, were tested as skewed distribution data

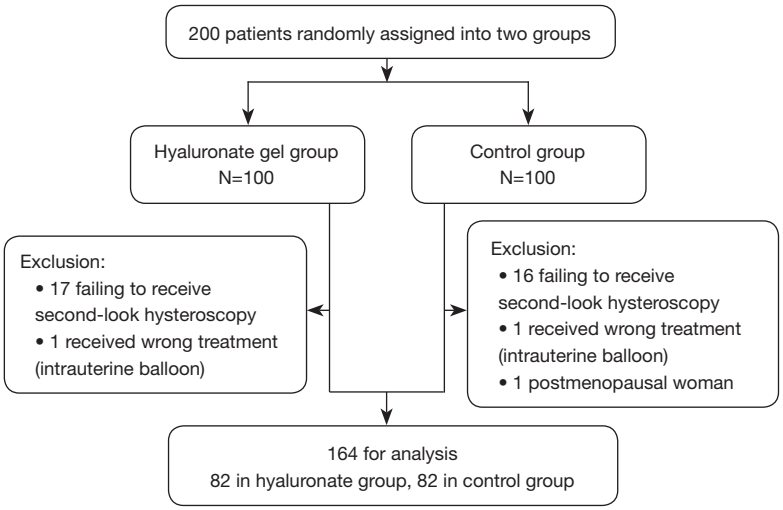

Figure 1 Flow chart of selecting patients in the trial.

Table 1 Baseline characteristic between the ACP gel group and the control group

Characteristics	ACP gel group (n=82)	Control group (n=82)
Age (years)	31 [7]	33 [12]
Weight (kg)	55 [6]	53 [10]
Gravidity	1 [2]	2 [3]
Parity	1 [1]	1 [1]
Previous uterine surgery	39 (47.56)	48 (58.54)
Uterine cavity disease		
Uterine myoma	9 (10.98)	16 (19.51)
Uterine septum	5 (6.10)	3 (3.66)
Endometrial polyp	64 (78.05)	57 (69.51)
Uterine myoma + polyp	3 (3.66)	6 (7.32)
Uterine septum + polyp	1 (1.22)	0
Wound area		
<1/3	45 (54.88)	40 (48.78)
1/3–2/3	31 (37.80)	39 (47.56)
>2/3	6 (7.32)	3 (3.66)
Previous IUA	0	0
Blood loss in surgery (mL)	5 [5]	5 [5]
Surgery time (min)	20 [10]	20 [15]

Data are shown as median [IQR] or N (%). ACP gel, auto-crossed-linked hyaluronic gel; IUA, intrauterine adhesion.

by Kolmogorov–Smirnov test, and thus represented as median (IQR) (*Table 1*). The baseline characteristics were comparable between groups. In total, there were 25 uterine myomas, 8 uterine septum, 121 endometrial polyps, 9 uterine myomas + polyps, and 1 uterine septum + polyps. None of the patients had previously been diagnosed with IUA. No adverse effects such as allergy, pain and fever were observed after the administration of the ACP gel.

The hysteroscopic and menstrual outcomes are listed in *Table 2*. The outcomes were assessed by using per-protocol analysis. Postoperative IUAs were found in 12 patients, of whom 3 were in the ACP gel group and 9 were in the control group. The incidence of IUA in the ACP gel group was lower than that in the control group, but the difference was not statistically significant (3.66% *vs.* 10.98%, RR =0.333, 95% CI: 0.094–1.187, P=0.072). All 3 cases of adhesion in the ACP gel group were mild (AFS scores 2, 2, and 3). In the control group, 2 cases of IUA were moderate (with AFS scores of 5 and 6), and the other 7 cases were mild (all with AFS scores of 2). There was no significant difference in menstruation change between the ACP gel group and the control group after hysteroscopic surgery. Menstrual volume remained unchanged in most cases (86.59% in ACP gel group *vs.* 89.02% in the control group, RR =0.877, 95% CI: 0.877–1.109, P=0.815). Menstrual volume decreased in 10 women in the ACP gel group and 8 in the control group (12.20% *vs.* 9.76%, RR =1.250, 95% CI: 0.520–3.007, P=0.617). In the control group, 1 patient

Table 2 Hysteroscopic and menstrual outcomes between the ACP gel group and the control group

Characteristics	ACP gel group (n=82), n (%)	Control group (n=82), n (%)	Risk ratio (95% CI)	P value
IUA	3 (3.66)	9 (10.98)	0.333 (0.094–1.187)	0.072
Menstrual volume change				
Less than before	10 (12.20)	8 (9.76)	1.250 (0.520–3.007)	0.617
Same as before	71 (86.59)	72 (89.02)	0.877 (0.877–1.109)	0.815
More than before	0	1 (1.22)		0.316
Amenorrhea	1 (1.22)	1 (1.22)	1.000 (0.064–15.719)	1.000

ACP gel, auto-crossed-linked hyaluronic gel; IUA, intrauterine adhesion; CI, confidence interval.

Table 3 Planned pregnancy outcomes between the ACP gel group and the control group

Characteristics	ACP gel group (n=41), n (%)	Control group (n=37), n (%)	Risk ratio (95% CI)	P value
Term delivery	15 (36.59)	9 (24.32)	1.504 (0.749–3.019)	0.241
Vaginal birth	7 (17.07)	5 (13.51)	1.263 (0.439–3.640)	0.663
Cesarean section	8 (19.51)	4 (10.81)	1.805 (0.592–5.504)	0.288
Preterm delivery	4 (9.76)	0		0.051
Spontaneous abortion	3 (7.32)	4 (10.81)	0.677 (0.162–2.827)	0.590
During pregnancy	3 (7.32)	2 (5.41)	1.354 (0.239–7.659)	0.731
Total pregnancy	25 (60.98)	15 (40.54)	1.504 (0.949–2.384)	0.071

ACP gel, auto-crossed-linked hyaluronic gel; CI, confidence interval.

had increased menstrual volume. After the surgery, 1 patient in each group had amenorrhea.

The pregnancy outcomes are listed in *Table 3*. In total, 78 patients were planning to fall pregnant (41 in the ACP gel group and 37 in the control group). The patients were followed-up for 9–40 months (median 19.6 months). In total, 40 patients fell pregnant after surgery, 25 in the ACP gel group and 15 in the control group. Additionally, 1 patient in the control group had an unplanned pregnancy and underwent an artificial abortion. The planned pregnancy rate of the ACP gel group was higher than that of the control group, but the difference was not statistically significant (60.98% *vs.* 40.54%, RR =1.504, 95% CI: 0.949–2.384, P=0.071). In total, 24 patients delivered to term, among them 12 delivered by cesarean section. Additionally, 4 women had preterm deliveries, 5 women had not yet delivered at the end of the follow-up period, and 7 women had spontaneous miscarriages. There was no significant difference between the ACP gel group and the control group in terms of the delivery rate, preterm delivery rate, and spontaneous abortion rate. No placental adhesion or implantation during pregnancy occurred in either group.

Discussion

The present study found that the number of postoperative IUAs in the control group (9 in 82 cases, 10.98%) was 3 times that of the ACP gel group (3 in 82 cases, 3.66%), and the severity of IUAs was lower in the ACP gel group. However, there was no statistical difference between the 2 groups (P>0.05), which may be due to the low incidence of IUA during hysteroscopic resection in the present study. The incidence of IUA after hysteroscopic surgery has been reported to range from 22–32% in control groups and 10–18% in ACP gel groups (18,19). Both these rates are significantly higher than those reported in the present study. Most clinical studies in this field have shown that ACP gel reduces both the tendency of IUA and AFS scores during the hysteroscopic resection of polyps, fibroids, and uterine septum (18,19,21).

In addition, ACP gel has also been reported to reduce the recurrence of IUAs after adhesiolysis (22). A network meta-analysis published in 2017 reported that the use of ACP plus a balloon was one of the most effective methods for reducing IUA recurrence and the most effective method for reducing IUA scores (23). Another recent network

meta-analysis (9) published in 2021 found that ACP gel (with or without the insertion of a copper intrauterine device) was the most effective method for preventing the recurrence of IUA after hysteroscopic adhesiolysis. The hyaluronic acid gel and the intrauterine device methods have been ranked as the most effective methods at reducing postsurgical adhesion severity.

Excluding the patients who were not planning to fall pregnant and those lost to follow-up, the planned pregnancy rate of the ACP gel group was higher than that of the control group, but the difference was not statistically significant (P<0.05). In general, no placental implantation or adhesion were observed after hysteroscopic resection. Other studies have found similar results. Thubert *et al.* assessed the effect of ACP gel on pregnancy following the hysteroscopic removal of IUAs (24), and noted that the pregnancy rate [45.8% (11/32) *vs.* 36.7% (18/58), respectively] and the viable pregnancy rate [33.3% (8/32) *vs.* 24.5% (12/58), respectively] tended to be higher in the ACP gel group than the control group. However, the results were not statistically significant (P>0.5). The authors suggested that ACP gel should be evaluated in a randomized control trial in a larger population. Mao *et al.* found that the application of ACP gel in patients with moderate to severe IUA during hysteroscopy improved the pregnancy outcomes after *in vitro* fertilization/intracytoplasmic sperm injection and frozen-thawed embryo transfer (25). The clinical pregnancy rate [26.3% (49/186) *vs.* 15.3% (13/85)], the implantation rate [17.7% (57/322) *vs.* 9.8% (15/153)], and the endometrial thickness on the day of embryo transfer (7.97±1.37 *vs.* 7.50±0.60 mm) were significantly higher in the ACP gel group than the control group (P<0.05). A recent network meta-analysis found that of the various methods used after hysteroscopic adhesiolysis (including intrauterine balloons, amnion grafts, and intrauterine devices), the ACP gel produced the highest pregnancy rate (9).

The present study had some limitations. The incidence rate of IUA after hysteroscopic resection in the present study was lower than the rates reported in the literature; thus, studies need to be conducted with larger sample sizes in the future. Additionally, 32 (16%) patients (17 in the ACP gel group and 16 in the control group) dropped out mainly due to the COVID-19 pandemic, which prevented the patients from undergoing a second-look hysteroscopy.

To conclude, the present study showed that ACP gel appears to reduce both the tendency of IUA and the AFS scores during hysteroscopic electrosurgical resection when treating polyps, fibroids, and uterine septum. However, the results were not statistically significant. The ACP gel group tended to have a higher pregnancy rate than the control group. The incidence rate of IUA after hysteroscopic resection in the present study was lower than the rates reported in the literature; thus, studies need to be conducted with larger sample sizes in the future.

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Footnote

Reporting Checklist: The authors have completed the CONSORT reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-4988/rc

Trial Protocol: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-4988/tp

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-4988/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-4988/coif). All authors report that the research was supported by Bioregen Biomedical Co., Ltd. (Changzhou, China). The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Medical Ethics Committee of the West China Second University Hospital, Sichuan University (No. 2017035). The other hospitals were informed and agreed with this study. Written consent was obtained from all the included participants.

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