

Auto-Cross Linked Hyaluronan Gel Enhances Effects of Hysteroscopic Adhesiolysis Treatment in Patients with Moderate to Severe Intrauterine Adhesions

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Submitted: 28 Jan 2022; Accepted: 31 Jan 2022; Published: 26 Feb 2022

Citation: Yuhua Zeng, Wei Ran, Li Lan, Aiping Wen, Qingqing Xiong, Lingbin Si, Min Yong. (2022). Auto-Cross Linked Hyaluronan Gel Enhances Effects of Hysteroscopic Adhesiolysis Treatment in Patients with Moderate to Severe Intrauterine Adhesions. *Adv Bioeng Biomed Sci Res* 5(1): 23-28.

Abstract

Background: Moderate to severe intrauterine adhesions affect women's reproductive and mental health. Hysteroscopic surgery alone cannot improve the prognosis of IUA patients. The present study was to analyse whether auto-cross linked hyaluronan gel facilitates the hysteroscopic adhesiolysis treatment effect and reproductive performance of patients with moderate to severe IUA.

Methods: Patients with moderate to severe IUA and fertility desire were included in this retrospective study. A total of 47 patients received standard hysteroscopic adhesiolysis alone served as control group. A total of 38 patients received cHA gel injection at the end of hysteroscopic adhesiolysis were included in the treatment group. The IUA recurrence rate, endometrial thickness, AFS score, clinical pregnancy rate, and live birth rate were analysed.

Results: The endometrial thickness (6.33 ± 1.160 vs. 5.72 ± 1.16 mm, $P=0.029$), clinical pregnancy rate [51.7 (26/42) vs. 14.29% (5/35); $P=0.000$] and live birth rate (36.2 vs. 13.2%; $P=0.000$) were significantly higher in the treatment group compared with the control group, and the American Fertility Society score ($P=0.018$) was lower in the treatment group compared with the control group.

Conclusion: The combination therapy of cHA gel plus hysteroscopic adhesiolysis in patients with moderate to severe IUA resulted in a better outcome in decreasing the severity of IUAs, and improving the quality of endometrium and enhancing the live birth rate compared with hysteroscopic adhesiolysis alone.

Trial Registration: Clinical trial register number ChiCTR2100051670. Date of Retrospectively registered on September 30, 2021.

Keywords: Asherman Syndrome, Auto-Cross-Linked Hyaluronan Gel, Hysteroscopic Adhesiolysis, Intrauterine Adhesion

Introduction

Intrauterine adhesions (IUAs), also known as Asherman syndrome, manifests as fibrous strings or scars between uterine walls [1]. Adhesions can be partially or completely covered with the uterine cavity and or cervical canal. The formation of IUAs is attributed to endometrium trauma mainly caused by mechanical operation of uterine cavity of miscarriage or induced abortion [2]. IUAs are associated with an increased risk of abnormal menstruation, recurrent pregnancy loss, secondary infertility, placenta previa, placental adhesion and placenta implantation, which affect women's reproductive health [3-6].

A clinically acknowledged effective method for treatment of

IUAs is surgery. Hysteroscopic surgery can effectively remove the adhesive tissues and restore the morphology [7, 8]. However, mechanical damages cause the procedure to contribute to re-adhesion. The recurrence rate may be up to 62.5% in severe adhesions after hysteroscopic adhesiolysis [9]. Undoubtedly, the prevention of IUA reoccurrence after surgical operation is a challenge for clinical therapeutics.

Postoperative estrogen therapy is often used for promoting endometrial regeneration and repairing the injured surface [10]. In addition, the most commonly used strategy to prevent re-adhesion is using physical barriers after hysteroscopic adhesiolysis. The intrauterine device (IUD) or Foley catheter balloon is often

used for preventing the reformation of adhesion after the hysteroscopic treatment. However, the recurrence rate was still as high as 30% in the group using IUDs for 1 week post-surgery [8]. This result may be attributed to the IUD limited self-repairing process and increased infection risk during the IUD insertion [10]. The superiority of Foley catheter compared with IUD for improving the pregnancy rate remains controversial [11, 12]. Highly biocompatible hyaluronic acid (HA) gel can act as a physical barrier to prevent postoperative re-adhesion. The safety and efficacy of HA gel for the prevention of IUAs had been verified [13]. In a rabbit model of endometrial curettage, injection of HA gel for prevention of postoperative adhesion could improve the natural fertility [14]. Auto-crosslinked HA gel effectively inhibited IUA formation and improve the pregnancy rate in women who underwent curettage in the second trimester [15]. Clinical trials demonstrated that HA gel could prevent the occurrence of IUAs with a lower adhesion score, but not enough to prevent the re-occurrence of severe IUAs [13].

Therefore, we conducted a prospective randomized controlled trial study to evaluate the clinical effectiveness of the combination of hysteroscopic adhesiolysis and auto-crosslinked HA gel injection on moderate to severe IUAs.

Materials and Methods

Patients. The present prospective randomized controlled trial was conducted at The Affiliated Hospital of North Sichuan Medical College, Sichuan, China. The study was approved by Ethics Committee of Affiliated Hospital of North Sichuan Medical College. Each patient signed informed consent. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patients with moderate to severe IUA were included between September 2017 and August 2018. The inclusion criteria included: i) diagnosed as moderate to severe IUA (score ≥ 5); i) provided written informed consent; iii) desiring fertility; iv) no previous history of hysteroscopic adhesiolysis; v) have second-look hysteroscopy; vi) no severe systemic diseases; and vii) no contraindications to estrogen or surgery. The exclusion criteria included: i) minimal adhesion (AFS score < 5); ii) previous hysteroscopic adhesiolysis; and ii) presence of contraindications to estrogen or surgery. Patients underwent standard hysteroscopy were served as control group, whereas patients received standard hysteroscopy followed with cross-linked hyaluronic acid (cHA) gel (MateRegen® gel; BioRegen Biomedical Ltd., Inc., Changzhou, China) were served as treatment group. The clinical application of Mate Regen® gel has been approved by the China NMPA.

Intervention

The control group underwent standard hysteroscopy, whereas the treatment group received cross-linked hyaluronic acid (cHA) gel (MateRegen® gel; BioRegen Biomedical Ltd., Inc., Changzhou, China) during hysteroscopy. The clinical application of Mate Regen® gel has been approved by the China NMPA.

Hysteroscopy Procedure

The surgery was performed by one experienced hysteroscopic surgeon using a 4.5-mm hysteroscope (Olympus Corporation) with saline solution perfusion under 100 mmHg pressure. The procedure was performed under general anesthesia and color doppler monitoring in a day surgery unit. The sequential inspec-

tion of the endocervical canal, uterine cavity, tubal orifices and endometrium was performed first. The findings were recorded by a digital camera (Olympus Corporation). Subsequently, the adhesion score was assessed according to the criteria of the American Fertility Society (AFS). Adhesions were divided or removed by hysteroscopic scissors to achieve a normal uterine anatomy. Following the hysteroscopic adhesiolysis, cHA gel was injected into the uterine cavity of the treatment group.

Postoperative Treatment

Three hormone replacement treatment cycles were used for endometrial repair. This consisted of 2 mg complex packing estradiol valerate tablets (PROGYNOVA®; Bayer Healthcare Co., Ltd.) b.i.d. orally for 28 days, followed by 10 mg Dydrogesterone (Abbott Biologicals B.V.) b.i.d. orally for 5 days. A second-look hysteroscopy was performed after the first and third withdrawal bleed. If adhesions recurred, hysteroscopic adhesiolysis was carried out. After all treatments were completed, ultrasonography was used for detecting endometrial thickness in the middle to late stages of the proliferation phase. Complications, live birth or ongoing pregnancy were followed up.

Statistical Analysis

Statistical analyses were performed using SPSS 22.0 statistical software (IBM Corp.). The age, abortion times, adhesion score, operative time and estimated blood loss of the baseline characteristics were expressed as mean \pm standard and compared using an unpaired t-test. The adhesion range, adhesion type, amenorrhea, oligomenorrhea and mean D/C number of the baseline characteristics were compared using a χ^2 test. The endometrium thickness, adhesion score and pregnancy rate in the clinical circumstances and outcome were compared using an unpaired t-test, Kruskal-Wallis and χ^2 test, respectively.

Results

Basic information of patients. A total of 99 patients with moderate to severe IUA were included in the present study. Among them, 5 women were lost to follow up and 9 women did not undergo a second-look hysteroscopy. Therefore, 85 patients were included in the data analysis; 47 cases were in the treatment group (accepted hysteroscopic adhesiolysis and cHA gel injection) and 38 in the control group (accepted hysteroscopic adhesiolysis) (Fig 1).

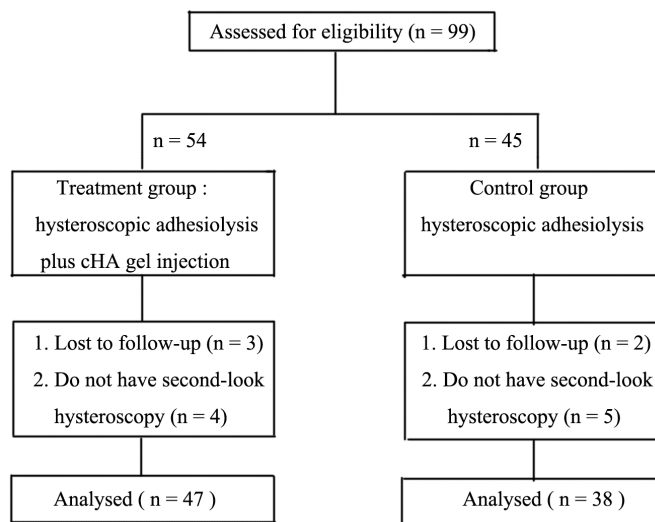


Figure 1: Flow chart showing the retrospective study process.

The baseline characteristics, including age and body mass index, did not differ between the two groups. More than half of patients experienced oligomenorrhea and nearly one third of patients experienced amenorrhea prior to surgery. The majority of patients had at least one D/C in the past. The operation time was 25-40

min and the estimated blood loss fluctuated between nearly 5-15 ml (Table I). No patient had uterine perforation. IUAs were separated successfully by hysteroscopic adhesiolysis. In addition, all patients received three cycles of hormonal replacement for endometrial repair.

Table 1: Baseline patient characteristics

Characteristic	Treatment group (n = 47)	Control group (n = 38)	P-value
Age (y)*	28.8 ± 4.6	31.4 ± 5.5	NS
BMI (median, min–max) ***	24 (19–30)	25 (19–31)	NS
Abortion times	2.7 ± 2.1	3.1 ± 1.7	NS
Amenorrhea n (%) **	15 (31.9)	13 (34.2)	NS
Oligomenorrhea n (%) **	28 (59.6)	23 (60.5)	NS
Previous D/C, n (%)	37 (78.7)	31 (81.6)	NS
Mean D/C number (median, min–max) **	1 (0–3)	1 (0–4)	NS
Adhesion score*	8.3 ± 1.4	8.3 ± 1.5	NS
Adhesion range**			NS
<1/3	4	2	
1/3–1/2	19	15	
1/2–2/3	15	14	
>2/3	9	7	
Adhesion type**			NS
Tight adhesion	39	33	
Mixed adhesion	8	5	
Operative time (min)*	31.7 ± 5.4	34.2 ± 6.9	NS
Estimated blood (mL)*	10.9 ± 4.8	12.3 ± 6.2	NS
BMI, body mass index; D/C, dilatation and curettage; NS, not significant Data are expressed as mean ± standard deviation or median (min–max) for continuous variables and number (percentage) for categorical variables. *unpaired t test; **Chi-square test, with P value set at 0.05; ***Kruskal–Wallis test			

Clinical Prognostic Indicators in the Two Groups

The thickness of the endometrium was monitored by color doppler before surgery and 3 months after surgery. Before the treatment, the intrauterine morphology and opening of fallopian tubes disappeared in the patient with severe IUAs. Following the treatment, the uterine cavity morphology recovered as before, and fallopian tube openings were clearly visible (Fig. 2). A total of 7 patients in the treatment group developed re-adhesion, with 5 exhibiting mild and 2 moderate adhesion, the recurrence

rate was 10.6% (5/47). In the control group the recurrence rate was 31.6% (12/38), with 8 mild and 4 moderate adhesion. No severe adhesions occurred in the two groups. Therefore, the second uterine adhesion separation was conducted. The thickness of the endometrium increased in the two groups as compared to prior the second-look hysteroscopy (P<0.05). The endometrium thickness in the treatment group was higher compared with in the control group (6.33±1.16 vs. 5.72±1.16) (Table II).

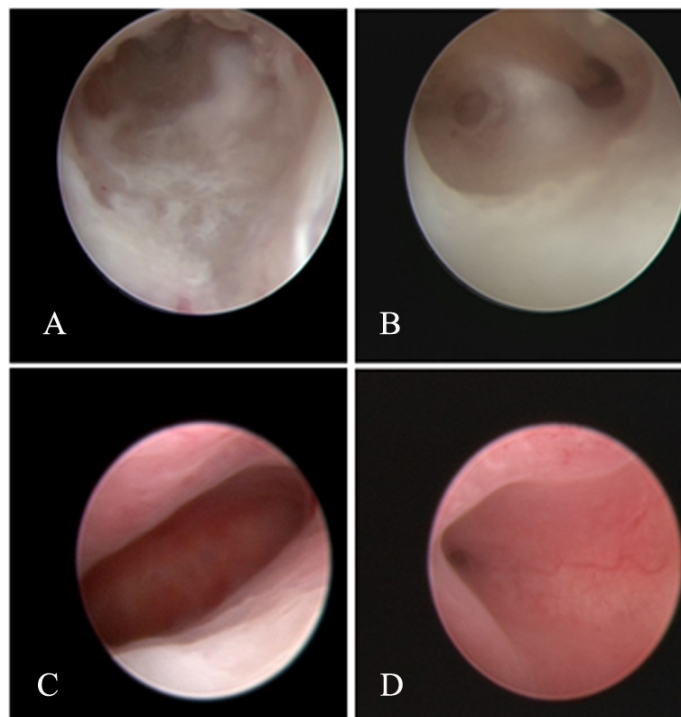


Figure 2: The uterine cavity images of one patient with severe intrauterine adhesions A and B show the intrauterine morphology and opening of fallopian tubes disappeared before the therapy in treatment group. C and D show that, after the treatment, the uterine cavity morphology and fallopian tube openings were clearly visible.

Table 2: Clinical circumstances and outcomes

	Treatment group	Control group	P-value
Endometrial thickness (mm)***			
Before surgery	5.13 ± 0.20	5.05 ± 0.19	0.76
After surgery	6.33 ± 1.16	5.72 ± 1.16	0.029
Adhesion score (median, min–max) **			
Before	8 (6–12)	8 (6–12)	0.179
1 month	2 (0–3)	2 (0–2)	0.328
3 months	2 (0–2)	2 (0–4)	0.018
Recurrence rate (%) *			
Yes	10.6 (5/47)	31.6 (12/38)	
No	89.4 (42/47)	68.4 (26/38)	
Pregnancy rate (%) *			
Yes	55.3 (26/47)	23.7 (9/38)	
No	44.7 (21/47)	76.3 (29/38)	
Live birth rate (%) *	36.2 (17/47)	13.2 (5/38)	0.024
Abortion (%) *	34.6 (9/26)	44.4(4/9)	0.698
Means of pregnancy (%) *			
Natural conception	61.5 (16/26)	44.4 (4/9)	
Assisted conception	38.5 (10/26)	55.6 (5/9)	
*Chi-square test; **Kruskal–Wallis test; ***unpaired <i>t</i> -test			

The median differences of AFS score between the treatment group and control group before and after 3 months treatment was 8 (6–12) and 2 (0–2), respectively ($P=0.018$). However, the AFS scores of the two groups were not comparable at 1month post-surgery.

Reproductive Prognosis in the Two Groups

The total of 35 patients were pregnant after the treatment. The pregnancy rate was 41.18% (35/85), the live birth rate was 25.88% (22/85) and the abortion rate was 37.14% (13/35). The pregnancy rate and live birth rate of the treatment group were higher compared with those of the control group (55.3 vs. 23.7%; 36.2 vs. 13.2%). There was no difference in natural or reproductive methods of pregnancy in the two groups (Table II). In this study, pregnancy complications occurred in some patients. Four patients developed placental adhesion, one patient developed placenta implantation and postpartum hemorrhage, and one patient developed placenta previa.

Therefore, hysteroscopic adhesiolysis combined with cHA gel for patients with moderate to severe IUA could obtain an improved outcome compared with treatment by hysteroscopic adhesiolysis alone.

Discussion

IUAs increase the risk of menstrual irregularity, recurrent miscarriage, infertility and pregnancy complications, which affect female reproductive and mental health. Hysteroscopic adhesiolysis is the clinically acknowledged effective method for treatment of IUAs. However, the higher recurrence rate in moderate to severe IUAs limits the clinical treatment. The prevention of IUAs reoccurrence following surgical operation is challenging. The present retrospective study demonstrated that the combination of hysteroscopic adhesiolysis and cHA gel could significantly ameliorate IUAs and further improve the pregnancy rate.

HA gel was served as a physical barrier agent to prevent adhesion formation. The safety and efficacy of HA gel for the prevention of IUAs has been verified [13]. Different from HA gel, auto-crosslinked HA gel possessed stronger durability for the auto-crosslinking process could slow down the natural degradation and maintain the hydrated structure. Can et al indicated that cHA gel can reduce the formation of IUAs in women who undergo curettage in the second trimester, and further improves the pregnancy rates [15]. In the present study, the effectiveness of cHA gel on the treatment of moderate to severe IUAs was detected. The data shows that followed by hysteroscopic adhesiolysis, the application of cHA gel significantly reduces the severity of IUAs, and further improves the pregnant rate.

Combination therapy may be a new strategy for treatment of IUAs. Two menstrual cycles copper IUD placement followed by hysteroscopy can improve the implantation and pregnancy rates in women with repeated implantation failure [16]. Inserting an IUD following hysteroscopic adhesiolysis attempts to reduce the occurrence of IUAs. However, the recurrence rate was still as high as 30% in a clinical trial using IUDs for 1 week post-surgery. This may be attributed to the increased infection risk caused by

the insertion of the IUD. In addition, the endometrium does not recover even after the removal of IUDs [8]. Notably, IUD plus a new crosslinked hyaluronan (NCH) gel obtain improved endometrial repair compared with using IUD alone [17]. In the present study, hysteroscopic adhesiolysis alone or the combination of hysteroscopic adhesiolysis and cHA gel was beneficial for the treatment of patients with moderate to severe IUAs. However, the combination group presented with improved endometrial thickness.

Conclusions

In summary, hysteroscopic adhesiolysis combined with cHA gel could benefit the patients with moderate to severe IUAs via promoting the endometrial recovery and improving the pregnancy rate. Therefore, cHA gel could be a potential candidate for combination therapy of IUAs.

Acknowledgements

Not applicable.

Funding

The present study was supported by education Department of Sichuan Province (grant no. 18ZA0204); The Nanchong City-School Science and Technology Strategic Cooperation Project (19SXHZ0293); The Key Scientific Research Project of North Sichuan Medical College (CBY18-A-ZD21), the Scientific Research Project of Affiliated Hospital of North Sichuan Medical College (2020JC021).

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

YM and ZYH designed the study, wrote and revised the manuscript. RW, LL, XQQ, WAP and SLB collected and analyzed the data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All participants provided written informed consent and the study was approved by the Ethics Committee of Affiliated Hospital of North Sichuan Medical College. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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