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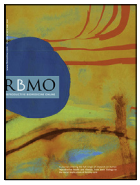

ARTICLE

A prospective randomized controlled trial comparing two different treatments of intrauterine adhesions

BIOGRAPHY

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KEY MESSAGE

High postoperative readhesions remains a challenge in treatment of IUAs. It's not clear which barrier agent individually or in combination are the optimum. Combination of intrauterine device and Foley balloon possibly had better efficacy in preventing readhesion than using COOK balloon alone, but not in the reproductive outcomes.

ABSTRACT

Research question: Intrauterine adhesions (IUA) are primarily caused by trauma to the endometrium, and hysteroscopy is presently the main treatment for IUA. However, high rates of post-operative adhesion re-formation remain a problem. In this study, the combination of an intrauterine device (IUD) with a Foley catheter and the balloon uterine stent were investigated to evaluate their efficacy in preventing adhesion re-formation and the subsequent reproductive outcomes in patients with moderate to severe adhesions.

Design: A prospective randomized controlled study was conducted in a university-affiliated hospital. A total of 171 women with Asherman's syndrome were initially recruited between August 2016 and December 2017 and were randomized to undergo either balloon uterine stent insertion or placement of a contraceptive IUD plus a Foley catheter after hysteroscopic adhesiolysis. Reduction of adhesion scores, incidence of adhesion re-formation, changes in menstrual flow and reproductive outcomes were analysed.

Results: A total of 118 participants were eligible for analysis. The American Fertility Society (AFS) scores were not significantly different between groups before hysteroscopic adhesiolysis. At the second-look hysteroscopy, the AFS scores and adhesion recurrence rates were significantly higher in the balloon uterine stent group compared with the combination group ($P < 0.01$ and $P = 0.024$, respectively). There were no statistically significant differences in pregnancy and live birth rates between the two groups.

Conclusions: The combination of an IUD and a Foley balloon catheter had better efficacy in preventing adhesion re-formation than the balloon uterine stent alone; however, it did not produce better reproductive outcomes.

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KEYWORDS

Asherman's syndrome
Balloon uterine stent
Foley balloon catheter
Hysteroscopic adhesiolysis
Intrauterine contraceptive device

INTRODUCTION

Intrauterine adhesions (IUA) are primarily caused by trauma to the endometrium, resulting in partial or complete obliteration in the uterine cavity and/or the cervical canal (*Yu et al., 2008*). IUA may result in menstrual disturbances, infertility, recurrent miscarriages or cyclical pelvic pain. The prevalence of IUA varies from 0.2% in patients who undergo intrauterine device (IUD) insertion to 17.3–30.0% in patients who undergo curettage for miscarriage (*Hooker et al., 2014*, *2016*).

Hysteroscopy is a more accurate method for confirming the presence and extent of adhesions than radiological tests (*Fernandez et al., 2006*). Hysteroscopic surgery is currently the treatment of choice for IUA because of its minimally invasive nature. However, the high rate of post-operative re-formation of adhesions remains a challenge, especially in patients with severe IUA, among whom the recurrence rate has been reported to be up to 62.5% (*Yu et al., 2008*). Therefore, preventing adhesion re-formation is essential for a successful treatment and various adjuvant treatments have been proposed to achieve this aim. The use of oestrogens has been suggested to stimulate endometrial regeneration and to promote re-epithelialization of scarred surfaces (*Cai et al., 2016*; *Guo et al., 2017*; *Johary et al., 2014*; *Liu et al., 2016*). However, there is no confirmed evidence based on randomized trials about the efficacy of oestrogens in reducing adhesion re-formation. Many investigators have focused on the insertion of IUD, such as intrauterine contraceptive devices (*Dubey et al., 2006*; *Lin et al., 2015*; *Vesce et al., 2000*), Foley balloon catheter (*Behrman, 1973*; *Orhue et al., 2003*) or Cook balloon uterine stent (*Lin et al., 2013*; *Rab et al., 2015*). Hyaluronic acid (*Guida et al., 2004*) and human amnion grafts (*Peng et al., 2017*; *Tsapanos et al., 2002*) have also been studied as barrier agents for preventing adhesion re-formation. Although all of these procedures have demonstrated success, it is not clear which procedures, individually or in combination, are the optimum treatments for IUA. This study was the first to investigate, via a randomized controlled trial (RCT), two well-known methods in the treatment of IUA. The aim was to determine the most effective technique for reducing the rate of adhesion recurrence in this group of patients.

In this RCT, combined placement of an intrauterine contraceptive device and a Foley catheter (IUD plus Foley catheter) was compared with insertion of a balloon uterine stent, in terms of efficacy in preventing adhesion re-formation and the subsequent reproductive outcomes in patients with moderate to severe IUA.

METHODS

Patients

This RCT was approved by the Institutional Review Board of the First Affiliated Hospital of Wenzhou Medical University in August 2016 (number: 2016160). Patients were recruited from the centre between August 2016 and December 2017, and written informed consent was provided by all participants or their guardians. The study was registered in the ClinicalTrials.gov Protocol Registration System (ClinicalTrials.gov identifier: NCT02867202) in June 2015 and participant enrolment began in August 2016.

All patients with suspected IUA underwent detailed pre-operative evaluations, including transvaginal ultrasonography, hysteroscopic examination, and assessment of prior menstrual cycle, menstrual patterns, any previous intrauterine surgery and reproductive history. The inclusion criteria were female sex, age 18–45 years, no previous hysteroscopic adhesiolysis, willingness to undergo a second-look hysteroscopy, moderate to severe IUA according to the American Fertility Society (AFS) scoring system (AFS score ≥5) (*Valle and Sciarra, 1988*) and provision of written informed consent. The exclusion criteria were the presence of other intrauterine lesions (e.g. myoma or septum); premature menopause (*Faubion et al., 2015*; *Okeke et al., 2013*); and severe intercurrent disease, such as coagulative disorders, systemic autoimmune disease (*Marder et al., 2016*) or severe disease of the liver or kidneys.

Sample size calculation

A pilot experiment involving 22 participants was designed to determine the necessary sample size. It was estimated that the adhesion recurrence rate was 41% in patients with balloon uterine stent insertion and 14% in patients receiving IUD plus a Foley catheter. Accepting a power of 90% (alpha error = 0.05, beta error = 0.10), the necessary sample size was calculated to be 53 in each treatment arm. After assuming a drop-out rate of 20%, the total number of participants required was 132. In addition, the patients involved in the pilot experiment were not included in the subsequent randomized study.

Randomization

Patients with IUA were re-recruited according to the pilot experiment. At the end of the procedure, the recruited participants were randomized into two groups at a 1:1 ratio using a computer-generated randomization scheduled by the first author: (i) a group undergoing insertion of a Cook balloon uterine stent (a heart-shaped intrauterine balloon) containing 3–5 ml saline and (ii) a group undergoing placement of an IUD followed by a Foley balloon catheter containing 3 ml saline.

Hysteroscopy method

All procedures were performed by an experienced endoscopic surgeon in the early proliferative phase, using a rigid hysteroscope (Wolf) with an outer diameter of 5.0 mm. In the balloon uterine stent group, the cervix needed to be dilated; however, in the combination group, the cervix was not dilated. Intraoperative ultrasound examination was performed in difficult cases, such as in the presence of a partially or completely blocked uterus. A hysteroscope was inserted into the uterine cavity, which was then distended with saline solution (0.9% NaCl), and adhesiolysis was performed with hysteroscopic scissors until the cavity was completely reopened.

As marginal and dense adhesions were more difficult to distinguish and might pose an increased risk of adhesion re-formation, filmy and central adhesions were divided first. After completion of the hysteroscopic adhesiolysis, a heart-shaped IUD (*Lin et al., 2015*) was introduced into the uterine cavity and its position was confirmed using a hysteroscope. Thereafter, a 12-F Foley catheter was introduced into the uterine cavity with 3 ml saline injected into the Foley balloon. In the other group, a Cook balloon uterine stent was introduced into the uterine cavity after cervical dilation to Hegar 8 with 3 ml saline. Post-operative pain was assessed using the Numerical

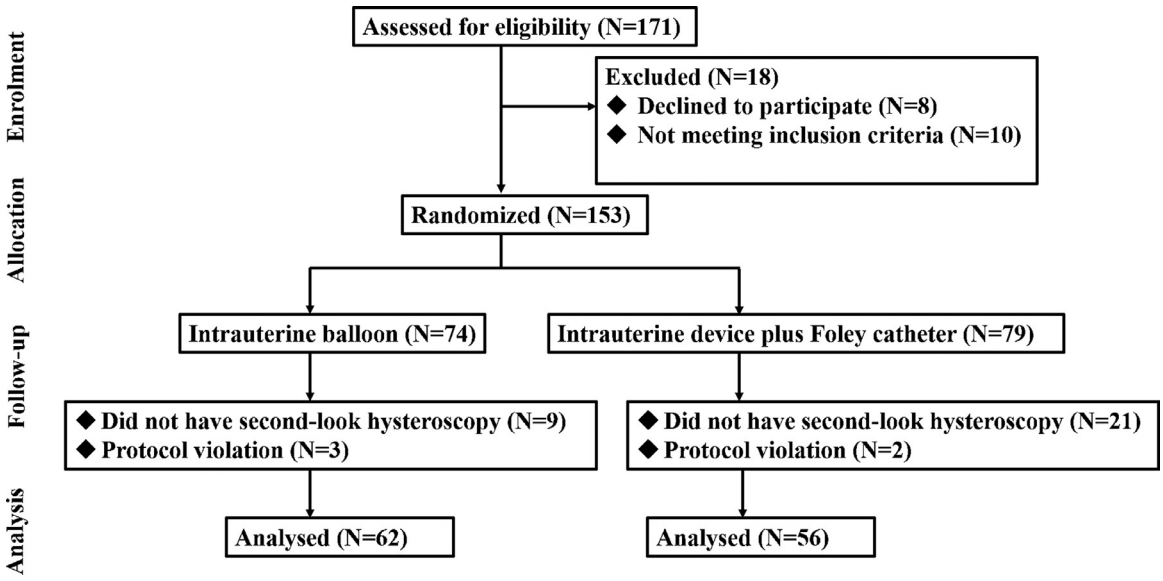

FIGURE 1 Flow chart showing the recruitment, inclusion and exclusion of patients in the study.

Rating Scale (NRS) (*Castarlenas et al., 2017*). Each procedure took between 20 and 40 min to complete. Non-intubated intravenous general anaesthesia was used. All procedures were completed in a day-case unit in the university hospital.

Post-operative treatments

All patients were treated with oestradiol valerate, 4 mg/day for 21 days, starting from day 5 of the menstruation cycle. Antibiotic therapy was given for 1 week after the adhesiolysis procedure in both arms. The patients were followed up before the second hysteroscopy. Changes in menstrual volume were queried and documented via telephone interviews or outpatient clinic consultations.

The balloon uterine stent was removed 1 week after the procedure. In the IUD plus Foley catheter group, the Foley catheter was removed 3 days after surgery to avoid infections and the IUD was retrieved at the second-look hysteroscopy. Second-look hysteroscopic examination was performed during the early proliferative phase of the menstrual cycle by the same endoscopic surgeon, 2–3 months after the initial procedure, to re-evaluate the extent and severity of any re-formed adhesions. If adhesion recurrence was found, a hysteroscopic adhesiolysis was performed again after the re-evaluation of the AFS score during surgery. The evaluated end-points were the incidence of post-procedure recurrent adhesions, AFS scores, restoration of the menstrual cycle and its normality, pain experienced by the patients during the course of the procedure, and reproductive outcomes. Pregnancy was defined as ultrasound visualization of at least one gestational sac with or without cardiac activity. Fetal deaths before 28 gestational weeks with a birthweight of less than 1000 g were considered a miscarriage in China.

Statistical analysis

Data analysis was performed with SPSS version 22.0 (IBM Corp., USA), using a two-sided test, and a *P*-value of <0.05 was considered statistically significant. Continuous variables were analysed using Student's *t*-test. Categorical variables are described as percentages and were evaluated using the chi-squared test or Fisher's exact test. In addition, the Mann–Whitney test was adopted to compare the AFS scores between the two groups.

RESULTS

The study flow chart is shown in FIGURE 1. Among the 171 patients who were initially recruited, 18 were excluded from the analysis (8 patients declined to participate and 10 patients did not meet the inclusion criteria). Therefore, the study included a total of 153 women. Of them, 74 women were randomized to the balloon uterine stent arm and 79 women were assigned to the combination arm (IUD plus Foley catheter). Thereafter, 30 participants subsequently refused to undergo a second-look hysteroscopy and five participants were excluded for protocol violation. All patients were prescribed 4 mg/day oestradiol valerate for 21 days from day 5 of the menstruation cycle; however, two participants discontinued the medication of their own accord. Another three participants were excluded because of immediate removal of the Foley balloon catheter after the procedure. Therefore, 118 women were eligible for the final analysis, including 62 women in the balloon uterine stent group and 56 women in the IUD plus Foley catheter group. No significant differences ($P > 0.05$) were observed in any of the pre-operative baseline characteristics between the two groups (TABLE 1).

The adhesion scores of the two groups before the operation and at the second-look hysteroscopy are presented in TABLE 2. The difference did not reach statistical significance at the initial hysteroscopy ($P > 0.05$). At the second-look hysteroscopy, the adhesion scores of the balloon uterine stent group were higher than those of the IUD plus Foley catheter group ($P < 0.01$).

The rate of adhesion re-formation in the IUD plus Foley catheter group (19.6%) was significantly lower ($P = 0.024$) than that in the balloon uterine stent group (38.7%) (TABLE 2).

Every patient underwent NRS score post-operative pain evaluation 30 min after the operation. The balloon uterine stent group had higher NRS scores, as shown in TABLE 2 ($P < 0.01$). The menstrual pattern changes after hysteroscopy are

TABLE 1 PATIENT CHARACTERISTICS AND PRE-OPERATIVE CLINICAL PARAMETERS

	Group A *n* = 62	95% CI	Group B *n* = 56	95% CI	*P*-value
Age (years)[a]	31.69 ± 5.268	30.47–33.62	32.63 ± 6.125	31.24–34.56	0.265
Parity[b]	0	0–1	1	0–1	0.424
Miscarriages[b]	2	2–3	2	2–3	0.382
Previous intrauterine operation[c]					0.620
Dilation and curettage	58 (93.5)	0.84–0.97	50 (89.3)	0.78–0.95	
Other uterine operation	2 (3.2)	0.00–0.11	2 (3.6)	0.00–0.12	
No operation (infection)	2 (1 tuberculous endometritis) (3.2)	0.00–0.11	4 (1 tuberculous endometritis) (7.1)	0.02–0.17	
Menstrual pattern[c]					0.654
No menses	4 (6.5)	0.02–0.15	3 (5.4)	0.01–0.15	
Light menses	48 (77.4)	0.65–0.86	47 (83.9)	0.72–0.91	
Normal menses	10 (16.1)	0.09–0.27	6 (10.7)	0.05–0.22	

All data are given as mean± SD or *n* (%) unless otherwise stated.

Group A: balloon uterine stent group; Group B: IUD plus Foley catheter group.

CI = confidence interval; IUD = intrauterine device.

[a] Mean ± SD, one-way analysis of variance test.

[b] Median, Mann–Whitney *U*-test.

[c] Chi-squared test.

shown in TABLES 2 and 3. In this study, women in both groups experienced large improvements in menstrual pattern. In the balloon uterine stent group, 66.1% of the patients (41 cases) had improvement in flow. Meanwhile, a significantly better improvement was observed in the IUD plus Foley catheter group, in which 88.5% of the patients (46 cases) reported improved menstrual flow (*P* = 0.048).

The reproductive outcomes are shown in TABLE 2. The mean time from surgery to pregnancy was 13.4 ± 5.4 months. Of the women, 71 (60.2%) succeeded in achieving pregnancy. The pregnancy rates in the balloon uterine stent group versus the Foley plus IUD group were not statistically significantly different (61.3% versus 58.9%, *P* = 0.852). A total of 64 patients (54.2%) had live births; however, there were no statistically significant differences in live birth rates between the two groups (58.1% versus 50.0%, *P* = 0.460). Among the 71 patients who achieved pregnancy, 23 patients (32.4%) became pregnant via IVF and the remainder had naturally conceived pregnancies. Further, no statistically significant differences were found in the naturally conceived pregnancy rate and the assisted pregnancy rate between groups (41.9% versus 39.3%, *P* = 0.770

TABLE 2 COMPARISON OF ADHESION SCORES (INITIAL AND SECOND HYSTEROSCOPY), MENSTRUAL PATTERN, PAIN SCORE (30 MIN AFTER THE OPERATION), AND PREGNANCY OUTCOMES BETWEEN THE TWO GROUPS

	Group A (*n* = 62)	95% CI	Group B (*n* = 56)	95% CI	*P*-value
AFS score before surgery[a]	8	5–12	8	6–12	0.063
Adhesion recurrence[b]					0.024
Yes / (yes + no) (%)	24/62 (38.7%)	0.27–0.51	11/56 (19.6%)	0.11–0.32	
No / (yes + no) (%)	38/62 (61.3%)	0.49–0.72	45/56 (80.4%)	0.68–0.89	
Menstrual pattern after surgery[b]					0.048
Improved (%)	41 (66.1%)	0.53–0.76	46 (82.1%)	0.70–0.90	
No change (%)	21 (33.9%)	0.23–0.46	10 (17.9%)	0.10–0.30	
AFS score after surgery[a]	0	0–8	0	0–6	<0.01
Median reduction of AFS score[a]	6	1–10	8	3–12	<0.01
Pain score after surgery[a]	3	2–3	2	1–2	<0.01
Pregnancy, *n*/*N* (%)[b]	38/62 (61.3%)	0.49–0.72	33/56 (58.9%)	0.46–0.71	0.852
Live birth, *n*/*N* (%)[b]	36/62 (58.1%)	0.46–0.69	28/56 (50%)	0.37–0.63	0.460
Naturally conceived pregnancy, *n*/*N* (%)[b]	26/62 (41.9%)	0.30–0.54	22/56 (39.3%)	0.28–0.52	0.770
IVF pregnancy *n*/*N* (%)[b]	12/62 (19.4%)	0.11–0.31	11/56 (19.6%)	0.11–0.32	0.969

Group A: balloon uterine stent group; Group B: IUD plus Foley catheter group.

AFS = American Fertility Society; CI = confidence interval; IUD = intrauterine device.

[a] Median, Mann–Whitney *U*-test.

[b] Chi-squared test.

TABLE 3 PRE-OPERATIVE AND POST-OPERATIVE MENSTRUAL PATTERN

Before treatment	Group A	Menstrual patterns after treatment			Group B	Menstrual patterns after treatment		
		No menses	Light menses	Normal menses		No menses	Light menses	Normal menses
No menses	*n* = 4	1	3	0	*n* = 3	1	2	0
Light menses	*n* = 48	0	10	38	*n* = 47	0	3	44
Normal menses	*n* = 10	0	0	10	*n* = 6	0	0	6
Total	*n* = 62	1	13	48	*n* = 56	1	5	50

Group A: balloon uterine stent group; Group B: intrauterine device plus Foley catheter group.

and 19.4% versus 19.6%, $P = 0.969$, respectively). In the balloon uterine stent group, the miscarriage rate was 5.3% (2/38), the term delivery rate was 89.5% (34/38), and the pre-term delivery rate was 5.3% (2/38). Only two patients had adherent placenta and one patient had post-partum haemorrhage due to placenta previa. Of the 33 pregnancies in the IUD plus Foley catheter group, five (15.2%) pregnancies ended in miscarriage and two (6.1%) pregnancies ended in pre-term delivery. Among the 28 patients with live births, the incidence of residual placenta was 7.1% (2/28) and that of post-partum haemorrhage was 3.6% (1/28).

Complications

A total of 17 women in this study reported adverse events. Among them, 15 participants experienced moderate to severe post-operative pain (NRS score ≥4), including 12 in the balloon uterine stent group and three in the IUD plus Foley catheter group. Two women discontinued the study because of failure of stent insertion. There were no cases of pelvic infection, uterine perforation, fluid overload or significant vaginal bleeding.

DISCUSSION

Hysteroscopic adhesiolysis is an effective and standard method in the treatment of IUA (*Fernandez et al., 2006*; *Pabuçcu et al., 1997*). However, IUA recurrence is an important consideration and adequate precautions must be taken to prevent this. Mechanical separation of the uterine cavity is recognized as an important aspect of improving the eventual outcome. Over the last two decades, IUD and the Foley balloon catheter have been widely used individually as mechanical barriers to maintain the freshly separated uterine cavity walls for subsequent endometrial regeneration (*March, 1995*; *Rab et al., 2015*).

Orhue et al. (2003) suggested that Foley balloon catheter insertion is a safer and more effective method for restoration of normal menstruation than IUD insertion. In their study, 81.4% of patients treated with the Foley catheter attained restoration of normal menstruation and 33.9% subsequently became pregnant. However, they focused on clinical symptoms rather than an objective evaluation of the uterine cavity, such as determination of AFS scores. No significant difference was found between the Foley catheter group and the IUD group in a cohort study by *Yu et al. (2016)*. Recently, the Cook balloon stent has been proposed to be a better-fitting device in the uterine cavity than the Foley catheter, and therefore may be more effective in preventing IUA. In 2013, a retrospective study in 107 participants was conducted by *Lin et al. (2013)*, who suggested that the efficacy of IUD and the Cook balloon stent was superior to that of hyaluronic acid gel. They also demonstrated that the Cook balloon stent was associated with less uterine adhesion re-formation. However, the number of patients recruited in the study was relatively small and thus had limited power to prove the difference in clinical outcomes. Recently, a new crosslinked hyaluronan (NCH) gel has been clinically recommended for preventing adhesion re-formation. However, a prospective study by *Pabuçcu et al. (2019)* showed that the application of IUD alone, NCH alone, and the combination of NCH with IUD had similar efficacy in preventing adhesion re-formation after hysteroscopic adhesiolysis in patients with moderate to severe IUA. An RCT spanning 2 years (*Lin et al., 2015*) was performed in the same centre, in which the efficacy of the Cook balloon stent and IUD was compared. No significant difference was found in the rate of IUA re-formation between the two groups, although this result may be due to early IUD removal (7 days after the initial hysteroscopic adhesiolysis without ultrasonography). *Myers and Hurst (2012)* suggested that the combination of different therapies showed a significant benefit compared with the application of any treatment alone; however, only 12 patients with the most severe disease, with AFS scores ranging from 10 to 12, were included. The rarity of severe disease precludes a large RCT. Hence, although the role of combined therapies after hysteroscopic adhesiolysis has been illustrated, the method of choice remains controversial. A meta-analysis (*Salma et al., 2014*) provided details and literature evidence on the use of IUD for the management of patients with IUA. It seems that IUD combined with at least one other ancillary treatment can obtain maximal outcomes, particularly in patients with moderate to severe IUA. To date, no comparative studies have confirmed the ideal subsequent treatments.

Regardless of the surgical intervention applied, reassessment of the uterine cavity is considered important. The American Association of Gynecologic Laparoscopists (*AAGL Elevating Gynecologic Surgery, 2017*) recommends that the uterine cavity should be reassessed two to three menstrual cycles after the operation. The optimal interval for performing a second-look hysteroscopy has not yet been established; however, it is believed that early second-look hysteroscopy (*Shokeir et al., 2008*) ultimately improves the success rate. *Pabuçcu et al. (2008)* first introduced second-look IUD-guided hysteroscopy as a safer and more comprehensive technique in a prospective comparative study in 71 patients. Both groups of patients underwent IUD insertion in the first hysteroscopic adhesiolysis. Patients in Group 1 had a second-look hysteroscopy at 1 week and a third-look hysteroscopy at 2 months after the removal of the IUD. Group 2 had a second-look hysteroscopy 2 months later. The IUA re-formation rate was significantly lower in Group 1. However, no statistically significant difference was found between groups

in the pregnancy rate. Further, patients in Group 1 tended to have favourable reproductive outcomes. Early second-look hysteroscopy may help improve the efficacy of re-formation prevention. Nevertheless, further studies with a larger sample size are needed in the future.

There are several reasons for designing such a study as the present one. First, it was found that there was no significant difference in the efficacy of preventing adhesion re-formation between IUD and balloon uterine stent in the preliminary experiment, consistent with the earlier study by *Lin et al. (2015)*. Moreover, in the second hysteroscopy for IUA with IUD alone (*Yang et al., 2016*), it was found that uterine adhesions often recurred in the IUD-free area. Studies (*Cai et al., 2017*; *Chen et al., 2017*) that used a combination of IUD and other ancillary treatments reported satisfactory results. Accordingly, it was postulated that the combined application of an IUD and a Foley catheter may prevent both central and peripheral adhesion re-formation, which may yield a favourable outcome. The IUD is the only barrier that can be placed in the uterine cavity for several months (*Johary et al., 2014*). In addition, retaining the IUD in the uterine cavity for 2–3 months has been considered the standard method of maintaining the uterine cavity (*Khan and Goldberg, 2018*). Considering that the combination of an IUD and a Foley catheter may result in increased infection rate, the Foley catheter was removed earlier than the IUD, 3 days after the original surgery. Lastly, the combined price of a Foley catheter and an IUD is less than that of a balloon uterine stent alone. This is an important advantage, particularly in developing countries with limited resources. Other than the strengths mentioned above, this study is the first RCT designed to compare the efficacy of the balloon uterine stent and an IUD plus a Foley catheter for preventing adhesion re-formation.

In this study, the application of an IUD with a Foley catheter was more effective in reducing adhesion re-formation. The resumption of normal menstruation is an indicator of a reproductive prognosis, and the rate of resumption was reported to range from 52.4% to 88.2% (*Preutthipan and Linasmita, 2000*; *Roy et al., 2010*). The pre-operative volume reflects the severity and extent of endometrial trauma, whereas the post-operative volume indicates the degree of endometrial repair. In this study, the menstrual volume was significantly improved. However, menstrual changes may have a limited role as an outcome, as they do not necessarily correlate with the live birth rate. For women wishing to become pregnant, live birth rate is another important clinical indicator. In this study, 58.1% of women in the balloon uterine stent group and 50% of women in another group achieved this aim. However, given the similar reproductive outcomes in the study and the limited number of included patients, no solid conclusion can be drawn about the live birth results. A larger study designed to evaluate the efficacy of these methods may enable further detection of this outcome.

One limitation of this study was that neither the surgeons nor the recruited patients were blinded to the therapies. Therefore, multicentre, prospective, double-blind RCT will be needed in the future. Compared with previous studies, another shortcoming of this study was the lack of a semi-quantitative assessment of menstrual flow before and after treatment.

In conclusion, this study suggests that after hysteroscopic adhesiolysis, the combination of an IUD and a Foley balloon catheter was more effective than the balloon uterine stent alone in preventing adhesion re-formation and in improving menstrual flow, without any increase in the complication rate. The live birth rates were similar between the two procedures. Further studies are needed to evaluate the reproductive outcomes.

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