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A randomized multi-center controlled study on the efficacy and safety of a new crosslinked hyaluronan gel to prevent intrauterine adhesion following hysteroscopic adhesiolysis

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Introduction

Intrauterine adhesion (IUA) is one of the common disorders in OB/GYN practice. Any procedures that result in endometrium damages could possibly lead to IUA. In a cohort study, Taskin et al. (1) find that IUA formation after resection was present in 31.3% patients with solitary fibroids and 45.5% with multiple myomas. Guida et al. (2) find that the incidence of IUA after hysteroscopic resection of myoma, polyps and septa were 33.3, 18.2 and 37.5%, respectively. As abortion procedures reached 40-50 million worldwide at 2012 (3) and association between IUA and abortion was demonstrated (4), the prevalence of IUA would likely increase. Effective and safe interventions to prevent IUA after intrauterine procedures are therefore in urgent need.
Hysteroscopic adhesiolysis is currently a widely-performed procedure to remove the adhesions, restore the shape of uterine cavity, and ideally the functionality of endometrium. The major concern for this procedure is postoperative adhesion reformation. It was reported that adhesion reformation occurs in about 60% of severe cases (5). Preventing adhesion reformation after adhesiolysis is essential for a successful adhesiolysis procedure.
It has been reported that hyaluronic acid (HA) molecules could modulate inflammatory processes, regulate secretion of cytokines by macrophages, and facilitate scar-free tissue repair. However, due to its fluid nature and rapid *in vivo* degradation nature HA was not demonstrated to achieve a satisfactory efficacy to prevent post-operative adhesion (6). Crosslinking modification is an effective way to enable that HA material has high viscosity and degrades slowly so that it would stay in the application site and cover tissue surface during the critical tissue healing processes to prevent adhesion (7, 8). MateRegen® Gel is a new crosslinked HA gel that was developed using a proprietary chemical modification to the non-animal sourced HA material.
The objectives of this study were to explore the efficacy and safety of MateRegen® Gel in reducing IUA after hysteroscopic adhesiolysis for patients with moderate to severe IUA.

Methods

This study was approved by the Institutional Review Board and Ethical Committee. In total, 120 patients diagnosed with moderate to severe IUA according to the AFS scoring system (Table 1) (9) and underwent hysteroscopic adhesiolysis for the first time were recruited. All patients were informed consent and signed the Informed Consent Forms. Patients who were allergic to hyaluronan or its derivatives, with infection or malignant tumor of reproductive organs and with systemic diseases that could cause coagulopathy were excluded.
All patients were first examined by an experienced physician under hysteroscopy; the severity of the IUA was scored. Sharp hysteroscopic adhesiolysis with blunt tipped scissors under continuous saline flow was then performed. Upon completion of the adhesiolysis, patients were randomly assigned into

TABLE 1 - THE AMERICAN FERTILITY SOCIETY SCORING SYSTEM FOR IUA (1988).

Extent of cavity involved	<1/3	1/3-2/3	>2/3
	1	2	4
Type of adhesions	Filmy	Filmy and dense	Dense
	1	2	4
Menopausal pattern	Normal	Hypomenorrhea	Amenorrhea
	0	2	4
Stage I	Mild	1-4	
Stage II	Moderate	5-8	
Stage III	Severe	9-12	

treatment group (N=60) or to the control group (N=60). For patients in the treatment group a Foley balloon catheter (Perak, Malaysia) was first placed into the uterine cavity. Through the balloon port, 3ml Normal saline was injected into the balloon; through the urine drainage port; 2 ml of MateRegen® Gel (BioRegen Biomedical Co., Ltd., Changzhou, China) was then injected into the uterine cavity. For the control group, only Foley balloon catheter was placed into the uterine; 5ml Normal saline was injected into the balloon. The Foley balloon catheter was removed at the 4th day postoperatively for all patients.

Patients were followed-up at 3 days, 1 month, and 3 months postoperatively. Second-look hysteroscopic examination was performed 3 month postoperatively at 3-7 days after the completion of menstruation. The physicians who performed the second-look hysteroscopy were not aware of the study group assignment of the patients. After the IUA was evaluated and scored according AFS scoring system and recorded. IUA, if any, was then further lysed as needed per the physician's discretion.

The primary endpoint was the percentile of patients with zero AFS total score (Zero-AFS score rate) in each group. Secondary endpoint was AFS total score and score for each subcategory. Percentage of patients with different stages in each group was calculated and compared. The safety was evaluated based on the frequency of complications and severe events.

Data was statistically analyzed with SAS9.13 software (SAS Institute Inc.). The quantitative data was compared with two-tailed *student- t* test, ANOVA, and rank test; qualitative data was analyzed with c^2 test. $P< 0.05$ was considered as statistically different.

Results

Among the 120 patients, 5 in the treatment group and 4 in the control group were dropped off due to reasons unrelated with testing materials and treatment methods. Therefore, 111 patients completed this study, 55 in treatment group and 56 in control group.

The demographic characteristics, medical history, and AFS scores at the baseline were not significantly different between two groups.

Zero-AFS score rate in the treatment group is significantly higher than the control group (38.2 *vs* 16.1%, P = 0.0078; Figure 1). Using MateRegen® Gel resulted in significantly lower total AFS score, scores for the extent of cavity involved and the menopausal pattern than the control group ($p< 0.05$) (Table 2). The treatment group had significantly lower proportion of patients with moderate to severe adhesive stages than the control group ($p <0.05$) (Figure 1).

No complications, adverse events, and SAE related to the material and treatment were observed for both groups.

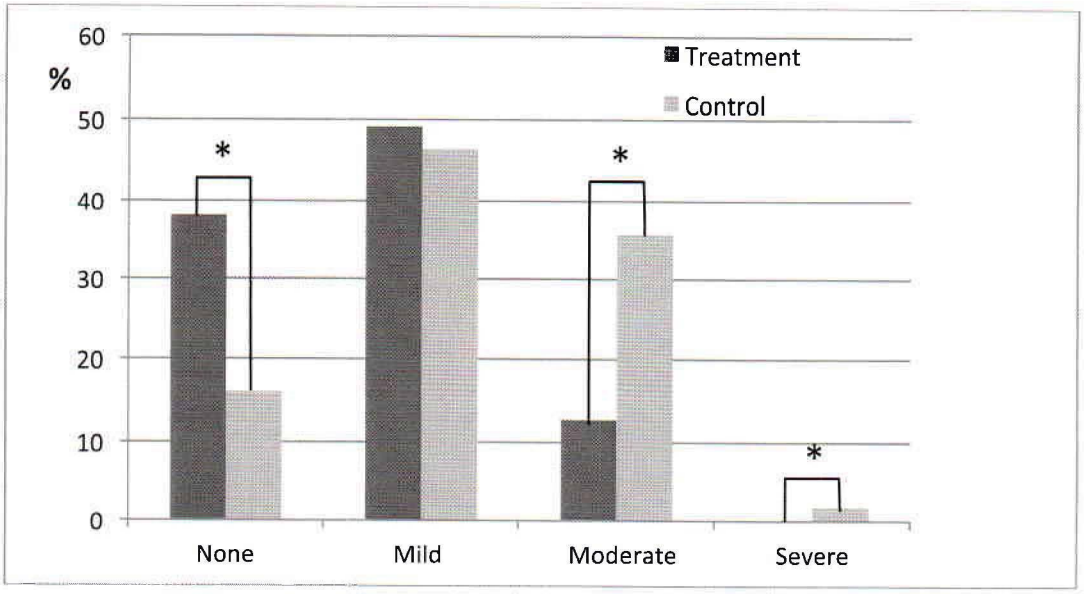

Figure 1 - Percentage of patients with different stages of IUA after treatment.
**** indicating significant differences between treatment and control group (p<0.05).***

TABLE 2 - THE SCORES OF IUA AT 3 MONTHS AFTER HYSTEROSCOPIC ADHESIOLYSIS (MEAN±SD).

Categories	Treatment group	Control group	*P* value
Extent of cavity involved	0.60 (0.74)	1.09 (1.08)	0.015
Type of adhesions	0.71 (0.85)	1.20 (1.26)	0.051
Menopausal pattern	0.80 (1.13)	1.39 (1.14)	0.005
Total score	2.11 (2.12)	3.68 (2.50)	0.001

Discussion

Only patients with moderate to severe IUA were enrolled in this study in order to evaluate the challenge situations dealt with during the clinical practice. Using of MateRegen® Gel significantly reduced reformation of IUA and its severity, and improved the endometrium function as shown by the normal menopausal pattern.

According to "Guidelines for treatment of IUAs" from AAGL (10), hysteroscopic adhesiolysis and use of anti-adhesion barrier are proposed to be the treatment choices. However, reformation of adhesion after adhesiolysis was observed in 60% of patients who initially had severe adhesion (2). Therefore, use of anti-adhesion barrier after adhesiolysis for those patients is obviously necessary. Formation of adhesion after surgery is associated with normal tissue healing processes where inflammatory reactions and re-vasculation of the repair tissue are physiological processes. HA has shown to modulate inflammatory reaction and reduce free-radicle production and scarring during tissue healing processes (11). However, nature HA material degrades too quickly *in vivo* and is not able to achieve the expected anti-adhesion efficacy.

Crosslink method was used to modify nature HA and improve its stability to prevent adhesions in abdominopelvic cavity and in uterine cavity. MateRegen® Gel is crosslinked hyaluronan that is from non-animal sources. The proprietary crosslinking technique improved the viscoelastic property meanwhile maintained the biological characteristics of natural HA molecules. This material is able to stay in the installation cavity for up to 14 days and cover the critical period of inflammatory phase during the wound healing (12). MateRegen® Gel could be also recommended for prophylactic application af-

ter intrauterine procedures that may cause injuries to endometrium.

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