

**Title:** *The efficacy of intrauterine balloon dilatation therapy in the prevention of adhesion reformation after hysteroscopic adhesiolysis*

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# **The efficacy of intrauterine balloon dilatation therapy in the prevention of adhesion reformation after hysteroscopic adhesiolysis**

The study was approved by Institutional review board of Capital Medical University, Beijing, China (reference No. 2016FXHEC-KY, Date: 20 October 2016)

## **Investigators**

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## **Background information**

Intrauterine adhesions, or Asherman's syndrome, occur after trauma to the basalis layer of the endometrium generally after endometrial curettage. It was first described by Heinrich Fritsch in 1894 and subsequently studied by Israeli gynecologist Joseph G. Asherman. In Asherman's description, he differentiated between traumatic intrauterine adhesions, which did not typically result in menstrual disturbances, and atretic amenorrhea, which resulted in amenorrhea and dysmenorrhea due to cervical adhesions (1, 2). The syndrome occurs most frequently after incomplete abortion (50%), postpartum hemorrhage (24%), and elective abortion (17.5%) (3). Other less common etiologic factors including myomectomy, hysterotomy, diagnostic curettage, cesarean section, tuberculosis, caustic abortifacients, and uterine packing have been reported(4–7).

With damage to the basalis layer, granulation tissue on either side of the endometrial cavity can fuse to form tissue bridges. In the most severe cases, the endometrial cavity can be entirely obliterated without any evidence of viable endometrium. Patients with Asherman's syndrome may present with amenorrhea with or without severe dysmenorrhea, oligo-menorrhea, infertility, or recurrent miscarriages (6). Patients with amenorrhea and cyclic pain associated with hematometria are likely to have viable endometrium above the occlusive adhesions. Sequelae of pregnancy in the presence of adhesions include higher incidences of ectopic pregnancy, recurrent miscarriage, premature labor, and abnormal placentation (8).

The main challenge of hysteroscopic adhesiolysis in Asherman syndrome is the high rate of reformation of adhesions, especially in those with severe adhesions, in whom the recurrence rate may be up to 62.5% (9). We recently conducted a study and found that a Foley-catheter made intrauterine balloon dilatation seemed to be effective in preventing adhesion reformation after intrauterine adhesiolysis. However, there has

never been any formal randomized, control trial designed to identify the efficacy of the intrauterine balloon dilatation in the prevention of adhesion reformation.

## **Objectives**

In this prospective, randomized, controlled study, we wish to determine the efficacy of intrauterine balloon dilatation in the prevention of adhesion reformation when compared with the conventional management.

## **Null hypothesis**

The null hypothesis is that intrauterine balloon dilatation therapy will not reduce the rate of adhesion reformation compared with conventional management following a primary hysteroscopic adhesiolysis procedure.

## **Patients**

The patients will be recruited from the Hysteroscopy Center of the Fuxing Hospital, Beijing, China. Before the surgery all patients with suspected Asherman syndrome will undergo preoperative evaluations, including a detailed history of the menstrual pattern, any previous intrauterine surgery, and reproductive history, as well as trans-vaginal ultrasonography. The severity and extent of intrauterine adhesions will be scored according to a classification system recommended by the American Fertility Society (AFS) (1988 version). The inclusion criteria include [1] women aged 18–40 years; [2] moderate to severe intrauterine adhesion (AFS score  $\geq 5$ ); [3] no previous history of hysteroscopic adhesiolysis; [4] written consent obtained; and [5] agreement to have second-look hysteroscopy. The exclusion criteria include [1] minimal adhesion (AFS score  $< 5$ ) and [2] previous hysteroscopic adhesiolysis.

## **Study Design**

After the completion of hysteroscopic adhesiolysis, recruited patients will be randomized to one of the two treatment groups by computer-generated numbers: [1] having a Foley-catheter intrauterine balloon dilatation 2 weeks and 6 weeks after hysteroscopic adhesiolysis; [2] the control group without any additional treatment. A second-look hysteroscopy will be carried out in the early proliferative phase 4 weeks the surgery and a third-look hysteroscopy was carried out 8 weeks after the surgery.

## **Power Calculation**

On the basis of the results of the two published retrospective cohort studies comparing the balloon and hormone therapy group (control group) in the prevention of adhesion reformation, we estimated that the adhesion reformation rate in the balloon group to be 20% and in the control group to be 45%. Accepting a type 1 error of 0.05, and a

type 2 error of 0.10, the number of subjects in each arm of the randomized, controlled trial would be 79. Assuming that the dropout rate to be 20%, the total number of subject to be recruited would be 100 in each arm.

## **Procedure**

### **Surgical procedure**

The surgery will be carried out by one of three experienced hysteroscopic surgeons with the use of a 4.5-mm rigid hysteroscope (Olympus) with 5% normal saline infusion under 100 mm Hg pressure. The procedure will be performed under general anaesthesia in a day surgery unit. Ultrasonographic guidance will be routinely used. Once the extent and severity of uterine adhesion has been assessed, the adhesions will be divided with the use of mono-polar instrument until normal uterine anatomy is achieved.

### **Postoperative treatments**

All subjects will be treated with oral antibiotics for 5 days. In all cases hormone therapy will also begin from the day of operation, consisting of estradiol valerate at a dose of 6 mg/d for 21 days, with the addition of dydrogesterone at a dose of 10 mg/d for the last 7 days of the estrogen therapy. After the withdrawal bleed, the hormone therapy will be repeated for another cycle. Second-look hysteroscopy will be carried out in the early proliferative phase, 4 weeks after the initial operation; a third-look hysteroscopy will be carried out 8 weeks after the initial operation. After assessment of the extent and severity of any reformed adhesion, hysteroscopic adhesiolysis will also be carried out at the time of the second-look procedure, if adhesion has recurred. The surgeon who performs the second-look and third-look hysteroscopy will be blinded to the randomization.

### **IUB dilatation**

IUB dilatation therapy will be performed according to the methodology published in the literature (10-11). In brief, a Foley catheter (size 8-12fr) will be prepared by cutting the excess catheter tip protruding beyond the balloon prior to insertion into the uterine cavity. Once the catheter has reached the fundus, 3-5mls of saline will be slowly introduced into the balloon under ultrasound guidance, in order to directly visualise the distention of the cavity and stretching and blunt dissection of any intrauterine adhesions, if present. The whole process requires merely a few minutes.

### **Statistical Analysis**

The rate of the recurrence of adhesion in the two groups will be compared using the  $\chi^2$  test. The reduction of AFS score in the two groups will be compared using the Mann-Whitney U test. A p value of  $< 0.05$  will be considered statistically significant. All statistical analysis will be carried out with the use of SPSS 21.0.

**Outcome measures**

The primary outcome measure will include the degree of intrauterine adhesions and AFS score at follow-up. The secondary outcome measures will include the menstrual improvement, need for re-operation and future reproductive outcome.

**Data processing and analysis**

The researchers will ensure the confidentiality of sensitive data by minimizing the number of personnel who handle subject data. In addition, computer data will be encrypted as required to maximize security, while paper documents will be locked in filing cabinets, with only authorized personnel having access to the information.

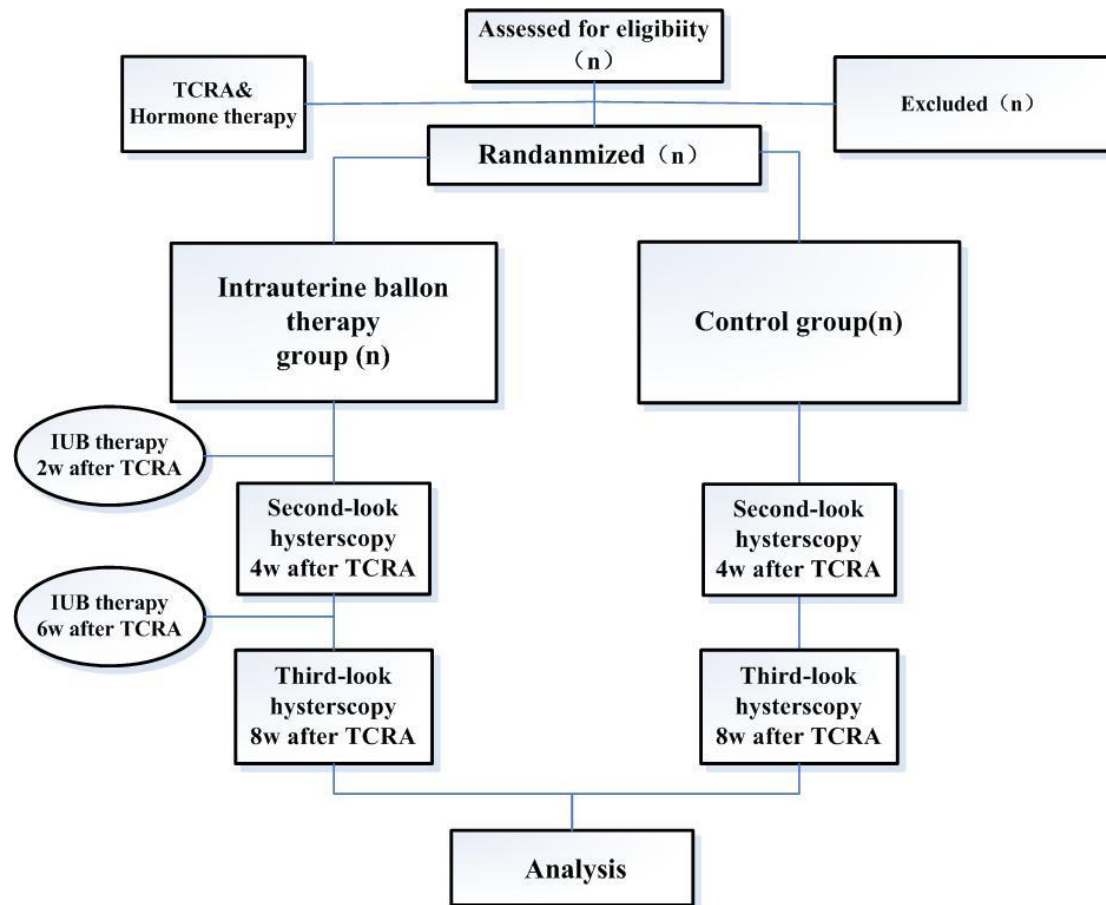
**Ethical considerations**

IUB dilatation has been published as a novel technique with no untoward complications identified to date (14-16). The procedure will be performed according to the methodology available in the literature and the study has gained approval from the local ethical committee (Approval Notice Number: 2016FXHEC—KY).

**Consent**

All subjects will be given a detailed explanation of the study and sufficient time to consider their participation. A written consent form will be signed by the patient and retained in our confidential records.

## Participant patient flow



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