Review Article
Effect of transcervical resection of adhesion combined with femoston on endometrium and MMP-9 levels in patients with severe intrauterine adhesions

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Abstract: Objective: This study aimed to investigate the effect of transcervical resection of adhesion combined with femoston on endometrium and serum matrix metalloproteinase-9 (MMP-9) in patients with severe intrauterine adhesions (IUA). Methods: Ninety-seven patients with severe IUA admitted to our hospital from January 2017 to November 2018 were selected as the research targets. Among them, 49 patients who only underwent transcervical resection of adhesions (TCRA) were set as a control group (CG), and on this basis, 48 patients who treated with femoston orally were set as a research group (RG). Recovery of postoperative uterine cavity, menstruation improvement, endometrium recovery, pregnancy rate, adverse reactions and serum MMP-9 and TGF-β levels were compared between the two groups. Results: Recovery of uterine cavity morphology and menstruation in the RG were better than those in the CG (P<0.05). Before treatment, the endometrial thickness of both groups had no statistical significance (P>0.05). After treatment, the endometrial thickness of the RG was dramatically larger than that of the CG on the day of ovulation, and endometrial thickness of both groups increased dramatically. Blood flow parameter RI under the endometrium of the RG was smaller than that of the CG (P<0.05). There was no difference in blood flow parameters PI and S/D between both groups (P>0.05). The clinical pregnancy rate in the RG was obviously higher than that in the CG within 1 year after operation (P<0.05), and the incidence of adverse reactions during treatment had no difference between the two groups (P>0.05). The results revealed that there was no significant difference in serum MMP-9 and TGF-β levels between both groups before treatment (P>0.05). After treatment, the MMP-9 level in the serum of patients in both groups was dramatically higher than that before treatment and the TGF-β level was dramatically lower than that before treatment. The MMP-9 level in the serum of the patients in the RG was obviously higher than that in the CG and the TGF-β level was obviously lower than that in the CG (P<0.05). Conclusion: TCRA combined with femoston can effectively improve menstruation and endometrium in patients with severe IUA, which is suitable for clinical use.

Keywords: Transcervical resection of adhesion, femoston, severe intrauterine adhesions, endometrium, MMP-9

Introduction

Intrauterine adhesion (IUA) is endometrial fibrosis caused by damage to the endometrial basal layer by infection during uterine cavity operation. Phenomenon of partial or complete closure of the uterine cavity is caused by adhesion between the uterine cavity walls of patients [1, 2] and manifested by symptoms such as reduced menstrual volume, amenorrhea, infertility and recurrent abortion, which greatly threatens the reproductive physiological health of women of childbearing age [3]. At present, transcervical resection of adhesion (TCRA) is the first choice therapy for IUA [4]. The factors that affect the efficacy during the treatment of IUA are mostly the severity of adhesion before operation and recurrence of adhesion after operation, and the patients with high recurrence rate are mostly those with severe IUA [5]. However, the rate of recurrent IUA in postoperative patients is still relatively high, and the pregnancy success rate of those with recurrent IUA after TCRA is fairly low [6]. It is vital to take measures in advance to prevent IUA patients from re-adhesion after TCRA. Prevention of postoperative adhesion formation has become a momentous part and goal of surgical treatment. The prevention methods mainly include intrauterine device surgery, conservative therapy,

stem cell therapy, traditional Chinese medicine therapy and artificial cycle therapy [7, 8]. TCRA has certain efficacy on patients with IUA, but its efficacy is limited. It has no repair effect on the damaged endometrium. In clinical practice, drug-assisted therapy and other methods are mostly employed to improve the efficacy. However, there is no unified standard for drug administration and dosage selection after IUA operation.

The large dose of estrogen contained in femoston has obvious preventive effect on uterine cavity re-adhesion, and can increase intracellular DNA and protein synthesis after being combined with estrogen receptors in endometrial gland epithelial cells and interstitial cells [9, 10]. Relevant reports show that estrogen can repair endometrium to prevent re-adhesion and obtain ideal endometrium [11]. It is concluded that the degree of improvement of IUA can be obtained by studying the restoration of endometrium. Therefore, we study and design the treatment scheme of femoston, a drug containing estrogen, to observe the restoration of endometrium and other functions after treatment of patients with severe IUA, and understand the effectiveness and feasibility of the experimental treatment methods for patients. MMP-9 can participate in extracellular matrix metabolism and neovascularization during post-traumatic tissue remodeling and repair by degrading various components of proteases in extracellular matrix [12]. During wound repair, extracellular matrix was used as a visual measurement and evaluation index. In this experiment, we also included MMP-9 and other related enzyme indexes to compare the prognosis of patients with severe IUA, in order to provide better and more reliable treatment measures for them. The specific research steps were as follows.

Materials and methods

Objects of research

From January 2017 to November 2018, 97 patients with severe IUA admitted to our hospital's gynecology department were selected as the research targets. Among them, 49 patients who only underwent transcervical resection of adhesion (TCRA) were set as a control group (CG), and on this basis, 48 patients who treated with femoston orally were set as a research

group (RG). Their average age was 25.57±5.25 years, average course of disease was 12.41±6.11 months, number of births was 2.65±1.22 times, and period before surgery was 2.35±0.32 days. Inclusion criteria were as below: (1) patients whose adhesion degree met the evaluation criteria defined by the American Reproductive Society intrauterine adhesion score [13]; (2) patients undergoing TCRA for the first time. Exclusion criteria were as below: (1) patients with unstable life, complicated infection and complicated uterine diseases; (2) patients receiving assisted reproductive therapy after operation; (3) patients with abnormal menstruation caused by other factors; (4) patients with contraindications (TCRA, application of estrogen and progesterone). This study was approved by the ethics committee of our hospital. All patients signed informed consent forms with their own authorized persons before treatment.

Treatment methods

All patients underwent routine hysteroscopy 7 days after the end of menstrual period understood the scope and types of IUA. Through hysteroscopy guidance, micro scissors were implanted into their uterine cavity to decompose the adherent uterine cavity, remove the adherent uterine band and restore its size and shape. Postoperative routine anti-infection treatment and nursing were carried out. The RG was given femoston (2 mg estradiol/10 mg dydrogesterone, Abbott Laboratories, USA) on the 1st day after TCRA, and the dose was controlled at 2 mg bid for 28 days. Pregnancy of the patients was followed up by telephones, mails and chat software for one year.

Outcome measures

(1) Hysteroscopy was performed one month after the treatment course was completed to evaluate the uterine cavity morphology and menstruation recovery. The uterine cavity morphology standard was as follows: cured (uterine cavity size and morphology, uterine angle and tubal opening were normal after treatment), effective (uterine cavity adhesion score decreased after treatment) and ineffective (uterine cavity adhesion score increased). Menstrual recovery evaluation criteria were as follows: The pre-existing patients' own menstrual amount was the reference basis; cure (the

Table 1. Comparison of general data of patients in the two groups

Group	Control group (CG) (n=49)	Research group (RG) (n=48)	t/X²	P
Age (years)	25.52±5.23	25.62±5.31	0.093	0.926
Course of disease (month)	12.43±6.12	12.37±6.09	0.048	0.962
BMI (kg/m²)	22.53±2.31	22.59±2.35	0.127	0.899
Number of births (times)	2.63±1.23	2.67±1.21	0.161	0.872
Intrauterine adhesion score (score)	23.44±4.24	23.41±4.29	0.035	0.972
Preoperative menstrual period (days)	2.32±0.33	2.37±0.31	0.769	0.444
History of tuberculosis (cases)			1.330	0.249
Yes	4 (8.16)	6 (12.50)		
No	45 (91.84)	42 (87.50)		
History of recurrent abortion (cases)			0.258	0.612
Yes	12 (24.49)	10 (20.83)		
No	37 (75.51)	38 (79.17)		
History of abdominal surgery (cases)			0.893	0.345
Yes	15 (30.61)	12 (25.00)		
No	34 (69.39)	36 (75.00)		
History of hysteroscopy (cases)			0.988	0.320
Yes	24 (48.98)	20 (41.67)		
No	25 (51.02)	28 (58.33)		

amount of menstruation recovered to their amount or more than normal), effective (the amount of menstruation increased but did not reach the normal amount) and ineffective (the amount of menstruation did not change or even decreased). The total effective rate of treatment = (cure+effective)/total number of cases × 100% [14, 15]. (2) Transvaginal color Doppler ultrasound (Philips HDi 4000 ultrasonic diagnostic instrument) was employed to evaluate the endometrial thickness and subendometrial blood flow parameters on the day of ovulation in the first ovulation cycle after completion of pretreatment. (3) Adverse reactions during treatment and clinical pregnancy within 1 year between the two groups were followed up. (4) 3 mL venous blood from patients before and after treatment was collected and MMP-9 and TGF-β levels were measured by enzyme-linked immunosorbent assay kit (Abcam).

Statistical methods

All data were recorded in SPSS 24.0 for statistical analysis. T-test was conducted after passing the normality test in advance and non-parametric rank sum test was conducted for non-normal distribution. The measurement data were analyzed via t-test, and the counting data were analyzed using chi-square test. P<0.05 was considered statistically significant.

Results

General information

There was no significant difference in general data between the two groups (P>0.05). More details were shown in **Table 1**.

Comparison of uterine cavity shape recovery between the two groups after treatment

After treatment, the size and shape of the uterine cavity, the angle of the uterus and the opening degree of the fallopian tube gradually recovered. The total effective rate of the RG was 91.67% (44/48) better than that of the CG (77.55%, 38/49) (P<0.05). More details were shown in **Table 2**.

Comparison of menstruation recovery after treatment between the two groups

The effective rate of menstruation recovery in the RG was 87.50% (42/48), higher than that in the CG (61.22%, 30/48) (P<0.05). More details were shown in **Table 3**.

Comparison of endometrial recovery between the two groups after treatment

Before treatment, the endometrial thickness of both groups had no statistical significance

Table 2. Comparison of uterine cavity shape recovery between the two groups after treatment [n (%)]

Group	Control group (CG) (n=49)	Research group (RG) (n=48)	X^2	P
Cure	18 (36.73)	27 (56.25)	-	-
Effective	20 (40.82)	17 (35.42)	-	-
Ineffective	11 (22.45)	4 (8.33)	-	-
Total efficiency	38 (77.55)	44 (91.67)	7.686	0.006

Table 3. Comparison of menstruation recovery between the two groups after treatment [n (%)]

Group	Control group (CG) (n=49)	Research group (RG) (n=48)	X^2	P
Cure	14 (28.57)	26 (54.17)	-	-
Effective	16 (32.65)	16 (33.33)	-	-
Ineffective	19 (38.78)	6 (12.50)	-	-
Total efficiency	30 (61.22)	42 (87.50)	13.141	<0.001

(P>0.05). After treatment, the endometrial thickness of the RG was obviously larger than that of the CG on the day of ovulation, and it increased obviously in both groups. Blood flow parameter RI under the endometrium of the RG was smaller than that of the CG (P<0.05). There was no difference in blood flow parameters PI and S/D between both groups (P>0.05). More details were shown in **Figure 1**.

Comparison of pregnancy rate and adverse reactions between the two groups after treatment

The clinical pregnancy rate of the RG was 52.08% (25/48) within one year after operation, which was significantly higher than that of the CG (34.69%, 17/49) (P<0.05). There was no difference in the incidence of adverse reactions between the two groups during the treatment period (P>0.05), and there was no serious discomfort in both groups after treatment. More details were shown in **Table 4**.

Comparison of serum MMP-9 and TGF-β levels between the two groups

The results revealed that there was no significant difference in serum MMP-9 and TGF-β levels between both groups before treatment (P>0.05). After treatment, the MMP-9 and TGF-β levels in the serum of them were dramatically higher than those before treatment, and improvement of each index in the RG was more
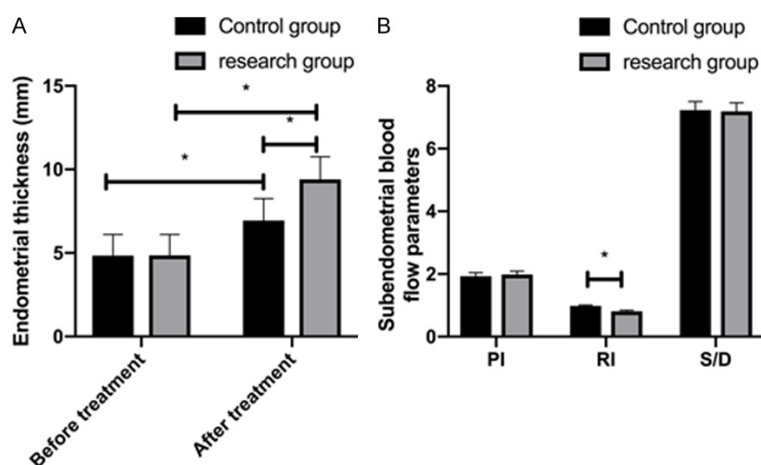
obvious (P<0.05). More details were shown in **Figure 2**.

Discussion

IUA is a narrow barrel-shaped multi-part closure of uterine cavity caused by adhesion between uterine cavity and cervical canal due to damage of endometrium, and poor exposure of tubal opening is unfavorable to normal pregnancy [16]. Studies on the pathogenesis of IUA have shown that the main mechanism of IUA formation is due to the increased activity of fibrocyte proliferation. When the endometrium is damaged, stress hyperplasia of collagen fibers leads to obstruction of endometrium proliferation, resulting in fibrotic scar adhesion of endometrium [17, 18]. IUA disease is essentially a pathological change of fibrosis, which causes serious obstacles to the repair of damaged endometrium. Prevention of adhesion focuses on inhibiting local inflammatory reaction to prevent its fibrosis process, promoting the regeneration and repair of damaged endometrium and improving physiological function, preventing new scar and isolating adjacent healing tissues from adhesion again [19, 20]. TCRA has good effects in separating adhesion, reducing uterine injury rate and preventing electrothermal injury, etc. It helps the growth and recovery of endometrium. In the case of increasingly mature endoscopic technology, accuracy of determining adhesion degree and type can be greatly improved through hysteroscopy assistance. High separation accuracy reduces the degree of damage to tissues and organs around lesions and accelerates the recovery rate of postoperative patients. Therefore, TCRA is often used as a scientific and effective treatment method for IUA [21]. However, most IUA patients have high expression of estrogen and progesterone receptors in uterine cavity tissues after operation. Changes in hormone levels have regulatory effects on endometrial growth cycle [22, 23]. Therefore, in this study, TCRA and femoston were applied to the patients with severe IUA excluded from the experiment, and their endometrial recovery status and extracellular matrix related indicators were observed, so as to analyze the influence degree of combined treatment on their IUA.

Figure 1. Comparison of endometrial recovery after combined treatment of patients between the two groups. A. The endometrial thickness of both groups before treatment has no remarkably statistical significance. After treatment, the endometrial thickness of the RG is markedly greater than that of the CG on the day of ovulation, and it in both groups increased greatly. B. There is no difference between both groups in the blood flow parameters PI and S/D under the endometrium. Blood flow parameter RI under the endometrium in the RG is smaller than that in the CG. Note: * represents the comparison between the two groups (P<0.05).

Patients with long-term IUA are easily affected by periodic abdominal pain, menstrual disorder and infertility, which prevent them from devoting their whole body to normal life. In order to restore their normal life and improve their condition, the uterine cavity state is investigated first from the perspective of uterine cavity morphology and menstruation recovery. The results revealed that the uterine cavity morphology recovery and menstruation recovery efficiency of the RG were better than those of the CG. Conventional intrauterine adhesions separation can accurately separate adhesions through direct vision under the microscope, but there is a problem of excessive damage to the endometrial basal layer caused by electrothermal cutting treatment in the uterine cavity, which is also the key to the recurrence of IUA [24]. Application of femoston in patients with IUA after operation can regulate estrogen in vivo, and play an effective role in controlling endometrial damage and preventing re-adhesion [25]. This indicates that femoston has better control and recovery of IUA by adjusting the combination of estrogen, progesterone and IUA. There have been reports that [26] there is a positive correlation between the severity of endometrial damage and IUA, and the more serious the endometrial damage was, the more obvious the IUA were. Our research results con-

firmed the conclusion of this literature by the indexes of intrauterine thickness and subendometrial blood flow parameters. Femoston is extracted from plants but has the same structure as human estradiol. Estradiol contained in the medicine is combined with estrogen receptor to artificially create progesterone cycle to increase endometrial thickness, promote hyperplasia of blood vessels and glands, improve endometrial receptivity, and exert the effect of assisting endometrial growth and development [27]. It shows that femoston can obviously increase the thickness of endometrium and treatment of IUA has better efficacy on the recovery of endometrium of patients. Then our observation results on the clinical symptoms and treatment side effects of the subjects revealed that the combined application of femoston did not increase the adverse reactions of patients after treatment, but their pregnancy status after combined treatment was effectively improved. Femoston is one of the compound preparations formed by packaging estradiol tablets and estradiol desquamate progesterone tablets. After taking it, the drug properties play a part in enabling patients to achieve normal menstruation. Estrogen can promote endometrial hyperplasia, and progesterone can promote endometrial secretion and transformation to stimulate menstrual recovery and improve pregnancy possibility [28]. Estradiol in femoston has no direct effect on liver transformation after absorption, so the absorption effect of liver burden reduction is good, and the content of estradiol and dydrogesterone in the drug has very little side effect in clinical treatment [29]. This displays that combined therapy can achieve the restoration of uterine function and improve pregnancy status of patients with reproductive needs on the premise of ensuring the safety and drug efficacy. To further understand the effect of femoston on the level of indexes tied to endometrial extracellular matrix in patients under combined treatment, our research signifies that there is no

Table 4. Comparison of pregnancy rate and adverse reactions between the two groups after treatment [n (%)]

Group		Control group (CG) (n=49)	Research group (RG) (n=48)	X^2	P
Clinical pregnancy		17 (34.69)	25 (52.08)	5.879	0.015
Adverse reactions	Gastrointestinal tract reaction	2 (4.08)	2 (4.17)	-	-
	Vaginal bleeding	3 (6.12)	2 (4.17)	-	-
	Breast distension	2 (4.08)	2 (4.17)	-	-
	Total incidence	7 (14.29)	6 (12.50)	0.043	0.836
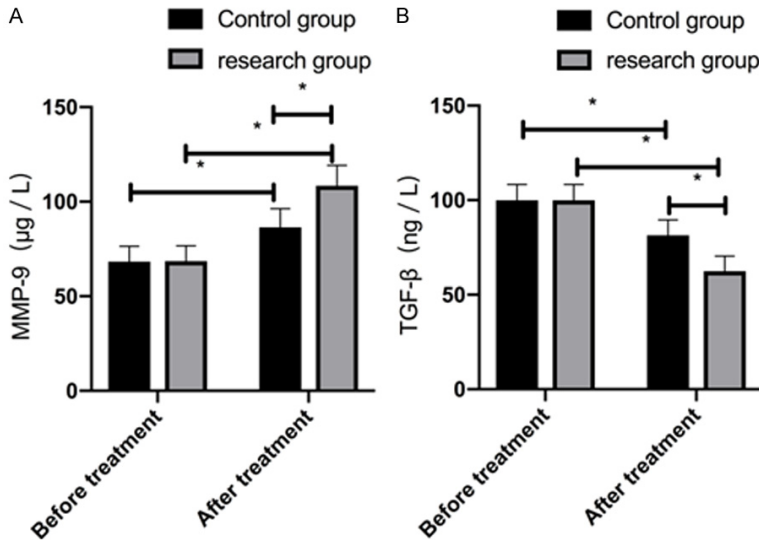
Figure 2. Comparison of serum MMP-9 and TGF-β levels between the two groups. A. The results revealed that there is no significant difference in MMP-9 between both groups before treatment. After treatment, the MMP-9 level in the serum of patients was markedly higher than that before treatment, and it in the serum of those in the RG was markedly higher than that in the CG. B. The results signified that there is no remarkable difference in serum TGF-β levels between both groups before treatment. After treatment, the TGF-β level in the serum of patients was markedly lower than that before treatment, and it in the serum of those in the RG was markedly lower than those in the CG. Note: * represents the comparison between the two groups (P<0.05).

synthesis. The extracellular matrix forms deposits in a large amount in the endometrium, and connective tissue gradually replaces the endometrium to form fibroblastic adherent uterus. This indicates that extracellular matrix is involved in the formation and development of diseases in patients with IUA. Femoston combined therapy can effectively improve fibrinolysis and maintain the balance of endometrial fibrosis inhibition.

Conclusion

All in all, TCRA combined with femoston can effectively improve menstruation and endometrium in patients with severe IUA. Control of fibrosis changes is a major treatment focus in the process of regulation of femoston. Previous literature has described the combination of the two methods in this study. On this basis, this study deeply explores the degree of fibrotic changes in the uterine cavity of patients after the implementation of this program, which can indirectly reflect the efficacy. However, in this study, there is still a lack of cognition on the efficacy of femoston. For example, we have studied the relevant indexes of extracellular matrix. These indexes change mostly indicates the change of fibrosis degree, which may interfere with the treatment results of patients' endometrial thickness. Clinically, these interference factors should be avoided to prevent the accuracy of experimental data from being affected. This experiment has not been discussed in time, which will be

remarkable difference in the MMP-9 and TGF-β levels in the serum of patients in both groups before treatment. After treatment, the MMP-9 level in the serum of the RG is obviously higher than that of the CG, and the TGF-β level is obviously lower. Previous literature reported [30, 31] that TGF-β stimulates the growth activity of interstitial cells by increasing the fibrogenic factor of extracellular matrix, and increases the content of collagen and fibronectin to promote the formation of tissue fibrosis. Nevertheless, the proteolytic activity of MMP-9 is specifically inhibited by TGF-β. High expression of TGF-β in endometrial cells can inhibit the MMP-9 expression and destroy the balance of fibrinolysis and

one of the directions for our continuous follow-up and improvement in the future studies, in order to provide better treatment schemes for the recovery of uterine environment of patients with severe IUA.

Disclosure of conflict of interest

None.

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