

# Post-hysteroscopy Duration of the Cook Balloon Uterine Stent Effect on the Re-adhesion Formation

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## ABSTRACT

**Objective:** To compare duration of Cook balloon uterine stent on re-adhesions formation, and observe its effect on serum transforming growth factor  $\beta$ 1 (TGF- $\beta$ 1) and plasminogen activator inhibitor-1 (PAI-1) levels in patients with intrauterine adhesions (IUA) undergoing hysteroscopic transcervical resection of adhesion (TCRA).

**Study Design:** Randomised controlled trial.

**Place and Duration of Study:** No. 215 Hospital of Shaanxi Nuclear Industry, Shaanxi Province, China, from January 2018 to January 2019.

**Methodology:** A total of 98 patients with IUA, who underwent hysteroscopic TCRA with cold scissors, were randomly divided into Group A (n=49) and Group B (n=49). Cook balloon uterine stent was placed for 37 days in Group A and 7 days in Group B. Efficacy of two groups was compared.

**Results:** Total effective rate in Group A was higher than that in Group B ( $p=0.021$ ). After treatment, levels of serum TGF- $\beta$ 1 and PAI-1 in Group A were lower than those in Group B ( $p < 0.001$ , and  $p=0.001$ , respectively). Recurrence rate of IUA at three months after treatment and total incidence of complications in Group A were lower than those in Group B ( $p=0.012$ , and  $0.037$ , respectively). Pregnancy rate in the 2-year follow-up period in Group A was higher than that in Group B ( $p=0.043$ ).

**Conclusion:** Placement of Cook balloon uterine stent for 37 days after hysteroscopic TCRA in patients with IUA can effectively prevent postoperative intrauterine re-adhesion, have few complications, low recurrence rate of IUA and high re-pregnancy rate, and reduce levels of serum TGF- $\beta$ 1 and PAI-1.

**Key Words:** Intrauterine adhesions (IUA), Transcervical resection of adhesion (TCRA), Transforming growth factor  $\beta$ 1 (TGF- $\beta$ 1), Plasminogen activator inhibitor-1 (PAI-1), Pregnancy.

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## INTRODUCTION

Intrauterine adhesions (IUA) refer to the adhesion of the inner wall of the uterus, resulting in total or partial occlusion of the uterine cavity.<sup>1</sup> IUA are mainly caused by intrauterine infection and trauma. IUA can induce hypomenorrhoea, amenorrhoea, periodic abdominal pain, recurrent abortion, and even sterility.

Transcervical resection of adhesion (TCRA) is the first choice for the treatment of IUA, which can effectively cut or separate the adhesion of uterine cavity under direct vision.<sup>2</sup> It has been pointed out that TCRA can achieve good results for the treatment of IUA.<sup>3</sup>

However, due to the serious destruction of the basal layer of the endometrium and the poor tolerance of the uterus, the physiological self-repair cycle of the uterus after operation is long in patients with moderate and severe IUA. Therefore, the postoperative recurrence rate of IUA is high.<sup>4</sup>

At present, the main methods to prevent postoperative intrauterine re-adhesion are intrauterine placement of physical barrier (such as Cook balloon uterine stent, IUD and Foley balloon) and postoperative drug therapy (such as estrogen), but the former is preferred in most medical institutions to prevent the occurrence of re-adhesion.<sup>5,6</sup> However, there is still no unified conclusion on the time, effectiveness, and safety of the physical barrier.

Among them, Cook balloon is a kind of silica gel made according to the morphology of uterine cavity.<sup>7,8</sup> Cook balloon uterine stent is similar to the morphology of uterine cavity with small volume and small stimulation to the endometrium, which is beneficial to the growth of the endometrium. It has been confirmed that the placement of Cook balloon uterine stent

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after operation in patients with IUA can effectively act as mechanical barrier and stent, help compression hemostasis, and prevent the recurrence of IUA.<sup>9</sup> However, the placement time of Cook balloon uterine stent is a key clinical problem.

Recurrence of adhesion is a factor affecting the outcome of pregnancy after the decomposition of uterine adhesion. At present, most of the IUA patients are women of childbearing age with fertility requirements, so the standard for surgery is more stringent. Operation-related re-injury should be minimised on the basis of the effectiveness of the operation. Currently, there are few reports about the effect of the placement time of Cook balloon uterine stent on the pregnancy outcome of patients undergoing TCRA.

Transforming growth factor  $\beta$ 1 (TGF- $\beta$ 1) is involved in the regulation of fibroblast proliferation and collagen metabolism. Signal transduction through downstream Smad2/3 can stimulate fibroblast growth and induce tissue adhesion.<sup>10,11</sup> Plasminogen activator inhibitor-1 (PAI-1) can inhibit the hydrolysis of fibrin and promote the formation of tissue adhesion.<sup>12</sup> At present, there are few reports about the effect of the placement time of Cook balloon uterine stent on serum TGF- $\beta$ 1 and PAI-1 levels in patients undergoing TCRA.

The objective of this study was to compare the duration of Cook balloon uterine stent on re-adhesion formation, and observe its effect on serum TGF- $\beta$ 1 and PAI-1 levels in patients with IUA undergoing hysteroscopic TCRA.

## METHODOLOGY

After approval by the Medical Ethics Committee, this randomised controlled trial study was conducted at No. 215 Hospital of Shaanxi Nuclear Industry, China, from January 2018 to January 2019. The mean follow-up period was 24 months after operation, and the follow-up deadline was January 2021. A total of 98 patients with IUA, who underwent hysteroscopic TCRA for the first time, were included. The inclusion criteria were that diagnosed with IUA by both preoperative hysteroscopy examination and biopsy under hysteroscopy taken for pathological examination (the biopsy findings showed that there were adhesions in the uterine cavity); moderate IUA (IUA accounted for 1/4-1/2 uterine cavity) or severe IUA (IUA greater than 1/2 uterine cavity); female patients aged 18-40 years; with surgical indication; no renal and liver dysfunction; women who desired childbearing and IUA were known to be the only infertile factor; with regular menstrual cycle (one menstruation per 21-35 days, the average bleeding time was 3-7 days, and the average blood loss per menstrual period was 20-60 mL) in the past; able to be followed up for average 24 months after treatment; and patients whose informed consent was obtained. The exclusion criteria were cases complicated with endometrial polyp, uterine myoma or other diseases that may cause vaginal bleeding; coagulation dysfunction; mental illness; complicated with heart disease, hypertension or other surgical contraindications; and in lactation or pregnancy.

A total of 98 patients with IUA, who underwent hysteroscopic TCRA with cold scissors, were randomly divided into Group A (n=49) and Group B (n=49) in a double-blind fashion. All patients were treated by hysteroscopic TCRA with cold scissors by the same surgeon. All patients had undergone postoperative pathological examination. The postoperative pathological results showed that fibrous connective tissue hyperplasia and a few inflammatory cells. Moreover, the IUA of diagnosis of all patients was obtained by combining with clinical manifestations and postoperative pathological results.

In Group A, Cook balloon uterine stent was placed for 37 days—namely, after operation, Cook balloon uterine stent was placed and filled with 5 mL saline, and Cook balloon catheter was cut at the level of the outer cervical orifice 7 days later. The stent was retained for 30 days. In Group B, Cook balloon uterine stent was placed for 7 days, namely, after operation, Cook balloon uterine stent was placed and filled with 5 mL saline. The balloon was replaced with GyneFix intrauterine contraceptive device (IUCD) 7 days later, and the GyneFix IUCD was placed for 30 days. On the first day after operation, both groups were treated with cephalosporin antibiotics. Estradiol valerate (progynova tablets) was given 4 mg per day for 21 days. On the 16th day, 2 tablets of progesterone soft capsule a day were added for 6 days.<sup>13</sup>

The curative effects of the two groups were compared after treatment. The criteria of therapeutical effect were as follows: Cured: Uterine cavity of patients was normal using hysteroscopy, and there was no adhesion in Uterine cavity, menstruation returned to normal, and periodic abdominal pain disappeared. Apparent: Uterine cavity of patients undergoing hysteroscopy was basically no adhesion, menstrual cycle, menstrual color and menstrual quality basically returned to normal but with reduced menstrual volume, and periodic abdominal pain disappeared or occasionally occurred. Improved: Hysteroscopy showed that IUA were ameliorated, menstruation recurred in amenorrhea patients, menstruation volume increased in patients with little menstruation volume, menstrual color and menstrual traits improved, and the frequency of periodic abdominal pain reduced. Invalid: There was no obvious changes in uterine cavity shape undergoing hysteroscopy when compared with before surgery, and even worsening; IUA and periodic hypogastrium pain were not improved, and there was no menstruation.<sup>14</sup>

Total effective rate = (number of cured cases + number of apparent cases + number of improved cases) / total number of cases  $\times$  100%.

Total 5 mL of venous blood was collected from all patients before and after treatment. Serum TGF- $\beta$ 1 and PAI-1 levels were measured by enzyme-linked immunosorbent assay before and after treatment. Three months after treatment, the recurrence rate of intrauterine re-adhesion and the total incidence of complications (implant dislocation, postoperative vaginal bleeding, uterine infection, etc.) during treatment. The mean follow-up period after treatment was 24 months, the deadline

for follow-up being January 2021, by phone call and outpatient. The pregnancy rate after treatment was compared between the two groups.

Data was analysed by SPSS version 25. Measurement data conforming to the normal distribution were expressed by mean  $\pm$  SD, and the independent sample t-test was used. Count data was expressed by n (%), and the Chi-square test was used. The  $p < 0.05$  was considered as the significant difference.

## RESULTS

All the 98 patients with IUA, aged 25-40 years with an average age of  $33.49 \pm 2.97$  years, of which 53 patients (54.08%) with moderate adhesion and 45 patients (45.92%) with severe adhesion.

The total effective rate in Group A (46 cases, 93.88%) was significantly higher than that in Group B (38 cases, 77.55%) ( $p = 0.021$ , Table I).

**Table I: Comparison of therapeutic efficacy between the two groups.**

Parameter	Group A (n=49)	Group B (n=49)
Cured [n (%)]	25(51.02)	15(30.61)
Apparent [n (%)]	13(26.53)	11(22.45)
Improved [n (%)]	8(16.33)	12(24.49)
Invalid [n (%)]	3(6.12)	11(22.45)
Total effective [n (%)]	46(93.88)	38(77.55)

**Table II: Comparison of serum markers between the two groups.**

Parameter	Group A (n=49)	Group B (n=49)	p-value
Serum TGF- $\beta$ 1 before treatment ( $\mu$ g/L)	$61.88 \pm 4.28$	$62.63 \pm 4.74$	0.411
Serum TGF- $\beta$ 1 after treatment ( $\mu$ g/L)	$37.57 \pm 2.69$	$43.51 \pm 2.86$	<0.001
Serum PAI-1 before treatment (ng/mL)	$35.59 \pm 2.82$	$35.23 \pm 2.75$	0.515
Serum PAI-1 after treatment (ng/mL)	$29.34 \pm 2.04$	$31.50 \pm 3.91$	0.001

**Table III: Comparison of relevant indexes between the two groups after treatment.**

Indexes	Group A (n=49)	Group B (n=49)	p-value
Recurrence rate of IUA at 3 months after treatment [n (%)]	3 (6.12)	12 (24.49)	0.012
Total incidence of complications (implant dislocation, postoperative vaginal bleeding, uterine infection, etc.) [n (%)]	3 (6.12)	10 (20.41)	0.037
Pregnancy rate in the 2-year follow-up period [n (%)]	29 (59.18)	19 (38.78)	0.043

Before treatment, there was no difference in serum TGF- $\beta$ 1 and PAI-1 levels between the two groups ( $p = 0.411$  and  $0.515$ , respectively, Table II). After treatment, the levels of serum TGF- $\beta$ 1 and PAI-1 in Group A were lower than those in Group B ( $p < 0.001$ , and  $p = 0.001$ , respectively, Table II).

The recurrence rate of IUA at three months after treatment and the total incidence of complications (implant dislocation, post-

operative vaginal bleeding, uterine infection, etc.) in Group A were lower than those in Group B ( $p = 0.012$ , and  $0.037$ , respectively, Table III). The pregnancy rate in the 2-year follow-up period in Group A was higher than that in Group B ( $p = 0.043$ , Table III).

## DISCUSSION

The effect of conventional IUD or hormone after TCRA to prevent postoperative adhesion is ideal in patients with mild IUA; but not in moderate and severe one, where the re-adhesion rate is high and the prognosis is poor. Barrier therapy is an effective preventive method for patients with moderate and severe IUA. Cook balloon uterine stent is identical to the shape of uterine cavity and is an important clinical method to prevent IUA.<sup>6,15</sup>

A study showed that there was no significant difference in the bacterial infection rate between the 30 patients, who placed Cook balloon in the uterine cavity for 30 days and the group without balloon.<sup>16</sup>

The results of this study showed that the total effective rate in Group A was higher than that in Group B, and the recurrence rate of IUA in Group A was lower than that in Group B, after three months' treatment, suggesting that the therapeutic effect of Cook balloon uterine stent for 37 days is better than that of Cook balloon uterine stent for 7 days. The results of this study are basically identical to those of Guo *et al.*<sup>13</sup>

Studies have confirmed that serum TGF- $\beta$ 1 can be used as an indicator of adhesion of pelvic cavity.<sup>17</sup> TGF- $\beta$ 1 is closely related to the occurrence and development of IUA and is an important risk factor for the early recurrence of IUA.<sup>18</sup>

One study found that reduce serum TGF- $\beta$ 1 level could avoid recurrence of adhesion in treatment of patients with severe IUA.<sup>19</sup> Increased expression of PAI-1 can promote extracellular matrix deposition, which is closely related to the formation of IUA.<sup>20</sup> The results of this study showed that the levels of serum TGF- $\beta$ 1 and PAI-1 in Group A were lower than those in Group B, suggesting that compared with placement of Cook balloon uterine stent for 7 days, placement of Cook balloon uterine stent for 37 days can better reduce serum of TGF- $\beta$ 1 and PAI-1 levels, thus preventing the occurrence of postoperative adhesion.

The occurrence of complications during treatment in the two groups was further analysed. The results showed that placement of Cook balloon uterine stent for 37 days was superior to placement of Cook balloon uterine stent for 7 days in postoperative complications, suggesting that the placement of Cook balloon uterine stent for 37 days may not cause serious side effects. In order to improve the effectiveness of preventing postoperative adhesion, the placement time of balloon can be prolonged appropriately.

At present, the conclusion about whether Cook balloon can improve the pregnancy rate after operation is not uniform. The pregnancy rate in the 2-year follow-up period in Group A was 59.18%, which is basically consistent with the pregnancy rate of

40-63% of the patients after TRCA in previous studies.<sup>21,22</sup> The results of this study showed that the pregnancy rate in Group A was higher than that in Group B. One article reported that increased level of blood PAI-1 could increase the risk of female infertility and bad pregnancy outcome.<sup>23</sup> It is speculated that the reason for the higher pregnancy rate in Group A may be the placement of Cook balloon uterine stent for 37 days, can more effectively reduce serum PAI-1 level. In addition, the placement of Cook balloon uterine stent for 37 days can be better in maintaining the patency of the tubal opening and restoration of the anatomical structure and function of the uterine cavity.<sup>5</sup>

## CONCLUSION

Placement of Cook balloon uterine stent for 37 days after hysteroscopic TCRA in patients with IUA can effectively prevent postoperative intrauterine re-adhesion, have few complications, low recurrence rate of IUA and high re-pregnancy rate, and reduce levels of serum TGF- $\beta$ 1 and PAI-1.

## ETHICAL APPROVAL:

Ethical approval was obtained from the Medical Ethics Committee, No. 215 Hospital of Shaanxi Nuclear Industry, China.

## PATIENTS' CONSENT:

Informed consents were obtained from all patients.

## CONFLICT OF INTEREST:

The authors declared no conflict of interest.

## AUTHORS' CONTRIBUTION:

SQ: Study design, analysis of data and writing of the manuscript.

PZ: Supervision and final approval.

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